

insulin resistance and administering the antigen binding protein reduces insulin resistance. In another example, the glucose metabolism disorder comprises diabetes mellitus. In another example, the subject is obese. In another example, administering the composition reduces body weight in an obese subject. In another example, administering the composition reduces body weight gain in an obese subject. In another example, administering the composition reduces fat mass in an obese subject. In another example, the glucose metabolism disorder comprises insulin resistance and administering the composition reduces insulin resistance in an obese subject. In another example, administering the composition reduces liver steatosis in an obese subject having increased liver steatosis. In another example, administering the composition reduces liver fat content in an obese subject having increased liver fat content.

[0008a] In one aspect, the present disclosure refers to a composition comprising a) an antibody or functional fragment thereof that specifically binds to a protein having an amino acid sequence having at least 90% amino acid sequence identity to an amino acid sequence of a human GIPR, wherein the antibody or functional fragment thereof comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein each CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively, comprises a sequence selected from the group consisting of SEQ ID NO: 702, SEQ ID NO: 859, SEQ ID NO: 1016, SEQ ID NO: 1173, SEQ ID NO: 1330; and SEQ ID NO: 1487; and the antibody or functional fragment thereof comprises a cysteine or non-canonical amino acid substitution at one or more conjugation site(s) selected from the group consisting of D70 of the antibody light chain relative to reference sequence SEQ ID NO: 455, E276 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612, and T363 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612; and b) a GLP-1 receptor agonist, wherein the GLP-1 receptor agonist comprises [Aib⁸;Tyr¹⁶;Glu²²;Gly³⁶]GLP-1₍₇₋₃₇₎ (SEQ ID NO: 3244) and is conjugated to the antibody or functional fragment thereof through the side-chain of the cysteine residue or non-canonical amino acid residue substituted at the one or more conjugation site(s).

[0008b] In another aspect, the present disclosure refers to the use of a composition comprising an antibody as defined in the claims in the manufacture of a medicament for treating a metabolic disorder, wherein the metabolic disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, glucose intolerance, insulin resistance, diabetes mellitus, Type 2 diabetes, elevated glucose levels, elevated insulin levels, dyslipidemia, metabolic syndrome (Syndrome X or insulin resistance syndrome), glucosuria, metabolic acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, Type 1 diabetes, obesity and conditions exacerbated by obesity.

[0009] In one example, the composition comprises an antibody or functional fragment thereof that specifically binds to a protein having an amino acid sequence having at least 90% amino acid sequence identity to an amino acid sequence of a human GIPR, wherein the antibody or functional fragment thereof comprises a cysteine or non-canonical amino acid substitution at one or more conjugation site(s) selected from the group consisting of D70 of the antibody light chain relative to reference sequence SEQ ID NO: 455; E276 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612, and T363 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612; and a GLP-1 receptor

CLAIMS

What is claimed is:

1. A composition comprising

a) an antibody or functional fragment thereof that specifically binds to a protein having an amino acid sequence having at least 90% amino acid sequence identity to an amino acid sequence of a human GIPR, wherein the antibody or functional fragment thereof comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein each CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively, comprises a sequence selected from the group consisting of SEQ ID NO: 702, SEQ ID NO: 859, SEQ ID NO: 1016, SEQ ID NO: 1173, SEQ ID NO: 1330; and SEQ ID NO: 1487; and

the antibody or functional fragment thereof comprises a cysteine or non-canonical amino acid amino acid substitution at one or more conjugation site(s) selected from the group consisting of

D70 of the antibody light chain relative to reference sequence SEQ ID NO: 455,

E276 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612, and

T363 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612; and

b) a GLP-1 receptor agonist, wherein the GLP-1 receptor agonist comprises [Aib⁸;Tyr¹⁶;Glu²²;Gly³⁶]GLP-1_(7-37) (SEQ ID NO: 3244) and is conjugated to the antibody or functional fragment thereof through the side-chain of the cysteine residue or non-canonical amino acid residue substituted at the one or more conjugation site(s).

2. The composition of claim 1, wherein said human GIPR has a sequence comprising a sequence selected from the group consisting of SEQ ID NO: 3141, SEQ ID NO: 3143, and SEQ ID NO: 3145.

3. The composition of claim 1 or 2, wherein said antibody or functional fragment thereof is a monoclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.

4. The composition of claim 3, wherein said antibody or functional fragment thereof is a human antibody.

5. The composition of claim 3, wherein said antibody or functional fragment thereof is a monoclonal antibody.

6. The composition of claim 3, wherein said antibody or functional fragment thereof is of the IgG1-, IgG2- IgG3- or IgG4-type.

7. The composition of claim 6, wherein said antibody or functional fragment thereof is of the IgG1- or the IgG2-type.

8. The composition of one of claim 3, wherein said antibody or functional fragment thereof inhibits binding of GIP to the extracellular portion of human GIPR.

9. The composition of claim 3, wherein said antibody or functional fragment thereof is an antibody or a fragment thereof, and wherein said antibody or fragment thereof comprises a light chain variable region comprising SEQ ID NO: 74 and a heavy chain variable region comprising SEQ ID NO: 231, wherein

the antibody or functional fragment thereof comprises a cysteine or non-canonical amino acid amino acid substitution at E276 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612.

10. The composition of claim 3, wherein said antibody or functional fragment thereof is an antibody, and wherein said antibody comprises NO: 388 and a heavy chain comprising SEQ ID NO: 545, wherein

the antibody or functional fragment thereof comprises a cysteine or non-canonical amino acid amino acid substitution at

E276 of the antibody heavy chain relative to reference sequence SEQ ID NO: 612.

11. The composition of claim 1, wherein the GLP-1 receptor agonist is conjugated to the antibody or fragment thereof at a C-terminal amine group of said agonist.

12. The composition of claim 1, wherein the GLP-1 receptor agonist if conjugated to the antibody or fragment thereof via a peptide linker comprising a sequence selected from

the group consisting of (Gly₃Ser)₂, (Gly₄Ser)₂, (Gly₃Ser)₃, (Gly₄Ser)₃, (Gly₃Ser)₄, (Gly₄Ser)₄, (Gly₃Ser)₅, (Gly₄Ser)₅, (Gly₃Ser)₆, and (Gly₄Ser)₆.

13. Use of a composition according to claim 1, in the manufacture of a medicament for treating a metabolic disorder, wherein the metabolic disorder is selected from
- 5 the group consisting of hyperglycemia, hyperinsulinemia, glucose intolerance, insulin resistance, diabetes mellitus, Type 2 diabetes, elevated glucose levels, elevated insulin levels, dyslipidemia, metabolic syndrome (Syndrome X or insulin resistance syndrome), glucosuria, metabolic acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, Type 1 diabetes, obesity and conditions exacerbated by obesity.