

Claims

1. A glucose-dependent insulinotropic peptide (GIP) analogue
consisting of amino acid sequence of :

5 3 4 5 6 7 8 9 10 11 12 13 14 15 16
E - G - T - F - I - S - E - Y - S - I - A - L/Nle - E - K -

17 18 19 20 21 22 23 24 25 26 27 28 29 30
I - K - Q - Q - E - F - V - E - W - L - L - A - Q - K - Z,

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or a functional variant thereof, wherein said variant has 1 or 2 individual amino acid substitutions at any amino acid of said amino acid sequence,

wherein said peptide is modified by attaching at least one fatty acid molecule at the amino acid residue at position 18 of said sequence, or said functional variant thereof,

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wherein Z is a peptide comprising one or more amino acid residues of GIP(31-42) (GKKNDWKHNITQ; SEQ ID NO: 2) or one or more amino acid residues of Exendin-4

(HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS; SEQ ID NO: 3),

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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 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
25 100%, optionally wherein inhibition of GIPR activity is determined as a decrease in intracellular cAMP.

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3. 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 50 nM or less than 50 nM.

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4. The GIP peptide analogue according to any one of the preceding claims, wherein:
the amino acid at position 11 is selected from S, K and A;
the amino acid at position 12 is selected from I, K and 2-Aminoisobutyric acid
35 (Aib);

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the amino acid at position 13 is selected from A and Aib;
the amino acid at position 16 is selected from K and R;
the amino acid at position 17 is selected from I and K;
the amino acid at position 18 is selected from K and Orn;
5 the amino acid at position 20 is selected from Q and K;
the amino acid at position 28 is selected from A and E;
the amino acid at position 29 is selected from Q and G; and/or
the amino acid at position 30 is selected from K, R, G and A.

- 10 5. The GIP peptide analogue according to any one of the preceding claims, wherein said functional variant has 1 individual amino acid substitution at any amino acid residue of said amino acid sequence, optionally wherein said substitutions are conservative amino acid substitutions.
- 15 6. The GIP peptide analogue according to any one of the preceding claims, wherein the S at position 11 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with an amino acid residue selected from the group consisting of A, K and Orn and/or wherein the I at position 12 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with an amino acid residue selected from the group consisting of K, Orn and 2-Aminoisobutyric acid (Aib) and/or wherein the K at position 16 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with R and/or wherein the I at position 17 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with an amino acid residue selected from the group consisting of K or Orn and/or wherein the Q at position 20 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with an amino acid residue selected from the group consisting of K and Orn and/or wherein the D at position 21 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with E and/or wherein the A at position 28 of said amino acid
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sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with E and/or wherein the Q at position 29 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with G and/or wherein the K at position 30 of said amino acid sequence, or a functional variant thereof, is substituted with any amino acid, such as a conservative amino acid substitution, such as substituted with an amino acid residue selected from the group consisting of R, A and G and/or wherein said GIP peptide analogue comprises at least one substitution to K and one substitution to E or Aib at any one of amino acid residues 3 to 30 of said amino acid sequence.

7. The GIP peptide analogue according to any one of the preceding claims, wherein Z consists of one or more consecutive amino acid residues of GIP(31-42) (SEQ ID NO: 2) and/or wherein Z consists of one or more consecutive amino acid residues of Exendin-4 (SEQ ID NO: 3) and/or wherein Z consists of one or more consecutive amino acid residues of the C-terminus of Exendin-4(30-39) (PSSGAPPPS; SEQ ID NO: CE31-39) and/or wherein Z consists of one or more consecutive amino acid residues of the C-terminus of Exendin-4(29-39) (GPSSGAPPPS; SEQ ID NO: CE30-39).

8. The GIP peptide analogue according to any one of the preceding claims, wherein Z comprises at least one G amino acid residue and/or one P amino acid residue and/or wherein Z comprises at least two P amino acid residues.

9. The GIP peptide analogue according to any one of the preceding claims, wherein Z is a peptide selected from the group consisting of

- a glycine, G, or a proline, P,
- GP, GPS, GPSS, GPSSG, GPSSGA, GPSSGAP, GPSSGAPP, GPSSGAPPP and GPSSGAPPPS,
- PS, PSS, PSSG, PSSGA, PSSGAP, PSSGAPP, PSSGAPPP and PSSGAPPPS,
- GK, GKK, GKKN, GKKNL, GKKNLW, GRKNLW, GKRNDW, GRRNDW, GKKNLWK, GKKNLWKH, GKKNLWKHN, GKKNLWKHNI, GKKNLWKHNIT and GKKNLWKHNITQ,
- GPSSGA, GPSSGAP, GPSSGAPP, GPSSGAPPP, GPSSGAPPPS,

GKKNDW, GKKKDW, GKKNDK GRKNDW, GKRNDW, GRRNDW, GKKNDWK, GKKNDWKH, GKKNDWKHN, GKKNDWKHNI, GKKNDWKHNIT and GKKNDWKHNITQ, or a variant thereof comprising 1 or 2 individual amino acid substitutions at any one of the amino acid residues, or

5 - PSSG, PSSGA, PSSGAP, PSSGAPP, PSSGAPPP and PSSGAPPPS, or a variant thereof comprising 1 or 2 individual amino acid substitutions at any one of the amino acid residues.

10 10. The GIP peptide analogue according to any of the preceding claims, wherein one or more fatty acid molecule(s) is attached to the side chain of an amino acid residue at position 18, of said GIP peptide analogue, or a functional variant thereof and/or wherein a fatty acid molecule is attached to the epsilon-amino group of a K or Orn at position 18 of residue of said GIP peptide analogue, or a

15 functional variant thereof comprising at least one K or Orn residue.

11. The GIP peptide analogue of any one of the preceding claims, wherein said GIP peptide analogue has an amino acid sequence selected from the group consisting of:

20 EGTFFISEYSIAIEKIKQQEFVQWLLAQK – Z; SEQ ID NO: 50; GIP(3-30) [D9E;D15E;H18K;D21E;N24Q],

EGTFFISEYSAibANleEKIKQQDFVEWLLAQK – Z; SEQ ID NO: 52; GIP(3-30) [D9E;I12Aib;M14Nle;D15E;H18K;N24E],

EGTFFISEYSIAibMEKIKQQDFVEWLLAQK – Z; SEQ ID NO: 53; GIP(3-30)

25 [D9E;A13Aib;D15E;H18K;N24E],

EGTFFISDYSAibLDKIKQQDFVEWLLAQK – Z; SEQ ID NO: 74; GIP(3-30) [A13Aib;M14L;H18K;N24E],

EGTFFISDYSAibNleDKIKQQDFVEWLLAQK – Z; SEQ ID NO: 75; GIP(3-30) [A13Aib;M14Nle;H18K;N24E],

30 EGTFFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO: 81; GIP(3-30) [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],

EGTFFISEYSIAibNleEKIKQQEFVEWLLAQK – Z; SEQ ID NO: 82; GIP(3-30) [D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],

EGTFFISEYSIALEKIKQQEFVEWLLAQK – Z; SEQ ID NO: 87; GIP(3-30)

35 [D9E;M14L;D15E;H18K;D21E;N24E], and

EGTFISEYSIANleEKIKQQEFVEWLLAQK – Z; SEQ ID NO: 88; GIP(3-30)
[D9E;M14Nle;D15E;H18K;D21E;N24E].

12. The GIP peptide analogue of any one of the preceding claims, wherein said GIP
5 peptide analogue has an amino acid sequence of:
EGTFISEYSIAibLEKIKQQEFVEWLLAQK – Z; SEQ ID NO: 81; GIP(3-30)
[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E].

13. The GIP peptide analogue of any one of the preceding claims, wherein said fatty
10 acid molecule is a straight-chain fatty acid and/or wherein said fatty acid molecule
is a branched fatty acid and/or wherein said fatty acid molecule is a monoacyl
fatty acid molecule, comprising one fatty acid and/or wherein said fatty acid
molecule is a diacyl fatty acid molecule and/or wherein said fatty acid molecule
comprises an acyl group of the formula $\text{CH}_3(\text{CH}_2)_n\text{CO}-$, wherein n is an integer
15 from 4 to 24.

14. The GIP peptide analogue according to any of the preceding claims, wherein said
fatty acid molecule comprises an acyl group selected from the group consisting
of $\text{COOH}(\text{CH}_2)_{14}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{16}\text{CO}-$, $\text{COOH}(\text{CH}_2)_{18}\text{CO}-$ and
20 $\text{COOH}(\text{CH}_2)_{20}\text{CO}-$.

15. 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 wherein said fatty
25 acid molecule is attached to an amino acid residue via a linker.

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

EGTFISEYSIAMEKIKQQEFVQWLLAQKPSSGAPPPS- C16-diacid; SEQ ID
30 NO: 141; GIP(3-30)+Cex(31-39) [CexD9E;D15E;H18K;D21E;N24Q],
EGTFISEYSIAMEKIKQQDFVEWLLAQKPSSGAPPPS- C16-diacid; SEQ ID
NO: 142; GIP(3-30)+Cex(31-39) [D9E;D15E;H18K;N24E],
EGTFISEYSAibANleEKIKQQDFVEWLLAQKPSSGAPPPS-C16-diacid/18K;
SEQ ID NO: 143; GIP(3-30)+Cex(31-39)
35 [D9E;I12Aib;M14Nle;D15E;H18K;N24E],

- EGTFISEY**SI****Aib**MEKIKQQDFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ
ID NO: 144; GIP(3-30)+Cex(31-39) [D9E;A13Aib;D15E;H18K;N24E],
EGTFISEY**SI****Aib**LEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ
ID NO: 174; GIP(3-30)+Cex(31-39)
- 5 [D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
EGTFISEY**SI****Aib**LEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEAAc+yGlu-C18-
diacid/18K; SEQ ID NO: 174; GIP(3-30)+Cex(31-39)
[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E],
EGTFISEY**SI****Aib**NleEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K;
10 SEQ ID NO: 175; GIP(3-30)+Cex(31-39)
[D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
EGTFISEY**SI****Aib**NleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEAAc+yGlu-
C18-diacid/18K; SEQ ID NO: 175; GIP(3-30)+Cex(31-39)
[D9E;A13Aib;M14Nle;D15E;H18K;D21E;N24E],
15 EGTFISEY**SI****A**LEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEAAc+yGlu-C18-
diacid/18K; SEQ ID NO: 180; GIP(3-30)+Cex(31-39)
[D9E;M14L;D15E;H18K;D21E;N24E], and
EGTFISEY**SI****A**NleEKIKQQEFVEWLLAQKPSSGAPPPS-2xAEAAc+yGlu-C18-
diacid/18K; SEQ ID NO: 181; GIP(3-30)+Cex(31-39)
20 [D9E;M14Nle;D15E;H18K;D21E;N24E].
17. The GIP peptide analogue of any one of the preceding claims, wherein said GIP
peptide analogue is
EGTFISEY**SI****Aib**LEKIKQQEFVEWLLAQKPSSGAPPPS-C16-diacid/18K; SEQ
25 ID NO: 174; GIP(3-30)+Cex(31-39)
[D9E;A13Aib;M14L;D15E;H18K;D21E;N24E].
18. Use of a GIP peptide analogue according to any of the preceding claims for the
manufacture of a medicament for the treatment of a condition selected from the
30 group consisting of metabolic syndrome, obesity, pre-diabetes, type I diabetes,
type 2 diabetes, insulin resistance, hyperglycemia, dyslipidemia, a cardiovascular
disease, and atherosclerosis.