

[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] Glucagon-like peptide-1 (“GLP-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 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-1 receptor agonists 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).

[0007] Collectively, these links to obesity and insulin resistance imply GIPR inhibition is a useful approach for therapeutic intervention, both as a monotherapy and in combination with GLP-1.

SUMMARY OF THE INVENTION

[0007a] In one aspect, the present invention provides an isolated antigen binding protein that specifically binds to a human gastric inhibitory peptide receptor (GIPR) polypeptide, wherein said antigen binding protein is an antibody or a fragment thereof, and wherein said antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein said CDRL1 comprises SEQ ID NO: 702 ; said CDRL2 comprises SEQ ID NO: 859; said CDRL3 comprises SEQ ID NO: 1016; said CDRH1 comprises SEQ ID NO: 1173; said CDRH2 comprises SEQ ID NO: 1330; and said CDRH3 comprises SEQ ID NO: 1487.

[0007b] In another aspect, the present invention provides a pharmaceutical composition comprising at least one antibody or fragment thereof as disclosed herein, and pharmaceutically acceptable excipient.

[0008] Disclosed is a method of treating a subject with a metabolic disorder, the method comprising administering to the subject a therapeutically effective amount of an antigen binding protein 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 GIPR. Also disclosed is a method of treating a subject with a metabolic disorder, the method comprising administering to the subject a therapeutically effective amount of a GLP-1 receptor agonist and a therapeutically effective amount of a GIPR antagonist 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 GIPR. 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 antigen binding protein reduces body weight in an obese subject. In another example, administering the antigen binding protein reduces body weight gain in an obese subject. In another example, administering the antigen binding protein reduces fat mass in an obese subject. In another example, the glucose metabolism disorder comprises insulin resistance and administering the antigen binding protein reduces insulin resistance in an obese subject. In another example, administering the antigen binding protein reduces liver steatosis in an obese subject having increased liver steatosis. In another example, administering the antigen binding protein reduces liver fat content in an obese subject having increased liver fat content.

[0009] Also disclosed is a method of treatment comprising administering to a subject a therapeutically effective amount of at least one GLP-1 receptor agonist in combination with administration of at least one GIPR antagonist which upon administration to a subject with symptoms of a metabolic disorder provides sustained beneficial effects.

[0010] In one example, administration of at least one GLP-1 receptor agonist in combination with administration of at least one GIPR antagonist provides sustained beneficial effects of at least one symptom of a metabolic disorder.

[0011] In one example, the therapeutically effective amounts of the GLP-1 receptor agonist and the GIPR antagonist are combined prior to administration to the subject.

[0012] In one example, the therapeutically effective amounts of the GLP-1 receptor agonist and the GIPR antagonist are administered to the subject sequentially.

[0013] In one example, the therapeutically effective amounts of a GLP-1 receptor agonist and a GIPR antagonist are synergistically effective amounts.

[0014] In one example, the molar ratio of a GLP-1 receptor agonist to a GIPR antagonist is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, 1:1

to 1:5, and 1:1. In one example, the molar ratio of a GIPR antagonist to a GLP-1 receptor agonist is from about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, and 1:1 to 1:5.

[0015] In one example, the GLP-1 receptor agonist is used in combination with the GIPR antagonist at therapeutically effective molar ratios of between about 1:1.5 to 1:150, preferably 1:2 to 1:50.

[0016] In one example, the GLP-1 receptor agonist and the GIPR antagonist are present in doses that are at least about 1.1 to 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold lower than the doses of each compound alone required to treat a condition and/or disease.

[0017] In one example, the GLP-1 receptor agonist is GLP-1(7-37) or a GLP-1(7-37) analog.

[0018] In one example, the GLP-1 receptor agonist is selected from the group consisting of exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, and taspoglutide.

[0019] 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; desamino-

His⁷,Arg²⁶,Lys³⁴(N^ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) (core peptide disclosed as 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); Aib^{8,35},Arg^{26,34},Phe³¹-GLP-1(7-36)) (SEQ ID NO: 3186);

HXaa₈EGTFTSDVSSYLEXaa₂₂Xaa₂₃AAKEFIXaa₃₀WLXaa₃₃Xaa₃₄G Xaa₃₆Xaa₃₇; wherein Xaa₃ 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,Gly³⁶Pro³⁷-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); and Gly^{8,36},Glu²²,Asn³⁴-GLP-1(7-

36) (SEQ ID NO: 3202).

[0020] In another example, the subject is a mammal. In another example, the subject is human. In another example, the GIPR is human GIPR. In another example, the administering is by parenteral injection. In another example, the administering is by subcutaneous injection.

[0021] Also disclosed is an antigen binding protein that specifically binds to a human GIPR polypeptide and inhibits activation of GIPR by GIP ligand. In one example, the antigen binding protein inhibits GIP ligand binding to GIPR. In another example, the antigen binding protein is a human antigen binding protein. In another example, the antigen binding protein is a human antibody. In another example, the antigen binding protein is a monoclonal antibody.

[0022] Also disclosed is a pharmaceutical composition comprising at least one antigen binding protein according to any one of the foregoing examples.

[0023] Also disclosed is a nucleic acid molecule encoding an antigen binding protein according to any one of the foregoing examples.

[0024] Also disclosed is a vector comprising a nucleic acid molecule encoding an antigen binding protein according to any one of the foregoing examples.

[0025] Also disclosed is a host cell comprising a nucleic acid molecule encoding an antigen binding protein according to any one of the foregoing examples or a vector comprising a nucleic acid molecule encoding an antigen binding protein according to any one of the foregoing examples. In another aspect the present disclosure provides an antigen binding protein that specifically binds to a human GIPR polypeptide expressed by the vector.

[0026] Also disclosed is a method of making an antigen binding protein according to any one of the foregoing examples, the method comprising expressing the antigen binding protein in a host cell that secretes the antigen binding protein, and then purifying the antigen binding protein from the cell culture media. Also disclosed is an antigen binding protein that specifically binds to a human GIPR polypeptide purified from the host cell.

[0027] Also disclosed is an antigen binding protein of any one of the foregoing examples or a pharmaceutical composition of any one of the foregoing examples for use in therapy.

CLAIMS

What is claimed is:

1. An isolated antigen binding protein that specifically binds to a human gastric inhibitory peptide receptor (GIPR) polypeptide, wherein said antigen binding protein is an antibody or a fragment thereof, and wherein said antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein said CDRL1 comprises SEQ ID NO: 702 ; said CDRL2 comprises SEQ ID NO: 859; said CDRL3 comprises SEQ ID NO: 1016; said CDRH1 comprises SEQ ID NO: 1173; said CDRH2 comprises SEQ ID NO: 1330; and said CDRH3 comprises SEQ ID NO: 1487.
2. The isolated antigen binding protein 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 isolated antigen binding protein of claim 1 or 2, wherein said antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof.
4. The isolated antigen binding protein of claim 3, wherein said antibody fragment is a Fab fragment, a Fab' fragment, or a F(ab')₂ fragment.
5. The isolated antigen binding protein of claim 3, wherein said antigen binding protein is a human antibody.
6. The isolated antigen binding protein of claim 3, wherein said antigen binding protein is a monoclonal antibody.
7. The isolated antigen binding protein of claim 3, wherein said antigen binding protein is of the IgG1-, IgG2- IgG3- or IgG4-type.
8. The isolated antigen binding protein of claim 7, wherein said antigen binding protein is of the IgG1- or the IgG2-type.
9. The isolated antigen binding protein of any of claim 3, wherein said antigen binding protein is coupled to a labeling group.

10. The isolated antigen binding protein of one of claim 3, wherein said antigen binding protein inhibits binding of GIP to the extracellular portion of human GIPR.

11. The isolated antigen binding protein of claim 3, wherein said antigen binding protein 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.

12. The isolated antigen binding protein of claim 3, wherein said antigen binding protein is an antibody, and wherein said antibody comprises a light chain comprising SEQ ID NO:388 and a heavy chain comprising SEQ ID NO: 231.

13. The isolated antigen binding protein of claim 1, wherein said antibody comprises a CDRL1, a CDRL2, a CDRL3, a CDRH1, a CDRH2, and a CDRH3, wherein said CDRL1 consists of SEQ ID NO: 702; said CDRL2 consists of SEQ ID NO: 859; said CDRL3 consists of SEQ ID NO: 1016; said CDRH1 consists of SEQ ID NO: 1173; said CDRH2 consists of SEQ ID NO: 1330; and said CDRH3 consists of SEQ ID NO: 1487.

14. A pharmaceutical composition comprising at least one antibody or fragment thereof according to any one of claims 1, 11, 12, and 13, and pharmaceutically acceptable excipient.