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811**Claims**

- 5 1. A glucose-dependent insulintropic peptide (GIP) analogue
consisting of an amino acid sequence selected from the group consisting of:
EGTFISEYSIAibMEKIKQQDFVEWLLAQK – Z; SEQ ID NO:72,
GIP(3-30)[D9E;A13Aib;D15E;H18K;N24E];
EGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO:79,
10 GIP(3-30)[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E];
EGTFISEYSIAibNleEKIKQQEFVEWLLAQK – Z; SEQ ID NO:80,
GIP(3-30)[D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E];
EGTFISEYSIAibLEKIKQQDFVEWLLAQK – Z; SEQ ID NO:84,
GIP(3-30)[D9E; A13Aib; M14L;D15E;H18K;N24E];
15 XGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO:85,
GIP(3-30) [E3Glutaric acid;D9E;A13Aib; M14L;D15E;H18K;D21E;N24E], wherein
X is Glutaric acid;
XGTFISEYSIAibNleEKIKQQEFVEWLLAQK – Z; SEQ ID NO:86,
GIP(3-30) [E3Glutaric acid;D9E;A13Aib; M14Nle;D15E;H18K;D21E;N24E],
20 wherein X is Glutaric acid;
XGTFISEYSIAibMEKIKQQEFVEWLLAQK – Z; SEQ ID NO:88,
GIP(3-30) [E3Glutaric acid;D9E;A13Aib;D15E;H18K;D21E;N24E], wherein X is
Glutaric acid;
EGTFISEYSIAibMEKIKQQEFVEWLLAQK – Z; SEQ ID NO:89,
25 GIP(3-30)[D9E;A13Aib;D15E;H18K;D21E;N24E];
EGTFISEYSIAibLDKIKQQDFVEWLLAQK – Z; SEQ ID NO:91,
GIP(3-30) [D9E;A13Aib; M14L;H18K;N24E];
EGTFISEYSIAibMEKIKQQDFVEWLLAQK – Z; SEQ ID NO:72,
GIP(3-30) [D9E;A13Aib;D15E;H18K;N24E];
30 XGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO:98,
GIP(3-30) [E3Succinic acid;D9E;A13Aib; M14L;D15E;H18K;D21E;N24E],
wherein X is Succinic acid, and
XGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO:99,
GIP(3-30) [E3Adipic acid;D9E;A13Aib; M14L;D15E;H18K;D21E;N24E], wherein X
35 is Succinic acid,
or a variant thereof having 1 or 2 individual amino acid substitutions at any amino
acid of said amino acid sequences.

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wherein Z is a peptide comprising one or more amino acid residues of the C-terminus of Exendin-4(31-39) (PSSGAPPPS; SEQ ID NO:67; CE31-39) or is omitted, and wherein said GIP peptide analogue is an antagonist of GIPR.

~~2. The GIP peptide analogue according to any one of the preceding claims, wherein said GIP peptide analogue is an antagonist of GIPR~~

~~32.~~ The GIP peptide analogue according to any one of the preceding claims, wherein the GIP peptide analogue has improved solubility as compared to GIP(3-30) and/or as compared to AT364 (SEQ ID NO:6) at pH 7 to 9, such as at pH 7 to 8.5, such as at pH 7.0 to 8.0 or pH 7.5 to 8.5.

~~43.~~ The GIP peptide analogue according to any one of the preceding claims, wherein the GIP peptide analogue has an aqueous solubility of at least 1 mg/ml, such as at least 5 mg/ml, such as at least 7.5 mg/ml, such as at least 10 mg/ml, such as at least 15 mg/ml.

~~54.~~ The GIP peptide analogue according to any one of the preceding claims, wherein the GIP peptide analogue has an aqueous solubility at pH between 7 to 9, such as around pH 7.5 or around 8, of at least 1 mg/ml, such as at least 5 mg/ml, such as at least 7.5 mg/ml, such as at least 10 mg/ml, such as at least 15 mg/ml.

~~65.~~ The GIP peptide analogue according to any one of the preceding claims, wherein the GIP peptide analogue has improved physical stability as measured by a fibrillation lag time in a ThT assay of more than about 24 hours, such as a fibrillation lag time in a ThT assay of more than about 50 hours, such as a fibrillation lag time in a ThT assay of more than about 96 hours, such as a fibrillation lag time in a ThT assay of more than about 168 hours.

~~76.~~ The GIP peptide analogue according to any one of the preceding claims, wherein the GIP peptide analogue has improved physical stability as compared to GIP(3-30) and/or as compared to AT364 (SEQ ID NO:6) at pH 7 to 9, such as at pH 7 to 8.5, such as at pH 7.0 to 8.0 or pH 7.5 to 8.5.

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87. The GIP peptide analogue according to any one of the preceding claims, wherein said GIP peptide analogue inhibits GIPR activity of at least 80%, such as of at least 85%, such as of at least 90%, such as of at least 95%, such as of about 100%.

98. The GIP peptide analogue according to any one of the preceding claims, wherein said GIP peptide analogue inhibits GIPR activity of at least 80%, such as of at least 85%, such as of at least 90%, such as of at least 95%, such as of about 100%, wherein inhibition of GIPR activity is determined as a decrease in intracellular cAMP.

109. The GIP peptide analogue according to any one of the preceding claims, wherein said GIP peptide analogue has a GIPR antagonistic potency corresponding to an IC50 value of less than 50 nM, such as an IC50 value of less than 10 nM, such as an IC50 value of less than 5 nM, such as an IC50 value of less than 1nM, such as an IC50 value of between 0.001 nM to 1 nM.

110. The GIP peptide analogue according to any of the preceding claims, wherein the GIP peptide analogue has a free N-terminus and/or wherein said peptide is C-terminally amidated (-NH₂) or C-terminally carboxylated (-COOH).

121. The GIP peptide analogue according to any of the preceding claims, wherein a fatty acid molecule is attached to the epsilon-amino group of the K residue at position 18 of said GIP peptide analogue.

~~13. The GIP peptide analogue of any one of the preceding claims, wherein said peptide is C-terminally amidated (-NH₂) or C-terminally carboxylated (-COOH).~~

~~14. The GIP peptide analogue of any one of the preceding claims, wherein said peptide is C-terminally carboxylated (-COOH).~~

1512. The GIP peptide analogue of ~~any one of the preceding claims~~ 11, wherein said fatty acid molecule is a straight-chain fatty acid and/or wherein said fatty acid molecule is a diacyl fatty acid molecule;

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16. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule is a diacyl fatty acid molecule~~

17. ~~such as The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule comprises an acyl group of the formula $\text{COOH}(\text{CH}_2)_n\text{CO-}$ (dicarboxylic acid), wherein n is an integer from 4 to 24;~~

~~such as -~~

18. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule comprises or consists of $\text{COOH}(\text{CH}_2)_{14}\text{CO-}$, and/or -~~

19. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule comprises or consists of $\text{COOH}(\text{CH}_2)_{16}\text{CO-}$, and/or -~~

20. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule comprises or consists of $\text{COOH}(\text{CH}_2)_{18}\text{CO-}$.~~

21. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule is attached to the epsilon amino group of the side chain of an amino acid residue of said GIP peptide analogue directly or via a linker.~~

22. ~~The GIP peptide analogue according to any of the preceding claims, wherein said fatty acid molecule is attached to an amino acid residue via a linker.~~

23. ~~The GIP peptide analogue according to any of the preceding claims, wherein the fatty acid molecule is attached to an amino acid residue via a linker in such a way that a carboxyl group of the fatty acid molecule forms an amide bond with an amino group of the linker.~~

24. ~~The GIP peptide analogue of any one of claims 22 and 23, such as wherein said linker comprises a γ -Glu, one or more 8-amino-3,6-dioxaoctanoic acid (AEEAc), or combinations thereof, such as~~

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25. ~~The GIP peptide analogue of any one of claims 22 to 24, wherein said linker comprises or consists of γ Glu-, such as~~

26. ~~The GIP peptide analogue of any one of claims 22 to 25, wherein said linker comprises or consists of a [8-amino-3,6-dioxaoctanoic acid]_n (AEEAc)_n, wherein n is an integer between 1 and 50, such as an integer between 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10, 10-11, 11-12, 12-13, 13-14, 14-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, preferably wherein n is 1, 2 or 3.~~

27. ~~The GIP peptide analogue of any one of claims 22 to 26, wherein said linker comprises or consists of a γ Glu and one AEEAc, such as a γ Glu and two AEEAc, for example a γ Glu and three AEEAc.~~

~~28~~15. The GIP peptide analogue of any one of claims 11 to 14~~22 to 27~~, wherein the fatty acid molecule is attached to an amino acid residue via a linker, and wherein the combination of linker and fatty acid is selected from the group consisting of:

- i. [15-Carboxy pentadecanoyl]- γ Glu
- ii. [17-carboxy-heptadecanoyl]- γ -Glu-AEEAc-AEEAc-, and
- iii. [17-carboxy-heptadecanoyl]- γ Glu- γ Glu

~~29~~16. The GIP peptide analogue of any one of the preceding claims selected from the group consisting of:

EGTFISEY**SI**A**ib**MEKIKQQDFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:33; GIP(3-30)+Cex(31-39) [D9E;A13Aib;D15E;H18K;N24E],
 EGTFISEY**SI**A**ib**LEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:18; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
 EGTFISEY**SI**A**ib**LEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+ γ Glu-C18-diacid/18K; SEQ ID NO:18; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
 EGTFISEY**SI**A**ib**N**le**EKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:19; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
 EGTFISEY**SI**A**ib**N**le**EKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+ γ Glu-C18-diacid/18K; SEQ ID NO:19; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14Nle;

D15E;H18K;D21E;N24E],

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:25; GIP(3-30)+Cex(31-39) [E3Glutaric acid;D9E;A13Aib;
M14L;D15E;H18K;D21E;N24E],

XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:26; GIP(3-30)-Cex(31-39) [E3Glutaric acid;D9E;
A13Aib;M14Nle;D15E;H18K;D21E;N24E],

XGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:28; GIP(3-30)-Cex(31-39) [E3Glutaric acid;D9E;A13Aib;
D15E;H18K;D21E;N24E],

EGTFISEYSIAibMEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:29; GIP(3-30)-Cex(31-39) [D9E;A13Aib;D15E;H18K;
D21E;N24E],

EGTFISEYSIAibLDKIKQQDFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:30; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;H18K;
N24E],

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:25; GIP(3-30)Cex(31-39) [E3Glutaric acid;D9E;A13Aib;
M14L;D15E;H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:18; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;
H18K;D21E;N24E],

EGTFISEYSIAibMEKIKQQDFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ
ID NO:33; GIP(3-30)Cex(31-39) [D9E;A13Aib;D15E;H18K;N24E],

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID
NO:25; GIP(3-30)Cex(31-39) [E3Glutaric acid;D9E;A13Aib;M14L;D15E;
H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(GGGS-C16-
diacid/18K); SEQ ID NO:18; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;
H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(ALEA-C16-
diacid/18K); SEQ ID NO:18; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;
H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQDFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-

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diacid/18K; SEQ ID NO:50; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;N24E],

XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K;
SEQ ID NO:26; GIP(3-30)Cex(31-39) [E3Glutaric acid;D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-(Aib-C16-diacid/18K);
SEQ ID NO:18; GIP(3-30)Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-
(KAAAEKAAAEKAAAE-C16-diacid/18K); SEQ ID NO:18; GIP(3-30)Cex(31-39)
[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:48; GIP(3-30)Cex(31-39) [E3Succinic acid;D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:49; GIP(3-30)Cex(31-39) [E3Adipic acid;D9E;A13Aib;M14L;D15E;H18K;D21E;N24E].

~~30~~17. The GIP peptide analogue of any one of the preceding claims selected from the group consisting of:

EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:18; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEEAc+yGlu-C18-
diacid/18K; SEQ ID NO:26; GIP(3-30)-Cex(31-39) [E3Glutaric acid; D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E], and

XGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:25; GIP(3-30)Cex(31-39) [E3Glutaric acid;D9E;A13Aib;M14L;D15E;H18K;D21E;N24E].

~~31. The GIP peptide analogue of any one of the preceding claims, wherein said GIP peptide analogue is EGTFISEYSIAibLEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ ID NO:18; GIP(3-30)+Cex(31-39) [D9E;A13Aib;M14L;~~

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D15E;H18K;D21E;N24E].

5 32. The GIP peptide analogue of any one of the preceding claims, wherein said GIP peptide analogue is ~~XGTFISEYSIAibNleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEAAc+yGlu-C18-diacid/18K; SEQ ID NO:26; GIP(3-30)-Cex(31-39) [E3Glutaric acid;D9E;A13Aib; M14Nle;D15E;H18K;D21E;N24E.~~

10 3318. Use of ~~T~~the GIP peptide analogue according to any of the preceding claims for the manufacture of a medicament ~~for use in a method of~~ inhibiting or reducing one or more of
 15 i) GIP-induced glucagon secretion, ii) GIP-induced insulin secretion, iii) GIP-induced somatostatin secretion, iv) GIP-induced glucose uptake, v) GIP-induced fatty acid synthesis and/or fatty acid incorporation, vi) high or increased expression or activity of a GIPR, vii) post-prandial GIP release, viii) serum levels of free fatty acids and/or triglycerides, ix) GIP-induced appetite increases, x) GIP-induced reduction in energy expenditure, xi) GIP-induced increase in absorption of nutrients from the gut, xii) GIP-induced decrease in GLP-1's appetite suppressive effect, xiii) GIP-induced leptin resistance.

20 3419. Use of ~~t~~The GIP peptide analogue according to any of the preceding claims for the manufacture of a medicament ~~for use in a method of~~ the treating/treatment of a condition selected from the group consisting of metabolic syndrome, obesity, pre-diabetes, type I diabetes, type 2 diabetes, insulin resistance, elevated fasting glucose, hyperglycemia,
 25 elevated fasting serum triglyceride levels, low levels of very low-density lipoprotein (VLDL), low high-density lipoprotein (HDL) levels, dyslipidemia, increased/decreased low-density lipoprotein (LDL), high cholesterol levels, abnormal deposition of lipids, a cardiovascular disease, elevated blood pressure and atherosclerosis.