The antibody described by Buggy *et al.* competed with glucagon for the hormone binding site of the receptor and recognized both the human and rat glucagon receptors, but not the mouse receptor. Wright *et al.* disclose a monoclonal antibody raised in a mouse against the human glucagon receptor and conducted detailed protein structure determination of the monoclonal antibody to the receptor (Wright, L.M. (2000) *Acta Crystallographica Section D.* 56(5): 573-580). Other antibodies to the glucagon receptor are described in US patents 5,770,445 and 7,947,809; European patent application EP2074149A2; EP patent EP0658200B1; US patent publications 2009/0041784; 2009/0252727; and 2011/0223160; and PCT publication WO2008/036341.

BRIEF SUMMARY

[0007] In one embodiment, the disclosure provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind to the human glucagon receptor (hGCGR) and inhibit or block its activity, for example, block the binding of glucagon to its receptor, thereby blocking the elevation of blood glucose levels. The antibodies or antigen binding fragments thereof may be useful for lowering blood glucose levels in a subject that suffers from a disease characterized by increased blood glucose levels, such as diabetes mellitus. The antibodies may also be used to treat a wide range of conditions and disorders in which blocking the interaction of glucagon with the glucagon receptor is desired, thereby having a beneficial effect. The antibodies may ultimately be used to prevent the long-term complications associated with elevated blood glucose levels in diabetic patients, or to ameliorate at least one symptom associated with elevated blood glucose levels in diabetic patients.

[0008] The antibodies of the disclosure can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.,* to eliminate residual effector functions (Reddy *et al.,* 2000, J. Immunol. 164:1925-1933).

[0009] Provided is 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.

[0009a] Also provided is an antibody or antigen-binding fragment thereof that competes for specific binding to hGCGR with the antibody or antigen-binding fragment thereof as defined above.

[0009b] Further provided is an antibody or antigen-binding fragment thereof that binds the same epitope on hGCGR as the antibody or antigen-binding fragment thereof as defined above.

[0010] In one embodiment, the disclosure provides an antibody or fragment thereof, which binds the N-terminal domain comprising amino acid residues ranging from about amino acid residue number 27 to about amino acid residue 144 of SEQ ID NO: 153, or binds an EC loop of hGCGR, wherein the EC loop is one or more of EC1, EC2, and EC3, wherein 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

levels observed in a normal mammal; or (viii) demonstrates no adverse effect on blood levels of LDL, HDL, or total cholesterol in a mammal.

[0037] In another related embodiment, the disclosure provides an antibody or antigen-binding fragment thereof that competes for specific binding to hGCGR with an antibody or antigen-binding fragment comprising heavy and light chain CDR domains contained within heavy and light chain sequence pairs 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.

[0038] In another related embodiment, the disclosure provides an antibody or antigen-binding fragment thereof that binds the same epitope on hGCGR that is recognized by an antibody comprising heavy and light chain sequence pairs 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.

[0039] In one embodiment, the disclosure provides for an anti-hGCGR antibody having one or more of the following characteristics:

a) capable of reducing blood glucose levels by about 25% to about 75% for a period of at least 7 days, when administered at a dose ranging from about 1 mg/kg to about 30 mg/kg;
b) capable of resulting in at least a 10% reduction in body weight when administered to a mammal in need of such therapy;
c) capable of reducing blood ketone levels by about 25% to 75% when administered at a dose ranging from about 1 mg/kg to about 30 mg/kg; or
d) capable of reducing blood glucose levels by about 20% to 40% without causing a significant elevation in blood lipids or cholesterol when administered with an antibody specific for proprotein convertase subtilisin/kexin (PCSK)-9, and sustaining lowered blood glucose levels for at least 7 days post treatment.

[0039a] In a first aspect, there is provided an isolated nucleic acid molecule encoding the antibody or antigen-binding fragment thereof comprising:
a) a HCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 72;
b) a HCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 74;
c) a HCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 76;
d) a LCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 80;
e) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 82; and
f) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84.

[0039b] In a second aspect, there is provided an expression vector comprising the nucleic acid molecule as defined in the first aspect.

[0039c] Provided is a method of producing an anti-human GCGR antibody or antigen-binding fragment thereof comprising the steps of introducing the expression vector as defined herein into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

[0040] In one embodiment, the disclosure provides nucleic acid molecules encoding anti-hGCGR antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the disclosure, and host cells into which such vectors have been introduced, are also encompassed by the disclosure, as are

encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 67, 77, 87, 97, 107, 117, 127, 137 and 147, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 41, 77, 87, 117 and 127.

[0043] In one embodiment, the disclosure also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 75, 95, 115 and 135, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 83, 103, 123 and 143, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0044] In one embodiment, the disclosure provides an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 71, 91, 111 and 131, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 73, 93, 113 and 133, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 79, 99, 119 and 139, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 81, 101, 121 and 141, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0045] In one embodiment, the disclosure features a human anti-hGCGR antibody or antigen-binding fragment of an antibody comprising a HCVR encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, with combinations as shown in Table 2.

[0046] The disclosure encompasses anti-hGCGR antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0046a] Provided is a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as defined herein and a pharmaceutically acceptable carrier or diluent.

[0047] In one embodiment, the disclosure features a pharmaceutical composition comprising a

recombinant human antibody or fragment thereof, which specifically binds hGCGR, and a pharmaceutically acceptable carrier or diluent.

[0048] In one embodiment, the disclosure features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the disclosure, and a second therapeutic agent. The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the disclosure.

[0048a] Provided is a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof as defined herein, 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.

[0049] In one embodiment, the second therapeutic agent may be an agent capable of lowering blood glucose or reducing at least one symptom in a patient suffering from a disease or condition characterized by high blood glucose levels, such as diabetes mellitus.

[0050] In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the disclosure, if such side effect(s) should occur. For example, in the event that any of the anti-hGCGR antibodies increases lipid or cholesterol levels, it may be beneficial to administer a second agent that is effective to lower lipid or cholesterol levels.

[0051] The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

[0052] In one embodiment, the second therapeutic agent may be a glucagon antagonist, or a second glucagon receptor antagonist, such as another antibody to the glucagon receptor, which is different than the antibodies described herein. It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present disclosure can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[0053] In one embodiment, the anti-hGCGR antibodies of the disclosure may be used in combination with one or more of the following type 2 diabetes treatments currently available. These include biguanide (metformin), sulfonylureas (such as glyburide, glipizide), peroxisome proliferator-activated receptor (PPAR) gamma agonists (pioglitazone, rosiglitazone); and alpha glucosidase inhibitors (acarbose, voglibose). Additional treatments include injectable treatments such as EXENATIDE® (glucagon-like peptide 1), and SYMLIN® (pramlintide).

embodiments, use of the isolated antibody or antigen-binding fragment of the disclosure is contemplated for preparation 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, or for ameliorating at least one symptom of such disease or condition, wherein the condition or disease is selected from any of the above-noted diseases or conditions.

[0071a] Provided is use of the antibody or antigen-binding fragment as defined herein, or the pharmaceutical composition as defined herein, 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.

[0072b] Provided is the isolated antibody or antigen-binding fragment thereof as defined herein, or the pharmaceutical composition as defined herein, 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.

[0072c] In a third aspect, there is provided the use of an isolated antibody or antigen-binding fragment thereof comprising

a) a HCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 72;

b) a HCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 74;

c) a HCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 76;

d) a LCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 80;

e) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 82; and

f) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84, or the pharmaceutical composition comprising said antibody or antigen-binding fragment thereof, 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, or at least one symptom or complication associated with the condition or disease, 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 is:

1. An isolated nucleic acid molecule encoding the antibody or antigen-binding fragment thereof comprising:
a) a HCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 72;
b) a HCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 74;
c) a HCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 76;
d) a LCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 80;
e) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 82; and
f) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84.

2. An expression vector comprising the nucleic acid molecule of claim 1.

3. Use of an isolated antibody or antigen-binding fragment thereof comprising
a) a HCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 72;
b) a HCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 74;
c) a HCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 76;
d) a LCDR1 domain having an amino acid sequence as set forth in SEQ ID NO: 80;
e) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 82; and
f) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84, or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof, 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, or at least one symptom or complication associated with the condition or disease, 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.

4. The use according to claim 3, wherein the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

5. The use according to claim 4, 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.

6. The use according to claim 4, wherein the second therapeutic agent is a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) inhibitor.

7. The use according to claim 6, wherein the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

8. The use according to claim 4, 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).