

[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 composition comprising a) an antibody or functional fragment thereof that specifically binds to 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); and b) 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).

[0008b] In another aspect, the present disclosure refers to the use of a composition comprising an antibody or functional fragment thereof that specifically binds to 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); 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); in the manufacture of a medicament for treating a metabolic disorder.

[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)-NH₂ (SEQ ID NO: 3185); liraglutide; albiglutide; taspoglutide; dulaglutide, semaglutide; LY2428757; Exendin-4 (SEQ ID NO: 3163); Exendin-3 (SEQ ID NO: 3164); Leu¹⁴-exendin-4 (SEQ ID NO: 3165); Leu¹⁴,Phe²⁵-exendin-4 (SEQ ID NO: 3166); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4 (SEQ ID NO: 3167); exendin-4(1-30) (SEQ ID NO: 3168); Leu¹⁴-exendin-4(1-30) (SEQ ID NO: 3169); Leu¹⁴,Phe²⁵-exendin-4(1-30) (SEQ ID NO: 3170); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4(1-30) (SEQ ID NO: 3171); exendin-4(1-28) (SEQ ID NO: 3172); Leu¹⁴-exendin-4(1-28) (SEQ ID NO: 3173); Leu¹⁴,Phe²⁵-exendin-4(1-28) (SEQ ID NO: 3174); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4 (1-28) (SEQ ID NO: 3175); Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Phe²⁵,Gln²⁸-exendin-4 (SEQ ID NO: 3176); Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Gln²⁸-exendin-4 (SEQ ID NO: 3177); octylGly¹⁴,Gln²⁸-exendin-4 (SEQ ID NO: 3178); Leu¹⁴,Gln²⁸,octylGly³⁴-exendin-4 (SEQ ID NO: 3179); Phe⁴,Leu¹⁴,Gln²⁸,Lys³³,Glu³⁴, Ile^{35,36},Ser³⁷-exendin-4(1-37) (SEQ ID NO: 3180); Phe⁴,Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Gln²⁸-exendin-4 (SEQ ID NO: 3181); Val¹¹,Ile¹³,Leu¹⁴,Ala¹⁶,Lys²¹,Phe²⁵-exendin-4 (SEQ ID NO: 3182); exendin-4-Lys⁴⁰ (SEQ ID NO: 3183); GLP-1(7-37) (SEQ ID NO: 3184); GLP-1(7-36)-NH₂ (SEQ ID NO: 3185); Aib^{8,35},Arg^{26,34},Phe³¹-GLP-1(7-36)) (SEQ ID NO: 3186); HXaa₈EGTFTSDVSSYLEXaa₂₂Xaa₂₃AAKEFIXaa₃₀WLXaa₃₃Xaa₃₄G Xaa₃₆Xaa₃₇; wherein Xaa₈ is A, V, or G; Xaa₂₂ is G, K, or E; Xaa₂₃ is Q or K; Xaa₃₀ is A or E; Xaa₃₃ is V or K;

Xaa₃₄ is K, N, or R; Xaa₃₆ is R or G; and Xaa₃₇ is G, H, P, or absent (SEQ ID NO: 3187); Arg³⁴-GLP-1(7-37) (SEQ ID NO: 3188); Glu³⁰-GLP-1(7-37) (SEQ ID NO: 3189); Lys²²-GLP-1(7-37) (SEQ ID NO: 3190); Gly^{8,36},Glu²²-GLP-1(7-37) (SEQ ID NO: 3191); Val⁸,Glu²²,Gly³⁶-GLP-1(7-37) (SEQ ID NO: 3192); Gly^{8,36},Glu²²,Lys³³,Asn³⁴-GLP-1(7-37) (SEQ ID NO: 3193); Val⁸,Glu²²,Lys³³,Asn³⁴,Gly³⁶-GLP-1(7-37) (SEQ ID NO: 3194); Gly^{8,36},Glu²²,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3195); Val⁸,Glu²²,Gly³⁶,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3196); Gly^{8,36},Glu²²,Lys³³,Asn³⁴,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3197); Val⁸,Glu²²,Lys³³,Asn³⁴,Gly³⁶,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3198); Gly^{8,36},Glu²²-GLP-1(7-36) (SEQ ID NO: 3199); Val⁸,Glu²²,Gly³⁶-GLP-1(7-36) (SEQ ID NO: 3200); Val⁸,Glu²²,Asn³⁴,Gly³⁶-GLP-1(7-36) (SEQ ID NO: 3201); Gly^{8,36},Glu²²,Asn³⁴-GLP-1(7-36) (SEQ ID NO: 3202); GLP-1 analog (SEQ ID NO: 3206); GLP-1 analog (SEQ ID NO: 3207); [N^ε-(17-carboxyheptadecanoic acid)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3208); [N^ε-(17-carboxyhepta-decanoyl)Lys³²]exendin-4-NH₂ (SEQ ID NO: 3209); [desamino-His¹,N^ε-(17-carboxyheptadecanoyl)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3210); [Arg^{12,27},NLe¹⁴,N^ε-(17-carboxy-heptadecanoyl)Lys³²]exendin-4-NH₂ (SEQ ID NO: 3211); [N^ε-(19-carboxy-nonadecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3212); [N^ε-(15-carboxypentadecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3213); [N^ε-(13-carboxytridecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3214); [N^ε-(11-carboxyundecanoyl-amino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3215); exendin-4-Lys⁴⁰(e-MPA)-NH₂ (SEQ ID NO: 3216); exendin-4-Lys⁴⁰(e-AEEA-AEEA-MPA)-NH₂ (SEQ ID NO: 3217); exendin-4-Lys⁴⁰(e-AEEA-MPA)-NH₂ (SEQ ID NO: 3218); exendin-4-Lys⁴⁰(e-MPA)-albumin (SEQ ID NO: 3219); exendin-4-Lys⁴⁰(e-AEEA-AEEA-MPA)-albumin (SEQ ID NO: 3220); exendin-4-Lys⁴⁰(e-AEEA-MPA)-albumin (SEQ ID NO: 3221); desamino-His⁷,Arg²⁶,Lys³⁴(N^ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) (core peptide disclosed as SEQ ID NO: 3222) (SEQ ID NO: 3222); desamino-His⁷,Arg²⁶,Lys³⁴(N^ε-octanoyl)-GLP-1(7-37) (SEQ ID NO: 3223); Arg^{26,34},Lys³⁸(N^ε-(ω-carboxypentadecanoyl)))-GLP-1(7-38) (SEQ ID NO: 3224); Arg^{26,34},Lys³⁶(N^ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-36) (core peptide disclosed as SEQ ID NO: 3225) (SEQ ID NO: 3225); [Aib⁸;Lys³⁷]GLP-1_(7-37) (SEQ ID NO: 3226); [Aib⁸,Lys²⁶]GLP-1_(7-37) (SEQ ID NO: 3227); [Aib^{8,22};Lys³⁶]GLP-1(7-36)-Amide (SEQ ID NO: 3228); [Aib^{8,22};BLeu³²;Lys³⁶]GLP-1(7-36)-Amide (SEQ ID NO: 3229); [Aib^{8,22};Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3230); [Aib^{8,22};BLeu³²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3231); [Aib^{8,22};aMeLeu³²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3232); [Aib^{8,22};AMEF¹²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3233); [Aib^{8,22};BLeu¹⁶;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3234); [Aib^{8,22};Gly³⁶;Lys³⁷]GLP-

1(7-37)-Amide (SEQ ID NO: 3235); [Aib^{8,22};Lys^{33,37};Asn³⁴;Gly³⁶]GLP-1(7-37)-Amide (SEQ ID NO: 3236); [Aib^{8,22};Lys³³;Asn³⁴;Gly³⁶;Aeea³⁷]GLP-1(7-37)-Aeea-Lys-Amide (SEQ ID NO: 3237); [Aib^{8,22};Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3238); cyclo[E²³-K²⁷][Aib⁸;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3239); cyclo[E²²-K²⁶][Aib⁸;Gly³⁶;Lys³⁷]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};Glu²²]GLP-1(7-37) (SEQ ID NO: 3242); [Aib⁸;Glu²²;Gly³⁶]GLP-1(7-37)-Amide (SEQ ID NO: 3243); [Aib⁸;Tyr¹⁶;Glu²²;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3244); [Aib⁸;Lys^{18,33};Glu^{22,23,30};Val²⁵;Arg²⁶;Leu²⁷;Asn³⁴;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3245); [Aib⁸;Lys^{18,33};Glu^{22,23,30};Leu²⁷;Asn³⁴;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3246); [Aib⁸;Lys¹⁸;Glu^{22,23,30};Leu²⁷;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3247); [Aib^{8,22};Ile⁹;Gly³⁶]GLP-1(7-36) (SEQ ID NO: 3248); and [Aib^{8,22};Glu¹⁵;Gly³⁶]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 (Gly₃Ser)₂, (Gly₄Ser)₂, (Gly₃Ser)₃, (Gly₄Ser)₃, (Gly₃Ser)₄, (Gly₄Ser)₄, (Gly₃Ser)₅, (Gly₄Ser)₅, (Gly₃Ser)₆, and (Gly₄Ser)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)

5 [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)

10 [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 composition comprising
 - a) an antibody or functional fragment thereof that specifically binds to human GIPR,
5 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);
and
 - b) a GLP-1 receptor agonist, wherein the GLP-1 receptor agonist is conjugated to the
10 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:
15 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 fragment is a Fab
20 fragment, a Fab' fragment, or a F(ab')₂ fragment.
5. The composition of claim 3, wherein said antibody or functional fragment thereof is a human antibody.
6. The composition of claim 3, wherein said antibody or functional fragment thereof is a monoclonal antibody.
- 25 7. The composition of claim 3, wherein said antibody or functional fragment thereof is of the IgG1-, IgG2- IgG3- or IgG4-type.
8. The composition of claim 7, wherein said antibody or functional fragment thereof is of the IgG1- or the IgG2-type.

9. 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.

10. The composition of claim 3, wherein said antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein said CDRL1 comprises a sequence selected from the group consisting of SEQ ID NOs: 629-785; said CDRL2 comprises a sequence selected from the group consisting of SEQ ID NOs: 786-942; said CDRL3 comprises a sequence selected from the group consisting of SEQ ID NOs: 943-1099; said CDRH1 comprises a sequence selected from the group consisting of SEQ ID NOs: 1100-1256; said CDRH2 comprises a sequence selected from the group consisting of SEQ ID NOs: 1257-1413; and said CDRH3 comprises a sequence selected from the group consisting of SEQ ID NOs: 1414-1570, 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.

11. The composition of claim 3, wherein said antibody 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: 629, SEQ ID NO: 786, SEQ ID NO: 943, SEQ ID NO: 1100, SEQ ID NO: 1257, and SEQ ID NO: 1414; SEQ ID NO: 630, SEQ ID NO: 787, SEQ ID NO: 944, SEQ ID NO: 1101, SEQ ID NO: 1258, and SEQ ID NO: 1415; SEQ ID NO: 631, SEQ ID NO: 788, SEQ ID NO: 945, SEQ ID NO: 1102, SEQ ID NO: 1259, and SEQ ID NO: 1416; SEQ ID NO: 632, SEQ ID NO: 789, SEQ ID NO: 946, SEQ ID NO: 1103, SEQ ID NO: 1260, and SEQ ID NO: 1417; SEQ ID NO: 633, SEQ ID NO: 790, SEQ ID NO: 947, SEQ ID NO: 1104, SEQ ID NO: 1261, and SEQ ID NO: 1418; SEQ ID NO: 634, SEQ ID NO: 791, SEQ ID NO: 948, SEQ ID NO: 1105, SEQ ID NO: 1262, and SEQ ID NO: 1419; SEQ ID NO: 635, SEQ ID NO: 792, SEQ ID NO: 949, SEQ ID NO: 1106, SEQ ID NO: 1263, and SEQ ID NO: 1420; SEQ ID NO: 636, SEQ ID NO: 793, SEQ ID NO: 950, SEQ ID

NO: 1107, SEQ ID NO: 1264, and SEQ ID NO: 1421; SEQ ID NO: 637, SEQ ID NO: 794,
SEQ ID NO: 951, SEQ ID NO: 1108, SEQ ID NO: 1265, and SEQ ID NO: 1422; SEQ ID
NO: 638, SEQ ID NO: 795, SEQ ID NO: 952, SEQ ID NO: 1109, SEQ ID NO: 1266, and
SEQ ID NO: 1423; SEQ ID NO: 639, SEQ ID NO: 796, SEQ ID NO: 953, SEQ ID NO:
5 1110, SEQ ID NO: 1267, and SEQ ID NO: 1424; SEQ ID NO: 640, SEQ ID NO: 797, SEQ
ID NO: 954, SEQ ID NO: 1111, SEQ ID NO: 1268, and SEQ ID NO: 1425; SEQ ID NO:
641, SEQ ID NO: 798, SEQ ID NO: 955, SEQ ID NO: 1112, SEQ ID NO: 1269, and SEQ ID
NO: 1426; SEQ ID NO: 642, SEQ ID NO: 799, SEQ ID NO: 956, SEQ ID NO: 1113, SEQ
ID NO: 1270, and SEQ ID NO: 1427; SEQ ID NO: 643, SEQ ID NO: 800, SEQ ID NO: 957,
10 SEQ ID NO: 1114, SEQ ID NO: 1271, and SEQ ID NO: 1428; SEQ ID NO: 644, SEQ ID
NO: 801, SEQ ID NO: 958, SEQ ID NO: 1115, SEQ ID NO: 1272, and SEQ ID NO: 1429;
SEQ ID NO: 645, SEQ ID NO: 802, SEQ ID NO: 959, SEQ ID NO: 1116, SEQ ID NO:
1273, and SEQ ID NO: 1430; SEQ ID NO: 646, SEQ ID NO: 803, SEQ ID NO: 960, SEQ ID
NO: 1117, SEQ ID NO: 1274, and SEQ ID NO: 1431; SEQ ID NO: 647, SEQ ID NO: 804,
15 SEQ ID NO: 961, SEQ ID NO: 1118, SEQ ID NO: 1275, and SEQ ID NO: 1432; SEQ ID
NO: 648, SEQ ID NO: 805, SEQ ID NO: 962, SEQ ID NO: 1119, SEQ ID NO: 1276, and
SEQ ID NO: 1433; SEQ ID NO: 649, SEQ ID NO: 806, SEQ ID NO: 963, SEQ ID NO:
1120, SEQ ID NO: 1277, and SEQ ID NO: 1434; SEQ ID NO: 650, SEQ ID NO: 807, SEQ
ID NO: 964, SEQ ID NO: 1121, SEQ ID NO: 1278, and SEQ ID NO: 1435; SEQ ID NO:
20 651, SEQ ID NO: 808, SEQ ID NO: 965, SEQ ID NO: 1122, SEQ ID NO: 1279, and SEQ ID
NO: 1436; SEQ ID NO: 652, SEQ ID NO: 809, SEQ ID NO: 966, SEQ ID NO: 1123, SEQ
ID NO: 1280, and SEQ ID NO: 1437; SEQ ID NO: 653, SEQ ID NO: 810, SEQ ID NO: 967,
SEQ ID NO: 1124, SEQ ID NO: 1281, and SEQ ID NO: 1438; SEQ ID NO: 654, SEQ ID
NO: 811, SEQ ID NO: 968, SEQ ID NO: 1125, SEQ ID NO: 1282, and SEQ ID NO: 1439;
25 SEQ ID NO: 655, SEQ ID NO: 812, SEQ ID NO: 969, SEQ ID NO: 1126, SEQ ID NO:
1283, and SEQ ID NO: 1440; SEQ ID NO: 656, SEQ ID NO: 813, SEQ ID NO: 970, SEQ ID
NO: 1127, SEQ ID NO: 1284, and SEQ ID NO: 1441; SEQ ID NO: 657, SEQ ID NO: 814,
SEQ ID NO: 971, SEQ ID NO: 1128, SEQ ID NO: 1285, and SEQ ID NO: 1442; SEQ ID
NO: 658, SEQ ID NO: 815, SEQ ID NO: 972, SEQ ID NO: 1129, SEQ ID NO: 1286, and
30 SEQ ID NO: 1443; SEQ ID NO: 659, SEQ ID NO: 816, SEQ ID NO: 973, SEQ ID NO:
1130, SEQ ID NO: 1287, and SEQ ID NO: 1444; SEQ ID NO: 660, SEQ ID NO: 817, SEQ
ID NO: 974, SEQ ID NO: 1131, SEQ ID NO: 1288, and SEQ ID NO: 1445; SEQ ID NO:
661, SEQ ID NO: 818, SEQ ID NO: 975, SEQ ID NO: 1132, SEQ ID NO: 1289, and SEQ ID
NO: 1446; SEQ ID NO: 662, SEQ ID NO: 819, SEQ ID NO: 976, SEQ ID NO: 1133, SEQ

ID NO: 1290, and SEQ ID NO: 1447; SEQ ID NO: 663, SEQ ID NO: 820, SEQ ID NO: 977, SEQ ID NO: 1134, SEQ ID NO: 1291, and SEQ ID NO: 1448; SEQ ID NO: 664, SEQ ID NO: 821, SEQ ID NO: 978, SEQ ID NO: 1135, SEQ ID NO: 1292, and SEQ ID NO: 1449; SEQ ID NO: 665, SEQ ID NO: 822, SEQ ID NO: 979, SEQ ID NO: 1136, SEQ ID NO: 1293, and SEQ ID NO: 1450; SEQ ID NO: 666, SEQ ID NO: 823, SEQ ID NO: 980, SEQ ID NO: 1137, SEQ ID NO: 1294, and SEQ ID NO: 1451; SEQ ID NO: 667, SEQ ID NO: 824, SEQ ID NO: 981, SEQ ID NO: 1138, SEQ ID NO: 1295, and SEQ ID NO: 1452; SEQ ID NO: 668, SEQ ID NO: 825, SEQ ID NO: 982, SEQ ID NO: 1139, SEQ ID NO: 1296, and SEQ ID NO: 1453; SEQ ID NO: 669, SEQ ID NO: 826, SEQ ID NO: 983, SEQ ID NO: 1140, SEQ ID NO: 1297, and SEQ ID NO: 1454; SEQ ID NO: 670, SEQ ID NO: 827, SEQ ID NO: 984, SEQ ID NO: 1141, SEQ ID NO: 1298, and SEQ ID NO: 1455; SEQ ID NO: 671, SEQ ID NO: 828, SEQ ID NO: 985, SEQ ID NO: 1142, SEQ ID NO: 1299, and SEQ ID NO: 1456; SEQ ID NO: 672, SEQ ID NO: 829, SEQ ID NO: 986, SEQ ID NO: 1143, SEQ ID NO: 1300, and SEQ ID NO: 1457; SEQ ID NO: 673, SEQ ID NO: 830, SEQ ID NO: 987, SEQ ID NO: 1144, SEQ ID NO: 1301, and SEQ ID NO: 1458; SEQ ID NO: 674, SEQ ID NO: 831, SEQ ID NO: 988, SEQ ID NO: 1145, SEQ ID NO: 1302, and SEQ ID NO: 1459; SEQ ID NO: 675, SEQ ID NO: 832, SEQ ID NO: 989, SEQ ID NO: 1146, SEQ ID NO: 1303, and SEQ ID NO: 1460; SEQ ID NO: 676, SEQ ID NO: 833, SEQ ID NO: 990, SEQ ID NO: 1147, SEQ ID NO: 1304, and SEQ ID NO: 1461; SEQ ID NO: 677, SEQ ID NO: 834, SEQ ID NO: 991, SEQ ID NO: 1148, SEQ ID NO: 1305, and SEQ ID NO: 1462; SEQ ID NO: 678, SEQ ID NO: 835, SEQ ID NO: 992, SEQ ID NO: 1149, SEQ ID NO: 1306, and SEQ ID NO: 1463; SEQ ID NO: 679, SEQ ID NO: 836, SEQ ID NO: 993, SEQ ID NO: 1150, SEQ ID NO: 1307, and SEQ ID NO: 1464; SEQ ID NO: 680, SEQ ID NO: 837, SEQ ID NO: 994, SEQ ID NO: 1151, SEQ ID NO: 1308, and SEQ ID NO: 1465; SEQ ID NO: 681, SEQ ID NO: 838, SEQ ID NO: 995, SEQ ID NO: 1152, SEQ ID NO: 1309, and SEQ ID NO: 1466; SEQ ID NO: 682, SEQ ID NO: 839, SEQ ID NO: 996, SEQ ID NO: 1153, SEQ ID NO: 1310, and SEQ ID NO: 1467; SEQ ID NO: 683, SEQ ID NO: 840, SEQ ID NO: 997, SEQ ID NO: 1154, SEQ ID NO: 1311, and SEQ ID NO: 1468; SEQ ID NO: 684, SEQ ID NO: 841, SEQ ID NO: 998, SEQ ID NO: 1155, SEQ ID NO: 1312, and SEQ ID NO: 1469; SEQ ID NO: 685, SEQ ID NO: 842, SEQ ID NO: 999, SEQ ID NO: 1156, SEQ ID NO: 1313, and SEQ ID NO: 1470; SEQ ID NO: 686, SEQ ID NO: 843, SEQ ID NO: 1000, SEQ ID NO: 1157, SEQ ID NO: 1314, and SEQ ID NO: 1471; SEQ ID NO: 687, SEQ ID NO: 844, SEQ ID NO: 1001, SEQ ID NO: 1158, SEQ ID NO: 1315, and SEQ ID NO: 1472; SEQ ID NO: 688, SEQ ID NO: 845, SEQ ID NO: 1002, SEQ ID NO: 1159, SEQ ID NO: 1316,

and SEQ ID NO: 1473; SEQ ID NO: 689, SEQ ID NO: 846, SEQ ID NO: 1003, SEQ ID NO: 1160, SEQ ID NO: 1317, and SEQ ID NO: 1474; SEQ ID NO: 690, SEQ ID NO: 847, SEQ ID NO: 1004, SEQ ID NO: 1161, SEQ ID NO: 1318, and SEQ ID NO: 1475; SEQ ID NO: 691, SEQ ID NO: 848, SEQ ID NO: 1005, SEQ ID NO: 1162, SEQ ID NO: 1319, and SEQ ID NO: 1476; SEQ ID NO: 692, SEQ ID NO: 849, SEQ ID NO: 1006, SEQ ID NO: 1163, SEQ ID NO: 1320, and SEQ ID NO: 1477; SEQ ID NO: 693, SEQ ID NO: 850, SEQ ID NO: 1007, SEQ ID NO: 1164, SEQ ID NO: 1321, and SEQ ID NO: 1478; SEQ ID NO: 694, SEQ ID NO: 851, SEQ ID NO: 1008, SEQ ID NO: 1165, SEQ ID NO: 1322, and SEQ ID NO: 1479; SEQ ID NO: 695, SEQ ID NO: 852, SEQ ID NO: 1009, SEQ ID NO: 1166, SEQ ID NO: 1323, and SEQ ID NO: 1480; SEQ ID NO: 696, SEQ ID NO: 853, SEQ ID NO: 1010, SEQ ID NO: 1167, SEQ ID NO: 1324, and SEQ ID NO: 1481; SEQ ID NO: 697, SEQ ID NO: 854, SEQ ID NO: 1011, SEQ ID NO: 1168, SEQ ID NO: 1325, and SEQ ID NO: 1482; SEQ ID NO: 698, SEQ ID NO: 855, SEQ ID NO: 1012, SEQ ID NO: 1169, SEQ ID NO: 1326, and SEQ ID NO: 1483; SEQ ID NO: 699, SEQ ID NO: 856, SEQ ID NO: 1013, SEQ ID NO: 1170, SEQ ID NO: 1327, and SEQ ID NO: 1484; SEQ ID NO: 700, SEQ ID NO: 857, SEQ ID NO: 1014, SEQ ID NO: 1171, SEQ ID NO: 1328, and SEQ ID NO: 1485; SEQ ID NO: 701, SEQ ID NO: 858, SEQ ID NO: 1015, SEQ ID NO: 1172, SEQ ID NO: 1329, and SEQ ID NO: 1486; 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; SEQ ID NO: 703, SEQ ID NO: 860, SEQ ID NO: 1017, SEQ ID NO: 1174, SEQ ID NO: 1331, and SEQ ID NO: 1488; SEQ ID NO: 704, SEQ ID NO: 861, SEQ ID NO: 1018, SEQ ID NO: 1175, SEQ ID NO: 1332, and SEQ ID NO: 1489; SEQ ID NO: 705, SEQ ID NO: 862, SEQ ID NO: 1019, SEQ ID NO: 1176, SEQ ID NO: 1333, and SEQ ID NO: 1490; SEQ ID NO: 706, SEQ ID NO: 863, SEQ ID NO: 1020, SEQ ID NO: 1177, SEQ ID NO: 1334, and SEQ ID NO: 1491; SEQ ID NO: 707, SEQ ID NO: 864, SEQ ID NO: 1021, SEQ ID NO: 1178, SEQ ID NO: 1335, and SEQ ID NO: 1492; SEQ ID NO: 708, SEQ ID NO: 865, SEQ ID NO: 1022, SEQ ID NO: 1179, SEQ ID NO: 1336, and SEQ ID NO: 1493; SEQ ID NO: 709, SEQ ID NO: 866, SEQ ID NO: 1023, SEQ ID NO: 1180, SEQ ID NO: 1337, and SEQ ID NO: 1494; SEQ ID NO: 710, SEQ ID NO: 867, SEQ ID NO: 1024, SEQ ID NO: 1181, SEQ ID NO: 1338, and SEQ ID NO: 1495; SEQ ID NO: 711, SEQ ID NO: 868, SEQ ID NO: 1025, SEQ ID NO: 1182, SEQ ID NO: 1339, and SEQ ID NO: 1496; SEQ ID NO: 712, SEQ ID NO: 869, SEQ ID NO: 1026, SEQ ID NO: 1183, SEQ ID NO: 1340, and SEQ ID NO: 1497; SEQ ID NO: 713, SEQ ID NO: 870, SEQ ID NO: 1027, SEQ ID NO: 1184, SEQ ID NO: 1341, and SEQ ID NO: 1498; SEQ ID NO: 714, SEQ ID NO: 871, SEQ ID NO: 1028, SEQ ID NO: 1185, SEQ ID NO: 1342,

and SEQ ID NO: 1499; SEQ ID NO: 715, SEQ ID NO: 872, SEQ ID NO: 1029, SEQ ID NO: 1186, SEQ ID NO: 1343, and SEQ ID NO: 1500; SEQ ID NO: 716, SEQ ID NO: 873, SEQ ID NO: 1030, SEQ ID NO: 1187, SEQ ID NO: 1344, and SEQ ID NO: 1501; SEQ ID NO: 717, SEQ ID NO: 874, SEQ ID NO: 1031, SEQ ID NO: 1188, SEQ ID NO: 1345, and SEQ ID NO: 1502; SEQ ID NO: 718, SEQ ID NO: 875, SEQ ID NO: 1032, SEQ ID NO: 1189, SEQ ID NO: 1346, and SEQ ID NO: 1503; SEQ ID NO: 719, SEQ ID NO: 876, SEQ ID NO: 1033, SEQ ID NO: 1190, SEQ ID NO: 1347, and SEQ ID NO: 1504; SEQ ID NO: 720, SEQ ID NO: 877, SEQ ID NO: 1034, SEQ ID NO: 1191, SEQ ID NO: 1348, and SEQ ID NO: 1505; SEQ ID NO: 721, SEQ ID NO: 878, SEQ ID NO: 1035, SEQ ID NO: 1192, SEQ ID NO: 1349, and SEQ ID NO: 1506; SEQ ID NO: 722, SEQ ID NO: 879, SEQ ID NO: 1036, SEQ ID NO: 1193, SEQ ID NO: 1350, and SEQ ID NO: 1507; SEQ ID NO: 723, SEQ ID NO: 880, SEQ ID NO: 1037, SEQ ID NO: 1194, SEQ ID NO: 1351, and SEQ ID NO: 1508; SEQ ID NO: 724, SEQ ID NO: 881, SEQ ID NO: 1038, SEQ ID NO: 1195, SEQ ID NO: 1352, and SEQ ID NO: 1509; SEQ ID NO: 725, SEQ ID NO: 882, SEQ ID NO: 1039, SEQ ID NO: 1196, SEQ ID NO: 1353, and SEQ ID NO: 1510; SEQ ID NO: 726, SEQ ID NO: 883, SEQ ID NO: 1040, SEQ ID NO: 1197, SEQ ID NO: 1354, and SEQ ID NO: 1511; SEQ ID NO: 727, SEQ ID NO: 884, SEQ ID NO: 1041, SEQ ID NO: 1198, SEQ ID NO: 1355, and SEQ ID NO: 1512; SEQ ID NO: 728, SEQ ID NO: 885, SEQ ID NO: 1042, SEQ ID NO: 1199, SEQ ID NO: 1356, and SEQ ID NO: 1513; SEQ ID NO: 729, SEQ ID NO: 886, SEQ ID NO: 1043, SEQ ID NO: 1200, SEQ ID NO: 1357, and SEQ ID NO: 1514; SEQ ID NO: 730, SEQ ID NO: 887, SEQ ID NO: 1044, SEQ ID NO: 1201, SEQ ID NO: 1358, and SEQ ID NO: 1515; SEQ ID NO: 731, SEQ ID NO: 888, SEQ ID NO: 1045, SEQ ID NO: 1202, SEQ ID NO: 1359, and SEQ ID NO: 1516; SEQ ID NO: 732, SEQ ID NO: 889, SEQ ID NO: 1046, SEQ ID NO: 1203, SEQ ID NO: 1360, and SEQ ID NO: 1517; SEQ ID NO: 733, SEQ ID NO: 890, SEQ ID NO: 1047, SEQ ID NO: 1204, SEQ ID NO: 1361, and SEQ ID NO: 1518; SEQ ID NO: 734, SEQ ID NO: 891, SEQ ID NO: 1048, SEQ ID NO: 1205, SEQ ID NO: 1362, and SEQ ID NO: 1519; SEQ ID NO: 735, SEQ ID NO: 892, SEQ ID NO: 1049, SEQ ID NO: 1206, SEQ ID NO: 1363, and SEQ ID NO: 1520; SEQ ID NO: 736, SEQ ID NO: 893, SEQ ID NO: 1050, SEQ ID NO: 1207, SEQ ID NO: 1364, and SEQ ID NO: 1521; SEQ ID NO: 737, SEQ ID NO: 894, SEQ ID NO: 1051, SEQ ID NO: 1208, SEQ ID NO: 1365, and SEQ ID NO: 1522; SEQ ID NO: 738, SEQ ID NO: 895, SEQ ID NO: 1052, SEQ ID NO: 1209, SEQ ID NO: 1366, and SEQ ID NO: 1523; SEQ ID NO: 739, SEQ ID NO: 896, SEQ ID NO: 1053, SEQ ID NO: 1210, SEQ ID NO: 1367, and SEQ ID NO: 1524; SEQ ID NO: 740, SEQ ID NO: 897, SEQ ID NO: 1054, SEQ ID NO: 1211, SEQ ID NO: 1368,

and SEQ ID NO: 1525; SEQ ID NO: 741, SEQ ID NO: 898, SEQ ID NO: 1055, SEQ ID NO: 1212, SEQ ID NO: 1369, and SEQ ID NO: 1526; SEQ ID NO: 742, SEQ ID NO: 899, SEQ ID NO: 1056, SEQ ID NO: 1213, SEQ ID NO: 1370, and SEQ ID NO: 1527; SEQ ID NO: 743, SEQ ID NO: 900, SEQ ID NO: 1057, SEQ ID NO: 1214, SEQ ID NO: 1371, and SEQ ID NO: 1528; SEQ ID NO: 744, SEQ ID NO: 901, SEQ ID NO: 1058, SEQ ID NO: 1215, SEQ ID NO: 1372, and SEQ ID NO: 1529; SEQ ID NO: 745, SEQ ID NO: 902, SEQ ID NO: 1059, SEQ ID NO: 1216, SEQ ID NO: 1373, and SEQ ID NO: 1530; SEQ ID NO: 746, SEQ ID NO: 903, SEQ ID NO: 1060, SEQ ID NO: 1217, SEQ ID NO: 1374, and SEQ ID NO: 1531; SEQ ID NO: 747, SEQ ID NO: 904, SEQ ID NO: 1061, SEQ ID NO: 1218, SEQ ID NO: 1375, and SEQ ID NO: 1532; SEQ ID NO: 748, SEQ ID NO: 905, SEQ ID NO: 1062, SEQ ID NO: 1219, SEQ ID NO: 1376, and SEQ ID NO: 1533; SEQ ID NO: 749, SEQ ID NO: 906, SEQ ID NO: 1063, SEQ ID NO: 1220, SEQ ID NO: 1377, and SEQ ID NO: 1534; SEQ ID NO: 750, SEQ ID NO: 907, SEQ ID NO: 1064, SEQ ID NO: 1221, SEQ ID NO: 1378, and SEQ ID NO: 1535; SEQ ID NO: 751, SEQ ID NO: 908, SEQ ID NO: 1065, SEQ ID NO: 1222, SEQ ID NO: 1379, and SEQ ID NO: 1536; SEQ ID NO: 752, SEQ ID NO: 909, SEQ ID NO: 1066, SEQ ID NO: 1223, SEQ ID NO: 1380, and SEQ ID NO: 1537; SEQ ID NO: 753, SEQ ID NO: 910, SEQ ID NO: 1067, SEQ ID NO: 1224, SEQ ID NO: 1381, and SEQ ID NO: 1538; SEQ ID NO: 754, SEQ ID NO: 911, SEQ ID NO: 1068, SEQ ID NO: 1225, SEQ ID NO: 1382, and SEQ ID NO: 1539; SEQ ID NO: 755, SEQ ID NO: 912, SEQ ID NO: 1069, SEQ ID NO: 1226, SEQ ID NO: 1383, and SEQ ID NO: 1540; SEQ ID NO: 756, SEQ ID NO: 913, SEQ ID NO: 1070, SEQ ID NO: 1227, SEQ ID NO: 1384, and SEQ ID NO: 1541; SEQ ID NO: 757, SEQ ID NO: 914, SEQ ID NO: 1071, SEQ ID NO: 1228, SEQ ID NO: 1385, and SEQ ID NO: 1542; SEQ ID NO: 758, SEQ ID NO: 915, SEQ ID NO: 1072, SEQ ID NO: 1229, SEQ ID NO: 1386, and SEQ ID NO: 1543; SEQ ID NO: 759, SEQ ID NO: 916, SEQ ID NO: 1073, SEQ ID NO: 1230, SEQ ID NO: 1387, and SEQ ID NO: 1544; SEQ ID NO: 760, SEQ ID NO: 917, SEQ ID NO: 1074, SEQ ID NO: 1231, SEQ ID NO: 1388, and SEQ ID NO: 1545; SEQ ID NO: 761, SEQ ID NO: 918, SEQ ID NO: 1075, SEQ ID NO: 1232, SEQ ID NO: 1389, and SEQ ID NO: 1546; SEQ ID NO: 762, SEQ ID NO: 919, SEQ ID NO: 1076, SEQ ID NO: 1233, SEQ ID NO: 1390, and SEQ ID NO: 1547; SEQ ID NO: 763, SEQ ID NO: 920, SEQ ID NO: 1077, SEQ ID NO: 1234, SEQ ID NO: 1391, and SEQ ID NO: 1548; SEQ ID NO: 764, SEQ ID NO: 921, SEQ ID NO: 1078, SEQ ID NO: 1235, SEQ ID NO: 1392, and SEQ ID NO: 1549; SEQ ID NO: 765, SEQ ID NO: 922, SEQ ID NO: 1079, SEQ ID NO: 1236, SEQ ID NO: 1393, and SEQ ID NO: 1550; SEQ ID NO: 766, SEQ ID NO: 923, SEQ ID NO: 1080, SEQ ID NO: 1237, SEQ ID NO: 1394,

and SEQ ID NO: 1551; SEQ ID NO: 767, SEQ ID NO: 924, SEQ ID NO: 1081, SEQ ID NO: 1238, SEQ ID NO: 1395, and SEQ ID NO: 1552; SEQ ID NO: 768, SEQ ID NO: 925, SEQ ID NO: 1082, SEQ ID NO: 1239, SEQ ID NO: 1396, and SEQ ID NO: 1553; SEQ ID NO: 769, SEQ ID NO: 926, SEQ ID NO: 1083, SEQ ID NO: 1240, SEQ ID NO: 1397, and SEQ ID NO: 1554; SEQ ID NO: 770, SEQ ID NO: 927, SEQ ID NO: 1084, SEQ ID NO: 1241, SEQ ID NO: 1398, and SEQ ID NO: 1555; SEQ ID NO: 771, SEQ ID NO: 928, SEQ ID NO: 1085, SEQ ID NO: 1242, SEQ ID NO: 1399, and SEQ ID NO: 1556; SEQ ID NO: 772, SEQ ID NO: 929, SEQ ID NO: 1086, SEQ ID NO: 1243, SEQ ID NO: 1400, and SEQ ID NO: 1557; SEQ ID NO: 773, SEQ ID NO: 930, SEQ ID NO: 1087, SEQ ID NO: 1244, SEQ ID NO: 1401, and SEQ ID NO: 1558; SEQ ID NO: 774, SEQ ID NO: 931, SEQ ID NO: 1088, SEQ ID NO: 1245, SEQ ID NO: 1402, and SEQ ID NO: 1559; SEQ ID NO: 775, SEQ ID NO: 932, SEQ ID NO: 1089, SEQ ID NO: 1246, SEQ ID NO: 1403, and SEQ ID NO: 1560; SEQ ID NO: 776, SEQ ID NO: 933, SEQ ID NO: 1090, SEQ ID NO: 1247, SEQ ID NO: 1404, and SEQ ID NO: 1561; SEQ ID NO: 777, SEQ ID NO: 934, SEQ ID NO: 1091, SEQ ID NO: 1248, SEQ ID NO: 1405, and SEQ ID NO: 1562; SEQ ID NO: 778, SEQ ID NO: 935, SEQ ID NO: 1092, SEQ ID NO: 1249, SEQ ID NO: 1406, and SEQ ID NO: 1563; SEQ ID NO: 779, SEQ ID NO: 936, SEQ ID NO: 1093, SEQ ID NO: 1250, SEQ ID NO: 1407, and SEQ ID NO: 1564; SEQ ID NO: 780, SEQ ID NO: 937, SEQ ID NO: 1094, SEQ ID NO: 1251, SEQ ID NO: 1408, and SEQ ID NO: 1565; SEQ ID NO: 781, SEQ ID NO: 938, SEQ ID NO: 1095, SEQ ID NO: 1252, SEQ ID NO: 1409, and SEQ ID NO: 1566; SEQ ID NO: 782, SEQ ID NO: 939, SEQ ID NO: 1096, SEQ ID NO: 1253, SEQ ID NO: 1410, and SEQ ID NO: 1567; SEQ ID NO: 783, SEQ ID NO: 940, SEQ ID NO: 1097, SEQ ID NO: 1254, SEQ ID NO: 1411, and SEQ ID NO: 1568; SEQ ID NO: 784, SEQ ID NO: 941, SEQ ID NO: 1098, SEQ ID NO: 1255, SEQ ID NO: 1412, and SEQ ID NO: 1569; and SEQ ID NO: 785, SEQ ID NO: 942, SEQ ID NO: 1099, SEQ ID NO: 1256, SEQ ID NO: 1413, and SEQ ID NO: 1570, 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.

12. 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 a sequence selected from the group consisting of SEQ ID NOs: 1-157 and a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 158-314, 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.

13. 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 combination of a light chain variable region and a heavy chain variable region selected from the group consisting of a light chain variable region comprising SEQ ID NO: 1 and a heavy chain variable region comprising SEQ ID NO: 158; a light chain variable region comprising SEQ ID NO: 2 and a heavy chain variable region comprising SEQ ID NO: 159; a light chain variable region comprising SEQ ID NO: 3 and a heavy chain variable region comprising SEQ ID NO: 160; a light chain variable region comprising SEQ ID NO: 4 and a heavy chain variable region comprising SEQ ID NO: 161; a light chain variable region comprising SEQ ID NO: 5 and a heavy chain variable region comprising SEQ ID NO: 162; a light chain variable region comprising SEQ ID NO: 6 and a heavy chain variable region comprising SEQ ID NO: 163; a light chain variable region comprising SEQ ID NO: 7 and a heavy chain variable region comprising SEQ ID NO: 164; a light chain variable region comprising SEQ ID NO: 8 and a heavy chain variable region comprising SEQ ID NO: 165; a light chain variable region comprising SEQ ID NO: 9 and a heavy chain variable region comprising SEQ ID NO: 166; a light chain variable region comprising SEQ ID NO: 10 and a heavy chain variable region comprising SEQ ID NO: 167; a light chain variable region comprising SEQ ID NO: 11 and a heavy chain variable region comprising SEQ ID NO: 168;

[illegible]

a heavy chain variable region comprising SEQ ID NO: 296; a light chain variable region comprising SEQ ID NO: 140 and a heavy chain variable region comprising SEQ ID NO: 297; a light chain variable region comprising SEQ ID NO: 141 and a heavy chain variable region comprising SEQ ID NO: 298; a light chain variable region comprising SEQ ID NO: 142 and
5 a heavy chain variable region comprising SEQ ID NO: 299; a light chain variable region comprising SEQ ID NO: 143 and a heavy chain variable region comprising SEQ ID NO: 300; a light chain variable region comprising SEQ ID NO: 144 and a heavy chain variable region comprising SEQ ID NO: 301; a light chain variable region comprising SEQ ID NO: 145 and a heavy chain variable region comprising SEQ ID NO: 302; a light chain variable region
10 comprising SEQ ID NO: 146 and a heavy chain variable region comprising SEQ ID NO: 303; a light chain variable region comprising SEQ ID NO: 147 and a heavy chain variable region comprising SEQ ID NO: 304; a light chain variable region comprising SEQ ID NO: 148 and a heavy chain variable region comprising SEQ ID NO: 305; a light chain variable region comprising SEQ ID NO: 149 and a heavy chain variable region comprising SEQ ID NO: 306;
15 a light chain variable region comprising SEQ ID NO: 150 and a heavy chain variable region comprising SEQ ID NO: 307; a light chain variable region comprising SEQ ID NO: 151 and a heavy chain variable region comprising SEQ ID NO: 308; a light chain variable region comprising SEQ ID NO: 152 and a heavy chain variable region comprising SEQ ID NO: 309; a light chain variable region comprising SEQ ID NO: 153 and a heavy chain variable region
20 comprising SEQ ID NO: 310; a light chain variable region comprising SEQ ID NO: 154 and a heavy chain variable region comprising SEQ ID NO: 311; a light chain variable region comprising SEQ ID NO: 155 and a heavy chain variable region comprising SEQ ID NO: 312; a light chain variable region comprising SEQ ID NO: 156 and a heavy chain variable region comprising SEQ ID NO: 313; and a light chain variable region comprising SEQ ID NO: 157
25 and a heavy chain variable region comprising SEQ ID NO: 314, 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:
30 455,
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.

14. The composition of claim 3, wherein said antibody or functional fragment thereof is an antibody, and wherein said antibody comprises a light chain comprising a sequence selected from the group consisting of SEQ ID NOs: 315-471 and a heavy chain comprising a sequence selected from the group consisting of SEQ ID NOs: 472-628, wherein

5 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,

10 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.

15 15. The composition of claim 3, wherein said antibody or functional fragment thereof is an antibody, and wherein said antibody comprises a combination of a light chain and a heavy chain selected from the group consisting of a light chain comprising SEQ ID NO: 315 and a heavy chain comprising SEQ ID NO: 472; a light chain comprising SEQ ID NO: 316 and a heavy chain comprising SEQ ID NO: 473; a light chain comprising SEQ ID NO: 317 and a heavy chain comprising SEQ ID NO: 474; a light chain comprising SEQ ID NO: 318 and a heavy chain comprising SEQ ID NO: 475; a light chain comprising SEQ ID NO: 319 and a heavy chain comprising SEQ ID NO: 476; a light chain comprising SEQ ID NO: 320 and a heavy chain comprising SEQ ID NO: 477; a light chain comprising SEQ ID NO: 321 and a heavy chain comprising SEQ ID NO: 478; a light chain comprising SEQ ID NO: 322 and a heavy chain comprising SEQ ID NO: 479; a light chain comprising SEQ ID NO: 323 and a heavy chain comprising SEQ ID NO: 480; a light chain comprising SEQ ID NO: 324 and a heavy chain comprising SEQ ID NO: 481; a light chain comprising SEQ ID NO: 325 and a heavy chain comprising SEQ ID NO: 482; a light chain comprising SEQ ID NO: 326 and a heavy chain comprising SEQ ID NO: 483; a light chain comprising SEQ ID NO: 327 and a heavy chain comprising SEQ ID NO: 484; a light chain comprising SEQ ID NO: 328 and a heavy chain comprising SEQ ID NO: 485; a light chain comprising SEQ ID NO: 329 and a heavy chain comprising SEQ ID NO: 486; a light chain comprising SEQ ID NO: 330 and a heavy chain comprising SEQ ID NO: 487; a light chain comprising SEQ ID NO: 331 and a heavy chain comprising SEQ ID NO: 488; a light chain comprising SEQ ID NO: 332 and a heavy chain comprising SEQ ID NO: 489; a light chain comprising SEQ ID

NO: 469 and a heavy chain comprising SEQ ID NO: 626; a light chain comprising SEQ ID NO: 470 and a heavy chain comprising SEQ ID NO: 627; and a light chain comprising SEQ ID NO: 471 and a heavy chain comprising SEQ ID NO: 628, 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.

16. The composition of any one of claims 1-15, wherein the GLP-1 receptor agonist is GLP-1(7-37) or a GLP-1(7-37) analog.

17. The composition of any one of claims 1-15, wherein the GLP-1 receptor agonist is selected from the group consisting of exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, and taspoglutide.

18. The composition of claim 16, wherein the GLP-1 receptor agonist is selected from the group consisting of GLP-1(7-37) (SEQ ID NO: 3184); GLP-1(7-36)-NH₂ (SEQ ID NO: 3185); liraglutide; albiglutide; taspoglutide; dulaglutide, semaglutide; LY2428757; Exendin-4 (SEQ ID NO: 3163); Exendin-3 (SEQ ID NO: 3164); Leu¹⁴-exendin-4 (SEQ ID NO: 3165); Leu¹⁴,Phe²⁵-exendin-4 (SEQ ID NO: 3166); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4 (SEQ ID NO: 3167); exendin-4(1-30) (SEQ ID NO: 3168); Leu¹⁴-exendin-4(1-30) (SEQ ID NO: 3169); Leu¹⁴,Phe²⁵-exendin-4(1-30) (SEQ ID NO: 3170); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4(1-30) (SEQ ID NO: 3171); exendin-4(1-28) (SEQ ID NO: 3172); Leu¹⁴-exendin-4(1-28) (SEQ ID NO: 3173); Leu¹⁴,Phe²⁵-exendin-4(1-28) (SEQ ID NO: 3174); Leu¹⁴,Ala¹⁹,Phe²⁵-exendin-4 (1-28) (SEQ ID NO: 3175); Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Phe²⁵,Gln²⁸-exendin-4 (SEQ ID NO: 3176); Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Gln²⁸-exendin-4 (SEQ ID NO: 3177); octylGly¹⁴,Gln²⁸-exendin-4 (SEQ ID NO: 3178); Leu¹⁴,Gln²⁸,octylGly³⁴-exendin-4 (SEQ ID NO: 3179); Phe⁴,Leu¹⁴,Gln²⁸,Lys³³,Glu³⁴, Ile^{35,36},Ser³⁷-exendin-4(1-37) (SEQ ID NO: 3180); Phe⁴,Leu¹⁴,Lys^{17,20},Ala¹⁹,Glu²¹,Gln²⁸-exendin-4 (SEQ ID NO: 3181); Val¹¹,Ile¹³,Leu¹⁴,Ala¹⁶,Lys²¹,Phe²⁵-exendin-4 (SEQ ID NO: 3182); exendin-4-Lys⁴⁰ (SEQ ID

NO: 3183); GLP-1(7-37) (SEQ ID NO: 3184); GLP-1(7-36)-NH₂ (SEQ ID NO: 3185); Aib^{8,35},Arg^{26,34},Phe³¹-GLP-1(7-36)) (SEQ ID NO: 3186); HXaa₈EGTFTSDVSSYLEXaa₂₂Xaa₂₃AAKEFIXaa₃₀WLXaa₃₃Xaa₃₄G Xaa₃₆Xaa₃₇; wherein Xaa₈ is A, V, or G; Xaa₂₂ is G, K, or E; Xaa₂₃ is Q or K; Xaa₃₀ is A or E; Xaa₃₃ is V or K; Xaa₃₄ is K, N, or R; Xaa₃₆ is R or G; and Xaa₃₇ is G, H, P, or absent (SEQ ID NO: 3187); Arg³⁴-GLP-1(7-37) (SEQ ID NO: 3188); Glu³⁰-GLP-1(7-37) (SEQ ID NO: 3189); Lys²²-GLP-1(7-37) (SEQ ID NO: 3190); Gly^{8,36},Glu²²-GLP-1(7-37) (SEQ ID NO: 3191); Val⁸,Glu²²,Gly³⁶-GLP-1(7-37) (SEQ ID NO: 3192); Gly^{8,36},Glu²²,Lys³³,Asn³⁴-GLP-1(7-37) (SEQ ID NO: 3193); Val⁸,Glu²²,Lys³³,Asn³⁴,Gly³⁶-GLP-1(7-37) (SEQ ID NO: 3194); Gly^{8,36},Glu²²,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3195); Val⁸,Glu²²,Gly³⁶,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3196); Gly^{8,36},Glu²²,Lys³³,Asn³⁴,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3197); Val⁸,Glu²²,Lys³³,Asn³⁴,Gly³⁶,Pro³⁷-GLP-1(7-37) (SEQ ID NO: 3198); Gly^{8,36},Glu²²-GLP-1(7-36) (SEQ ID NO: 3199); Val⁸,Glu²²,Gly³⁶-GLP-1(7-36) (SEQ ID NO: 3200); Val⁸,Glu²²,Asn³⁴,Gly³⁶-GLP-1(7-36) (SEQ ID NO: 3201); Gly^{8,36},Glu²²,Asn³⁴-GLP-1(7-36) (SEQ ID NO: 3202); GLP-1 analog (SEQ ID NO: 3206); GLP-1 analog (SEQ ID NO: 3207); [N^ε-(17-carboxyheptadecanoic acid)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3208); [N^ε-(17-carboxyhepta-decanoyl)Lys³²]exendin-4-NH₂ (SEQ ID NO: 3209); [desamino-His¹,N^ε-(17-carboxyheptadecanoyl)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3210); [Arg^{12,27},NLe¹⁴,N^ε-(17-carboxy-heptadecanoyl)Lys³²]exendin-4-NH₂ (SEQ ID NO: 3211); [N^ε-(19-carboxy-nonadecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3212); [N^ε-(15-carboxypentadecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3213); [N^ε-(13-carboxytridecanoylamino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3214); [N^ε-(11-carboxy-undecanoyl-amino)Lys²⁰]exendin-4-NH₂ (SEQ ID NO: 3215); exendin-4-Lys⁴⁰(e-MPA)-NH₂ (SEQ ID NO: 3216); exendin-4-Lys⁴⁰(e-AEEA-AEEA-MPA)-NH₂ (SEQ ID NO: 3217); exendin-4-Lys⁴⁰(e-AEEA-MPA)-NH₂ (SEQ ID NO: 3218); exendin-4-Lys⁴⁰(e-MPA)-albumin (SEQ ID NO: 3219); exendin-4-Lys⁴⁰(e-AEEA-AEEA-MPA)-albumin (SEQ ID NO: 3220); exendin-4-Lys⁴⁰(e-AEEA-MPA)-albumin (SEQ ID NO: 3221); desamino-His⁷,Arg²⁶,Lys³⁴(N^ε-(γ-Glu(N-α-hexadecanoyl))) -GLP-1(7-37) (core peptide disclosed as SEQ ID NO: 3222) (SEQ ID NO: 3222); desamino-His⁷,Arg²⁶,Lys³⁴(N^ε-octanoyl)-GLP-1(7-37) (SEQ ID NO: 3223); Arg^{26,34},Lys³⁸(N^ε-(ω-carboxypentadecanoyl))-GLP-1(7-38) (SEQ ID NO: 3224); Arg^{26,34},Lys³⁶(N^ε-(γ-Glu(N-α-hexadecanoyl))) -GLP-1(7-36) (core peptide disclosed as SEQ ID NO: 3225) (SEQ ID NO: 3225); [Aib⁸;Lys³⁷]GLP-1_(7-37) (SEQ ID NO: 3226); [Aib⁸,Lys²⁶]GLP-1_(7-37) (SEQ ID NO: 3227); [Aib^{8,22};Lys³⁶]GLP-1(7-36)-Amide (SEQ ID NO: 3228); [Aib^{8,22};BLeu³²;Lys³⁶]GLP-1(7-36)-Amide (SEQ ID NO: 3229);

[Aib^{8,22};Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3230); [Aib^{8,22};BLeu³²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3231); [Aib^{8,22};aMeLeu³²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3232); [Aib^{8,22};AMEF¹²;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3233); [Aib^{8,22};BLeu¹⁶;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3234); [Aib^{8,22};Gly³⁶;Lys³⁷]GLP-1(7-37)-Amide (SEQ ID NO: 3235); [Aib^{8,22};Lys^{33,37};Asn³⁴;Gly³⁶]GLP-1(7-37)-Amide (SEQ ID NO: 3236); [Aib^{8,22};Lys³³;Asn³⁴;Gly³⁶;Aeea³⁷]GLP-1(7-37)-Aeea-Lys-Amide (SEQ ID NO: 3237); [Aib^{8,22};Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3238); cyclo[E²³-K²⁷][Aib⁸;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3239); cyclo[E²²-K²⁶][Aib⁸;Gly³⁶;Lys³⁷]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};Glu²²]GLP-1(7-37) (SEQ ID NO: 3242); [Aib⁸;Glu²²;Gly³⁶]GLP-1(7-37)-Amide (SEQ ID NO: 3243); [Aib⁸;Tyr¹⁶;Glu²²;Gly³⁶]GLP-1_(7-37) (SEQ ID NO: 3244); [Aib⁸;Lys^{18,33};Glu^{22,23,30};Val²⁵;Arg²⁶;Leu²⁷;Asn³⁴;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3245); [Aib⁸;Lys^{18,33};Glu^{22,23,30};Leu²⁷;Asn³⁴;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3246); [Aib⁸;Lys¹⁸;Glu^{22,23,30};Leu²⁷;Gly³⁶]GLP-1(7-37) (SEQ ID NO: 3247); [Aib^{8,22};Ile⁹;Gly³⁶]GLP-1_(7-36) (SEQ ID NO: 3248); and [Aib^{8,22};Glu¹⁵;Gly³⁶]GLP-1_(7-36) (SEQ ID NO: 3249).

19. The composition of claim 16, wherein 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 .

20. The composition of claim 1, wherein the GLP-1 receptor agonist is 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.

21. Use of a composition comprising an antibody or functional fragment thereof that specifically binds to 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); 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); in the manufacture of a medicament for treating a metabolic disorder.