

What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that binds specifically to glucagon-like peptide 1 receptor (GLP1R) protein, wherein the antibody or antigen-binding fragment thereof attenuates GLP1R activity and elevates blood glucose levels.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody has one or more properties selected from the group consisting of:

- (a) is a fully human monoclonal antibody;
- (b) binds to human GLP1R at 25°C with a dissociation constant (K_D) of less than 6nM, as measured in a surface plasmon resonance (SPR) assay;
- (c) binds to human GLP1R at 37°C with a K_D of less than 20nM, as measured in a SPR assay;
- (d) binds to monomeric cynomolgus GLP1R at 25°C with a K_D of less than 20 nM, as measured in a SPR assay;
- (e) binds to monomeric cynomolgus GLP1R at 37°C with a K_D of less than 60 nM, as measured in a SPR assay;
- (f) binds to monomeric mouse GLP1R at 25°C with a K_D of less than 22 nM, as measured in a SPR assay;
- (g) binds to monomeric mouse GLP1R at 37°C with a K_D of less than 75 nM, as measured in a SPR assay;
- (h) blocks the interaction of GLP1 and GLP1R with an IC_{50} value of less than about 10 nM as measured in an in vitro receptor/ligand binding assay at 37°C;
- (i) reduces GLP1-induced hypoglycemia without causing hyperglycemia; and
- (j) elevates blood glucose to a normalized level and maintains the elevated level for up to 2 months without causing hyperglycemia.

3. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody is a fully human monoclonal antibody.

4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises an IgG1 or IgG4 isotype.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain

complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR); and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR), wherein:

the HCVR comprises:

- (i) an amino acid sequence of SEQ ID NO: 2, 22, or 40;
- (ii) an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 2, 22, or 40;
- (iii) an amino acid sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 2, 22, or 40; or
- (iv) an amino acid sequence of SEQ ID NO: 2, 22, or 40 having no more than 12 amino acid substitutions; and

the LCVR comprises:

- (i) an amino acid sequence of SEQ ID NO: 10, 30, or 48;
- (ii) an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 10, 30, or 48;
- (iii) an amino acid sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 10, 30, or 48; or
- (iv) an amino acid sequence of SEQ ID NO: 10, 30, or 48 having no more than 12 amino acid substitutions.

6. The antibody or antigen-binding fragment thereof of claim 5, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, and 40/48.

7. The antibody or antigen-binding fragment thereof of claim 5, wherein:
- (a) HCDR1 comprises an amino acid sequence of SEQ ID NO: 4, 24, or 42;
 - (b) HCDR2 comprises an amino acid sequence of SEQ ID NO: 6, 26, or 44;
 - (c) HCDR3 comprises an amino acid sequence of SEQ ID NO: 8, 28, or 46;
 - (d) LCDR1 comprises an amino acid sequence of SEQ ID NO: 12, 32, or 50;
 - (e) LCDR2 comprises an amino acid sequence of SEQ ID NO: 14 or 52; and
 - (f) LCDR3 comprises an amino acid sequence of SEQ ID NO: 16, 34, or 54.

8. The antibody or antigen-binding fragment thereof of claim 7 comprising HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 comprising amino acid sequences of SEQ ID NOs: 4/6/8/12/14/16, 24/26/28/32/14/34, or 42/44/46/50/52/54.

9. The antibody or antigen-binding fragment thereof of any one of claims 1-8 comprising a heavy chain (HC) and a light chain (LC), wherein the HC comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 36 and 56.
10. The antibody or antigen-binding fragment thereof of any one of claims 1-9 comprising a HC and a LC, wherein the LC comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 38 and 58.
11. The antibody or antigen-binding fragment thereof of any one of claims 1-9 comprising a HC and a LC, wherein the HC comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 18, 36 and 56; and the LC comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 38 and 58.
12. The antibody or antigen-binding fragment thereof of any one of claims 1-11 comprising a HC/LC comprising amino acid sequences of SEQ ID NOs: 18/20, 36/38 or 56/58.
13. An isolated antibody or antigen-binding fragment thereof that competes for binding to GLP1R with the antibody or antigen-binding fragment thereof of any one of claims 1-12.
14. An isolated antibody or antigen-binding fragment thereof that binds to the same epitope as the antibody or antigen-binding fragment thereof of any one of claims 1-12.
15. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof that binds to GLP1R according to any one of claims 1-12 and a pharmaceutically acceptable carrier or diluent.
16. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a HCVR and/or LCVR of an antibody as set forth in any one of claims 5-12.
17. An isolated vector comprising the polynucleotide molecule of claim 16.
18. An isolated host cell expressing the vector of claim 17.
19. The isolated host cell of claim 18 expressing a first vector comprising a polynucleotide sequence that encodes a HCVR of an antibody as set forth in any one of claims 5-12 and a second vector comprising a polynucleotide sequence that encodes a LCVR of an antibody as set forth in any one of claims 5-12.

20. A method of producing an anti-GLP1R antagonist antibody or antigen-binding fragment thereof, comprising growing the host cell of claim 18 or 19 under conditions permitting production of the antibody or fragment, and recovering the antibody or fragment so produced.

21. The method of claim 20, further comprising formulating the antibody or antigen-binding fragment thereof as a pharmaceutical composition comprising an acceptable carrier.

22. ~~A method of~~ Use of the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating, preventing or ameliorating at least one symptom or indication of a GLP1R-associated disease or disorder, ~~the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof of any one of claims 1-12 to~~ in a subject in need thereof.

23. The ~~method of~~ use according to claim 22, wherein the GLP1R-associated disease or disorder is hypoglycemia.

24. The ~~method of~~ use according to claim 23, wherein the hypoglycemia is post-bariatric hypoglycemia.

25. The ~~method of~~ use according to any one of claims 22-24, wherein the pharmaceutical composition is to be administered to the subject after upper abdominal surgery.

26. The ~~method of~~ use according to any one of claims 22-25, wherein the pharmaceutical composition is to be administered prophylactically or therapeutically to the subject in need thereof.

27. The ~~method of~~ use according to any one of claims 22-26, wherein the pharmaceutical composition is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly.

28. ~~A method of~~ Use of the antibody or antigen-binding fragment thereof of any one of claims 1-12 in the manufacture of a medicament for elevating blood glucose levels, ~~comprising administering a therapeutically effective amount of an anti-GLP1R antagonist antibody or antigen-binding fragment thereof of any one of claims 1-12 to~~ in a subject in need thereof.

29. The ~~method of~~use according to claim 28, wherein the subject has a GLP1R-associated disease or disorder.

30. The ~~method of~~use according to claim 29, wherein the GLP1R-associated disease or disorder is hypoglycemia.

31. The ~~method of~~use according to claim 30, wherein the hypoglycemia is post-bariatric hypoglycemia.

32. The ~~method of~~use according to any one of claims 28-31, wherein the antibody or antigen-binding fragment thereof is to be administered to the subject after upper abdominal surgery.

33. The ~~method of~~use according to any one of claims 28-32, wherein the antibody or antigen-binding fragment thereof is to be administered prophylactically or therapeutically to the subject in need thereof.

34. The ~~method of~~use according to any one of claims 28-33, wherein the antibody or antigen-binding fragment thereof is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, or intramuscularly.

35. The ~~method of~~use according to any one of claims 28-34, wherein the blood glucose level of the subject is elevated to a normalized level.