[0005] GIPR knockout mice ($Gipr^{-/-}$) are resistant to high fat diet-induced weight gain and have improved insulin sensitivity and lipid profiles. (Yamada et al., Diabetes. 2006, 55:S86; Miyawaki et al. Nature Med. 2002, 8:738-742). In addition, a novel small molecule GIPR antagonist SKL-14959 prevents obesity and insulin resistance. (Diabetologia 2008, 51:S373, 44th EASD Annual meeting poster).

[0006] Collectively, these links to obesity and insulin resistance imply GIPR inhibition is a useful approach for therapeutic intervention.

[0007] Glucagon-like peptide-1 is a 31-amino acid peptide derived from the proglucagon gene. It is secreted by intestinal L-cells and released in response to food ingestion to induce insulin secretion from pancreatic β–cells (Diabetes 2004, 53:S3, 205-214). In addition to the incretin effects, GLP-1 also decreases glucagon secretion, delays gastric emptying and reduces caloric intake (Diabetes Care, 2003, 26(10): 2929-2940). GLP-1 exerts its effects by activation of the GLP-1 receptor, which belongs to a class B G-protein-coupled receptor (Endocrinology. 1993, 133(4):1907-10). The function of GLP-1 is limited by rapid degradation by the DPP-IV enzyme, resulting in a half-life of approximately 2 minutes. Recently, long-lasting GLP-1 receptor agonists (GLP-1 RAs) such as exenatide, liraglutide, dulaglutide have been developed and are now being used clinically to improve glycemic control in patients with type 2 diabetes. Furthermore, GLP-1RAs also promote body weight reduction as well as reduction in blood pressure and plasma cholesterol levels in patients (Bioorg. Med. Chem.Lett 2013, 23:4011-4018).

SUMMARY

[0008] In one example, the present disclosure provides a method of treating a subject with a metabolic disorder, the method comprising administering to the subject a therapeutically effective amount of a composition comprising an antigen binding protein that specifically binds to human GIPR, wherein the antigen binding protein is conjugated to a GLP-1 receptor agonist. In one example, the metabolic disorder is a disorder of glucose metabolism. In another example, the glucose metabolism disorder comprises hyperglycemia and administering the antigen binding protein reduces plasma glucose. In another example, the glucose metabolism disorder comprises hyperinsulinemia and administering the antigen binding protein reduces plasma insulin. In another example, the glucose metabolism disorder comprises glucose intolerance and administering the antigen binding protein reduces increases glucose tolerance. In another example, the glucose metabolism disorder

comprises 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 polypeptide comprising a GLP-1 receptor agonist comprising the amino acid sequence of SEQ ID NO: 3244.

[0008b] In another aspect, the present disclosure refers to a composition comprising: the polypeptide as disclosed hererin, and an anti-GIPR antibody, wherein the polypeptide as disclosed hererin is conjugated to a cysteine residue on the anti-GIPR antibody.

[0008c] In yet another aspect, the present disclosure refers to a composition comprising: a polypeptide comprising: a GLP-1R agonist wherein the GLP-1R agonist comprises the amino acid sequence of SEQ ID NO: 3244, and a linker comprising the sequence GGGGSGGGGSGGGGSK, wherein the N-terminus of the linker is fused to C-terminus of the amino acid sequence of SEQ ID NO: 3244; and an anti-GIPR antibody comprising two light chains comprising the amino acid sequence of SEQ ID NO: 338 and two heavy chains comprising the amino acid sequence of SEQ ID NO: 545, wherein the heavy chains each comprise a cysteine substitution at position E384 according to AHo; wherein the C-terminus lysine of the polypeptide is conjugated to the cysteine at position E384 of the anti-GIPR antibody.

[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 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 agonist, wherein the GLP-1 receptor agonist 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).

[0010] In one example, the 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. In one example, the 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. In one example, the antibody fragment is a Fab fragment, a Fab' fragment, or a F(ab')2 fragment. In one example, the antibody or functional fragment thereof is of the IgG1-, IgG2- IgG3- or IgG4-type. In one example, the antibody or functional fragment thereof inhibits binding of GIP to the extracellular portion of human GIPR.

[0011] In one example, the GLP-1 receptor agonist is GLP-1(7-37) or a GLP-1(7-37) analog. In one example, the GLP-1 receptor agonist is selected from the group consisting of exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, and taspoglutide.

In one example, the GLP-1 receptor agonist is selected from the group consisting of GLP-1(7-37) (SEQ ID NO: 3184); GLP-1(7-36)-NH_2 (SEQ ID NO: 3185); liraglutide; albiglutide; taspoglutide; dulaglutide, semaglutide; LY2428757; Exendin-4 (SEQ ID NO: 3163); Exendin-3 (SEQ ID NO: 3164); Leu^{14}-exendin-4 (SEQ ID NO: 3165); Leu^{14},Phe^{25}-exendin-4 (SEQ ID NO: 3166); Leu^{14},Ala^{19},Phe^{25}-exendin-4 (SEQ ID NO: 3167); exendin-4(1-30) (SEQ ID NO: 3168); Leu^{14}-exendin-4(1-30) (SEQ ID NO: 3169); Leu^{14},Phe^{25}-exendin-4(1-30) (SEQ ID NO: 3170); Leu^{14},Ala^{19},Phe^{25}-exendin-4(1-30) (SEQ ID NO: 3171); exendin-4(1-28) (SEQ ID NO: 3172); Leu^{14}-exendin-4(1-28) (SEQ ID NO: 3173); Leu^{14},Phe^{25}-exendin-4(1-28) (SEQ ID NO: 3174); Leu^{14},Ala^{19},Phe^{25}-exendin-4 (1-28) (SEQ ID NO: 3175); Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Phe^{25},Gln^{28}-exendin-4 (SEQ ID NO: 3176); Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Gln^{28}-exendin-4 (SEQ ID NO: 3177); octylGly^{14},Gln^{28}-exendin-4 (SEQ ID NO: 3178); Leu^{14},Gln^{28},octylGly^{34}-exendin-4 (SEQ ID NO: 3179); Phe^{4},Leu^{14},Gln^{28},Lys^{33},Glu^{34}, $Ile^{35,36}$,Ser^{37}-exendin-4(1-37) (SEQ ID NO: 3180); Phe^{4},Leu^{14},$Lys^{17,20}$,Ala^{19},Glu^{21},Gln^{28}-exendin-4 (SEQ ID NO: 3181); Val^{11},Ile^{13},Leu^{14},Ala^{16},Lys^{21},Phe^{25}-exendin-4 (SEQ ID NO: 3182); exendin-4-Lys^{40} (SEQ ID NO: 3183); GLP-1(7-37) (SEQ ID NO: 3184); GLP-1(7-36)-NH_2 (SEQ ID NO: 3185); $Aib^{8,35}$,$Arg^{26,34}$,Phe^{31}-GLP-1(7-36)) (SEQ ID NO: 3186); $HXaa_8EGTFTSDVSSYLEXaa_{22}Xaa_{23}AAKEFIXaa_{30}WLXaa_{33}Xaa_{34}G\ Xaa_{36}Xaa_{37}$; wherein Xaa_8 is A, V, or G; Xaa_{22} is G, K, or E; Xaa_{23} is Q or K; Xaa_{30} is A or E; Xaa_{33} is V or K; Xaa_{34} is K, N, or R; Xaa_{36} is R or G; and Xaa_{37} is G, H, P, or absent (SEQ ID NO: 3187); Arg^{34}-GLP-1(7-37) (SEQ ID NO: 3188); Glu^{30}-GLP-1(7-37) (SEQ ID NO: 3189); Lys^{22}-GLP-1(7-37) (SEQ ID NO: 3190); $Gly^{8,36}$,Glu^{22}-GLP-1(7-37) (SEQ ID NO: 3191); Val^{8},Glu^{22},Gly^{36}-GLP-1(7-37) (SEQ ID NO: 3192); $Gly^{8,36}$,Glu^{22},Lys^{33},Asn^{34}-GLP-1(7-37) (SEQ ID NO: 3193); Val^{8},Glu^{22},Lys^{33},Asn^{34},Gly^{36}-GLP-1(7-37) (SEQ ID NO: 3194); $Gly^{8,36}$,Glu^{22},Pro^{37}-GLP-1(7-37) (SEQ ID NO: 3195); Val^{8},Glu^{22},Gly^{36},Pro^{37}-GLP-1(7-37) (SEQ ID NO: 3196); $Gly^{8,36}$,Glu^{22},Lys^{33}, Asn^{34},Pro^{37}-GLP-1(7-37) (SEQ ID NO: 3197); Val^{8},Glu^{22},Lys^{33},Asn^{34},Gly^{36},Pro^{37}-GLP-1(7-37) (SEQ ID NO: 3198); $Gly^{8,36}$,Glu^{22}-GLP-1(7-36) (SEQ ID NO: 3199); Val^{8},Glu^{22},Gly^{36}-GLP-1(7-36) (SEQ ID NO: 3200); Val^{8},Glu^{22},Asn^{34},Gly^{36}-GLP-1(7-36) (SEQ ID NO: 3201); $Gly^{8,36}$,Glu^{22},Asn^{34}-GLP-1(7-36) (SEQ ID NO: 3202); GLP-1 analog (SEQ ID NO: 3206); GLP-1 analog (SEQ ID NO: 3207); [N^{e}-(17-carboxyheptadecanoic acid)Lys^{20}]exendin-4-NH_2 (SEQ ID NO: 3208); [N^{e}-(17-carboxyhepta-decanoyl)Lys^{32}]exendin-4-NH_2 (SEQ ID NO: 3209); [desamino-His^{1},N^{e}-(17-carboxyheptadecanoyl)Lys^{20}]exendin-4-NH_2 (SEQ ID NO: 3210); [$Arg^{12,27}$,NLe^{14},N^{e}-(17-carboxy-heptadecanoyl)Lys^{32}]exendin-4-NH_2 (SEQ ID NO: 3211); [N^{e}-(19-carboxy-

nonadecanoylamino)Lys^{20}]-exendin-4-NH$_2$ (SEQ ID NO: 3212); [N^e-(15-carboxypentadecanoylamino)Lys^{20}]-exendin-4-NH$_2$ (SEQ ID NO: 3213); [N^e-(13-carboxytridecanoylamino)Lys^{20}]exendin-4-NH$_2$ (SEQ ID NO: 3214); [N^e-(11-carboxy-undecanoyl-amino)Lys^{20}]exendin-4-NH$_2$ (SEQ ID NO: 3215); exendin-4-Lys^{40}(e-MPA)-NH$_2$ (SEQ ID NO: 3216); exendin-4-Lys^{40}(e-AEEA-AEEA-MPA)-NH$_2$ (SEQ ID NO: 3217); exendin-4-Lys^{40}(e-AEEA-MPA)-NH$_2$ (SEQ ID NO: 3218); exendin-4-Lys^{40}(e-MPA)-albumin (SEQ ID NO: 3219); exendin-4-Lys^{40}(e-AEEA-AEEA-MPA)-albumin (SEQ ID NO: 3220); exendin-4-Lys^{40}(e-AEEA-MPA)-albumin (SEQ ID NO: 3221); desamino-His^7,Arg^{26},Lys^{34}(N$^{\varepsilon}$-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) (core peptide disclosed as SEQ ID NO: 3222) (SEQ ID NO: 3222); desamino-His^7,Arg^{26},Lys^{34}(N$^{\varepsilon}$-octanoyl)-GLP-1(7-37) (SEQ ID NO: 3223); Arg^{26,34},Lys^{38}(N$^{\varepsilon}$-(ω-carboxypentadecanoyl))-GLP-1(7-38) (SEQ ID NO: 3224); Arg^{26,34},Lys^{36}(N$^{\varepsilon}$-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-36) (core peptide disclosed as SEQ ID NO: 3225) (SEQ ID NO: 3225); [Aib^8;Lys^{37}]GLP-1_(7-37) (SEQ ID NO: 3226); [Aib^8, Lys^{26}]GLP-1_(7-37) (SEQ ID NO: 3227); [Aib^{8,22};Lys^{36}]GLP-1(7-36)-Amide (SEQ ID NO: 3228); [Aib^{8,22};BLeu^{32};Lys^{36}]GLP-1(7-36)-Amide (SEQ ID NO: 3229); [Aib^{8,22};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3230); [Aib^{8,22};BLeu^{32};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3231); [Aib^{8,22};aMeLeu^{32};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3232); [Aib^{8,22};AMEF^{12};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3233); [Aib^{8,22};BLeu^{16};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3234); [Aib^{8,22};Gly^{36};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3235); [Aib^{8,22};Lys^{33,37};Asn^{34};Gly^{36}]GLP-1(7-37)-Amide (SEQ ID NO: 3236); [Aib^{8,22};Lys^{33};Asn^{34};Gly^{36};Aeea^{37}]GLP-1(7-37)-Aeea-Lys-Amide (SEQ ID NO: 3237); [Aib^{8,22};Gly^{36}]GLP-1(7-37) (SEQ ID NO: 3238); cyclo[E^{23}-K^{27}][Aib^8;Gly^{36}]GLP-1(7-37) (SEQ ID NO: 3239); cyclo[E^{22}-K^{26}][Aib^8;Gly^{36};Lys^{37}]GLP-1(7-37)-Amide (SEQ ID NO: 3240); [Aib^{8,22}]-GLP-1(7-22)-Ex4(17-39) (SEQ ID NO: 3241); [Gly^{8,36};Glu^{22}]GLP-1(7-37) (SEQ ID NO: 3242); [Aib^8;Glu^{22};Gly^{36}]GLP-1(7-37)-Amide (SEQ ID NO: 3243); [Aib^8;Tyr^{16};Glu^{22};Gly^{36}]GLP-1_(7-37) (SEQ ID NO: 3244); [Aib^8;Lys^{18,33};Glu^{22,23,30};Val^{25};Arg^{26};Leu^{27};Asn^{34};Gly^{36}]GLP-1(7-37) (SEQ ID NO: 3245); [Aib^8;Lys^{18,33};Glu^{22,23,30};Leu^{27};Asn^{34};Gly^{36}]GLP-1(7-37) (SEQ ID NO: 3246); [Aib^8;Lys^{18};Glu^{22,23,30};Leu^{27};Gly^{36}]GLP-1(7-37) (SEQ ID NO: 3247); [Aib^{8,22};Ile^9;Gly^{36}]GLP-1_(7-36) (SEQ ID NO: 3248); and [Aib^{8,22};Glu^{15};Gly^{36}]GLP-1_(7-36) (SEQ ID NO: 3249).

[0012] In one example, the GLP-1(7-37) or GLP-1(7-37) analog is conjugated to the antibody or fragment thereof at a residue that corresponds to K26, K36, K37, K39 or a C-terminal amine group of said analog.

[0013] In one example, 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 $(Gly_3Ser)_2$, $(Gly_4Ser)_2$, $(Gly_3Ser)_3$, $(Gly_4Ser)_3$, $(Gly_3Ser)_4$, $(Gly_4Ser)_4$, $(Gly_3Ser)_5$, $(Gly_4Ser)_5$, $(Gly_3Ser)_6$, and $(Gly_4Ser)_6$.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1. Reaction scheme for the generation of anti-GIPR/GLP-1 peptide conjugate

[0015] FIGS. 2A-2T. GLP-1 receptor agonist activity in CHOK1-GLP-1R H20 recombinant cells and GIPR antagonist activity in 293 HEK-GIPR #10 recombinant cells

[0016] FIGS. 3A-3C. GLP-1 agonist activity of 2G10 conjugate is more potent in cells expressing both GLP-1R and GIPR (CHOK1 hGLP-1R/hGIPR M1) compared to cells only expressing GLP-1R (CHOK1 hGLP-1R H20)

[0017] FIGS. 4A-4R. In vivo activity- glucose and body weight effects in db/db mice

[0018] FIGS. 5A-5D. GLP-1 receptor agonist and GIPR Antagonist In vivo Activity of 5G12 and 2G10 Chemical Conjugates in C57Bl6 mice (glucose tolerance test)

[0019] FIGS. 6A-6B. GLP-1 receptor agonist and GIPR Antagonist In vivo Activity of 5G12 and 2G10 Chemical Conjugates in DIO mice (plasma glucose and change in body weight)

[0020] FIG. 7. GLP-1R-GIPR bispecific conjugate 1273 reduces body weight in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0021] FIG. 8. GLP-1R-GIPR bispecific conjugate 1273 reduces total energy intake in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0022] FIG. 9. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting insulin in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0023] FIG. 10. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting triglycerides in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0024] FIG. 11. GLP-1R-GIPR bispecific conjugate 1273 reduces fasting total cholesterol in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0025] FIG. 12. GLP-1R-GIPR bispecific conjugate 1264 reduces body weight in male spontaneously obese cynomolgus monkeys (% change from baseline)

[0026] FIG. 13. GLP-1R-GIPR bispecific conjugate 1264 reduces total energy intake in male spontaneously obese cynomolgus monkeys (% change from baseline)

CLAIMS

What is claimed is:

1. A polypeptide comprising a GLP-1 receptor agonist comprising the amino acid sequence of SEQ ID NO: 3244.

2. The polypeptide according to claim 1 further comprising a linker comprising the sequence of SEQ ID NO: 3253, wherein the N-terminus of the linker is fused to the C-terminus of the amino acid sequence of SEQ ID NO: 3244.

3. The polypeptide according to claim 1 further comprising a linker comprising the sequence GGGGSGGGGSGGGGSK, wherein the N-terminus of the linker is fused to the C-terminus of the amino acid sequence of SEQ ID NO: 3244.

4. A composition comprising: the polypeptide of claim 3, and an anti-GIPR antibody, wherein the polypeptide of claim 3 is conjugated to a cysteine residue on the anti-GIPR antibody.

5. The composition according to claim 4, wherein the cysteine residue on the anti-GIPR antibody is located at a position selected from the group consisting of: D88 of both light chains, E384 of both heavy chains, and T487 of both heavy chains, wherein the numbering is according to AHo.

6. The composition according to claim 5, wherein the cysteine residue is located at E384 of both heavy chains, wherein the numbering is according to AHo.

7. The composition according to claim 6, wherein the anti-GIPR antibody comprises two light chains comprising the amino acid sequence of SEQ ID NO: 388 and two heavy chains comprising the amino acid sequence of SEQ ID NO: 545, wherein the heavy chains each comprise a cysteine substituted at position E384 according to AHo.

8. A composition comprising:

a polypeptide comprising:

a GLP-1R agonist wherein the GLP-1R agonist comprises the amino acid sequence of SEQ ID NO: 3244, and

a linker comprising the sequence GGGGSGGGGSGGGGSK,

wherein the N-terminus of the linker is fused to C-terminus of the amino acid sequence of SEQ ID NO: 3244; and

an anti-GIPR antibody comprising two light chains comprising the amino acid sequence of SEQ ID NO: 338 and two heavy chains comprising the amino acid sequence of SEQ ID NO: 545, wherein the heavy chains each comprise a cysteine substitution at position E384 according to AHo;

wherein the C-terminus lysine of the polypeptide is conjugated to the cysteine at position E384 of the anti-GIPR antibody.