What is claimed is:

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds human glucagon receptor (hGCGR), wherein the antibody binds an ectodomain and/or an extracellular (EC) loop of human GCGR, wherein the ectodomain is the N-terminal domain of GCGR and wherein the EC loop is one or more of EC1, EC2 and EC3.

2. An antibody or fragment thereof according to claim 1, wherein the N-terminal domain comprises amino acid residues ranging from about amino acid residue number 27 to about amino acid residue 144 of SEQ ID NO: 153; EC1 comprises amino acid residues ranging from about amino acid residue 194 to about amino acid residue 226 of SEQ ID NO: 153; EC2 comprises amino acid residues ranging from about amino acid residue 285 to about amino acid residue 305 of SEQ ID NO: 153; and EC3 comprises amino acid residues ranging from about amino acid residue 369 to about amino acid residue 384 of SEQ ID NO: 153.

3. An antibody or fragment thereof according to claim 1 or 2, comprising the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence selected from one of SEQ ID NOs: 2, 18, 34, 50, 66, 70, 86, 90, 106, 110, 126, 130 and 146; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected from one of SEQ ID NOs: 10, 26, 42, 58, 68, 78, 88, 98, 108, 118, 128, 138 and 148.

4. An antibody or fragment thereof according to any one of claims 1 through 3, wherein the HCVR comprises a HCDR1 domain having an amino acid sequence selected from one of SEQ ID NO: 4, 20, 36, 52, 72, 92, 112 and 132; a HCDR2 domain having an amino acid sequence selected from one of SEQ ID NO: 6, 22, 38, 54, 74, 94, 114 and 134; a HCDR3 domain having an amino acid sequence selected from one of SEQ ID NOs: 8, 24, 40, 56, 76, 96, 116 and 136; and

a LCVR comprising a LCDR1 domain having an amino acid sequence selected from one of SEQ ID NO: 12, 28, 44, 60, 80, 100, 120 and 140; a LCDR2 domain having an amino acid sequence selected from one of SEQ ID NO: 14, 30, 46, 62, 82, 102, 122 and 142; and a LCDR3 domain having an amino acid sequence selected from one of SEQ ID NO: 16, 32, 48, 64, 84, 104, 124 and 144.

5. An antibody or antigen-binding fragment thereof according to any one of claims 1 through 4, comprising: (a) a HCVR having an amino acid sequence selected from one of SEQ ID NO: 2, 18, 34, 50, 66, 70, 86, 90, 106, 110, 126, 130 and 146; and (b) a LCVR having an

amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 68, 78, 88, 98, 108, 118, 128, 138 and 148.

6. An antibody or antigen-binding fragment thereof according to any of claims 1 through 5, comprising a HCVR/LCVR sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/68, 70/78, 86/88, 90/98, 106/108, 110/118, 126/128, 130/138, and 146/148.

7. An antibody or antigen-binding fragment thereof that competes for specific binding to hGCGR with the antibody or antigen-binding fragment thereof according to any one of claims 1 through 6.

8. An antibody or antigen-binding fragment thereof that binds the same epitope on hGCGR as the antibody or antigen-binding fragment thereof according to any one of claims 1 through 6.

9. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of an antibody of any of claims 1 through 8.

10. An expression vector comprising the nucleic acid molecule of claim 9.

11. A method of producing an anti-human GCGR antibody or antigen-binding fragment thereof comprising the steps of introducing the expression vector of claim 10 into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

12. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1 through 8 and a pharmaceutically acceptable carrier or diluent.

13. Use of the antibody or antigen-binding fragment according to any one of claims 1 through 8, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for lowering blood glucose or ketone levels, or for treating a condition or disease associated with, or characterized in part by high blood glucose or ketone levels, or at least one symptom or complication associated with the condition or disease, such that blood glucose or ketone levels are lowered or that the condition or disease is mediated, or at least one symptom or complication associated with the condition or disease is alleviated or reduced in severity.

14. The use according to claim 13, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.

15. The use according to either one of claims 13 or 14, wherein the antibody or antigen-binding fragment is to be administered to the patient in combination with a second therapeutic agent.

16. The use according to claim 15, wherein the second therapeutic agent is selected from the group consisting of insulin, a biguanide (metformin), a sulfonylurea (such as glyburide, glipizide), a PPAR gamma agonist (pioglitazone, rosiglitazone), an alpha glucosidase inhibitor (acarbose, voglibose), EXENATIDE® (glucagon-like peptide 1), SYMLIN® (pramlintide), a glucagon antagonist, and a second GCGR antagonist.

17. The use according to claim 15, wherein the second therapeutic agent is a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitor.

18. The use according to claim 17, wherein the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

19. The use according to claim 15, wherein the second therapeutic agent is an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9).

20. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to any one of claims 1 through 8, and a second therapeutic agent comprising an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to human PCSK9, and a pharmaceutically acceptable carrier or diluent.

21. The isolated antibody or antigen-binding fragment thereof according to any one of claims 1 through 8, or the pharmaceutical composition of either of claim 12 or 20, for use in lowering blood glucose or ketone levels, or for treating a patient having a disease or condition associated with, or characterized in part by high blood glucose or ketone levels, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar

syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.

22. Use of the isolated antibody or antigen-binding fragment thereof according to any one of claims 1 through 8, or the pharmaceutical composition of either of claim 12 or 20, in the manufacture of a medicament for lowering blood glucose or ketone levels, or for treating a patient having a disease or condition associated with, or characterized in part by high blood glucose or ketone levels, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.

What is claimed:

1. An isolated human antibody or antigen-binding fragment thereof that specifically binds human glucagon receptor (hGCGR), wherein the antibody comprises the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR), wherein the HCVR has an amino acid sequence as set forth in SEQ ID NO: 2; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence selected as set forth in SEQ ID NO: 10.

2. An isolated human antibody or antigen-binding fragment thereof that specifically binds human glucagon receptor (hGCGR), wherein the antibody comprises:
(a) a HCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 4;
(b) a HCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 6;
(c) a HCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 8;
(d) a LCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 12;
(e) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 14; and
(f) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 16.

3. An antibody or antigen-binding fragment thereof according to claims 1 or 2, comprising a HCVR/LCVR sequence pair as set forth in SEQ ID NO: 2/10.

4. An antibody or antigen-binding fragment thereof that competes for specific binding to hGCGR with the antibody or antigen-binding fragment thereof according to any one of claims 1-3.

5. An antibody or antigen-binding fragment thereof that binds the same epitope on hGCGR as the antibody or antigen-binding fragment thereof according to any one of claims 1-3.

6. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment of an antibody of any of claims 1-5.

7. An expression vector comprising the nucleic acid molecule of claim 6.

8. A method of producing an anti-human GCGR antibody or antigen-binding fragment

thereof comprising the steps of introducing the expression vector of claim 7 into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

9. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1-5 and a pharmaceutically acceptable carrier or diluent.

10. Use of the antibody or antigen-binding fragment according to any one of claims 1-5, or the pharmaceutical composition of claim 9 in the manufacture of a medicament for lowering blood glucose or ketone levels, or for treating a condition or disease associated with, or characterized in part by high blood glucose or ketone levels, or at least one symptom or complication associated with the condition or disease, such that blood glucose or ketone levels are lowered or that the condition or disease is mediated, or at least one symptom or complication associated with the condition or disease is alleviated or reduced in severity.

11. The use according to claim 10, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.

12. The use according to either one of claims 10 or 11, wherein the antibody or antigen-binding fragment is to be administered to the patient in combination with a second therapeutic agent.

13. The use according to claim 12, wherein the second therapeutic agent is selected from the group consisting of insulin, a biguanide (metformin), a sulfonylurea (such as glyburide, glipizide), a PPAR gamma agonist (pioglitazone, rosiglitazone), an alpha glucosidase inhibitor (acarbose, voglibose), EXENATIDE® (glucagon-like peptide 1), SYMLIN® (pramlintide), a glucagon antagonist, and a second GCGR antagonist.

14. The use according to claim 12, wherein the second therapeutic agent is a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitor.

15. The use according to claim 14, wherein the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

16. The use according to claim 12, wherein the second therapeutic agent is an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9).

17. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof according to any one of claims 1-5, and a second therapeutic agent comprising an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to human PCSK9, and a pharmaceutically acceptable carrier or diluent.

18. The isolated antibody or antigen-binding fragment thereof according to any one of claims 1-5, or the pharmaceutical composition of either of claim 9 or 17, for use in lowering blood glucose or ketone levels, or for treating a patient having a disease or condition associated with, or characterized in part by high blood glucose or ketone levels, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.

19. Use of the isolated antibody or antigen-binding fragment thereof according to any one of claims 1-5, or the pharmaceutical composition of either of claim 9 or 17, in the manufacture of a medicament for lowering blood glucose or ketone levels, or for treating a patient having a disease or condition associated with, or characterized in part by high blood glucose or ketone levels, wherein the condition or disease is selected from the group consisting of diabetes, impaired glucose tolerance, obesity, nephropathy, neuropathy, retinopathy, cataracts, stroke,

atherosclerosis, impaired wound healing, diabetic ketoacidosis, hyperglycemia, hyperglycemic hyperosmolar syndrome, perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome and impaired fasting glucose.