

[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

[0008] In one aspect, the present disclosure refers to 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 an antigen binding fragment thereof, and wherein said antibody is a GIPR antagonist and 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 SEQ ID NO: 1290, SEQ ID NO: 1291, SEQ ID NO: 1292, SEQ ID NO: 1293, SEQ ID NO: 1294, and SEQ ID NO: 1295. In another aspect, the present disclosure refers to a nucleic acid molecule encoding the antibody or antigen binding fragment thereof as described herein.

[0008a] In yet another aspect, the present disclosure refers to a vector comprising a nucleic acid molecule as described herein. In yet another aspect, the present disclosure refers to a host cell comprising the nucleic acid molecule as described herein.

In still another aspect, the present disclosure refers to a method of making the antibody or antigen binding fragment thereof as described herein, comprising the step of preparing said antibody or antigen binding fragment thereof from a host cell that secretes said antibody.

[0008b] In still another aspect, the present disclosure refers to a pharmaceutical composition comprising at least one antibody or antigen binding fragment thereof as described herein, and pharmaceutically acceptable excipient.

[0008c] 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 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. In one example the present disclosure is directed to 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,

CLAIMS

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 an antigen binding fragment thereof, and wherein said antibody is a GIPR antagonist and 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 SEQ ID NO: 1290, SEQ ID NO: 1291, SEQ ID NO: 1292, SEQ ID NO: 1293, SEQ ID NO: 1294, and SEQ ID NO: 1295.
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: 1201, SEQ ID NO: 1203, and SEQ ID NO: 1205.
3. The isolated antigen binding protein of claim 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 antigen binding fragment thereof.
4. The isolated antigen binding protein of claim 3, wherein said antigen binding 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 an antigen binding fragment thereof, and wherein said antibody or antigen binding fragment thereof comprises a light chain variable region comprising SEQ ID NO: 1286 and a heavy chain variable region comprising SEQ ID NO: 1287.

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: 1288 and a heavy chain comprising SEQ ID NO: 1289.

13. A nucleic acid molecule encoding the antibody or antigen binding fragment thereof according to any one of claims 11 and 12.

14. The nucleic acid molecule according to claim 13, wherein said nucleic acid molecule is operably linked to a control sequence.

15. A vector comprising a nucleic acid molecule according to claim 14.

16. A host cell comprising the nucleic acid molecule according to claim 13.

17. A method of making the antibody or antigen binding fragment thereof according to any one of claims 11 and 12, comprising the step of preparing said antibody or antigen binding fragment thereof from a host cell that secretes said antibody.

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