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 ~~OF THE INVENTION~~

[0007] In ~~a first aspect~~one embodiment, the ~~invention~~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 ~~invention~~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] In one embodiment, the ~~invention~~disclosure provides 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.

[0010] In one embodiment, the ~~invention~~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

SEQ ID NO: 153.

[0010a] In one aspect, there is provided 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: 86; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence as set forth in SEQ ID NO: 88.

[0011] In one embodiment, the human antibody or antigen-binding fragment of a human antibody that binds hGCGR comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 70, 86, 90, 106, 110, 126, 130 and 146, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In certain embodiments, the antibody or antigen-binding fragment of an antibody that binds hGCGR comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 34, 70, 86, 110 and 126, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0012] In one embodiment, the human antibody or antigen-binding fragment of a human antibody that binds hGCGR comprises a light chain variable region (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, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. In certain embodiments, the antibody or antigen-binding fragment of an antibody that binds hGCGR comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 42, 78, 88, 118 and 128, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0013] In certain embodiments, the human antibody or fragment thereof that binds hGCGR comprises a HCVR/LCVR amino acid 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. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NO: 34/42, 70/78, 86/88, 110/118 and 126/128.

[0014] In a related embodiment, the ~~invention~~disclosure includes an antibody or antigen-binding fragment of an antibody which specifically binds hGCGR, wherein the antibody or fragment thereof comprises the 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. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA*

86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0015] In certain embodiments, the present ~~invention~~disclosure provides an isolated human antibody or an antigen-binding fragment thereof that binds specifically to hGCGR, wherein the antibody comprises a HCVR comprising the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within the HCVR sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 70, 86, 90, 106, 110, 126, 130 and 146; and a LCVR comprising the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the LCVR sequences selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 68, 78, 88, 98, 108, 118, 128, 138 and 148.

[0016] In one embodiment, the present ~~invention~~disclosure provides an isolated human antibody or antigen-binding fragment of a human antibody that binds hGCGR, comprising a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 76, 96, 116 and 136, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 84, 104, 124 and 144, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0016a] In one aspect, there is provided an isolated 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: 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;
(f) a LCDR2 domain having an amino acid sequence as set forth in SEQ ID NO: 82; and
(g) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84.

[0017] In one embodiment, the ~~invention~~disclosure provides an antibody or fragment thereof that further comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 72, 92, 112 and 132, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 74, 94, 114 and 134, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 80, 100, 120 and 140, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46,

62, 82, 102, 122 and 142, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0018] In one embodiment, the antibody or antigen-binding fragment of an antibody comprises:

(a) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 76, 96, 116 and 136; and

(b) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 84, 104, 124 and 144.

[0019] In one embodiment, the antibody or antigen-binding fragment of the antibody further comprises:

[0031] In one embodiment, the antibody or antigen-binding fragment binds human, monkey, mouse and rat GCGR.

[0032] In one embodiment, the antibody or antigen-binding fragment binds human, monkey and mouse GCGR, but does not bind rat GCGR.

[0033] In one embodiment, the antibody or antigen-binding fragment binds human, monkey and rat GCGR, but does not bind mouse GCGR.

[0034] In one embodiment, the antibody or antigen-binding fragment binds human and monkey GCGR, but does not bind rat or mouse GCGR.

[0035] In one embodiment, the antibody or antigen-binding fragment binds human GCGR, but does not bind monkey, mouse or rat GCGR.

[0036] In one embodiment, the ~~invention~~disclosure provides a fully human monoclonal antibody or antigen-binding fragment thereof that neutralizes hGCGR activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 70, 86, 90, 106, 110, 126, 130 and 146; (ii) comprises 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; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 76, 96, 116 and 136, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 84, 104, 124 and 144, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 72, 92, 112 and 132, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 74, 94, 114 and 134, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 80, 100, 120 and 140, 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 having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 82, 102, 122 and 142, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds any one or more of human, monkey, mouse or rat GCGR; (vi) may or may not block GCGR activity in at least one species other than human; (v) demonstrates a K_D ranging from about 10^{-8} to about 10^{-12}; (vi) lowers blood glucose levels by at least about 25% to about 75% in a mammal experiencing elevated blood glucose levels; (vii) may or may not lower triglyceride levels to

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 ~~invention~~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 ~~invention~~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 ~~invention~~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.

[0040] In ~~a second aspect~~one embodiment, the ~~invention~~disclosure provides nucleic acid molecules encoding anti-hGCGR antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the ~~invention~~disclosure, and host cells into which such vectors have been introduced, are also encompassed by the ~~invention~~disclosure, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0041] In one embodiment, the ~~invention~~disclosure provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 69, 85, 89, 105, 109, 125, 129 and 145, 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 HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 33, 69, 85, 109 and 125.

[0042] In one embodiment, the antibody or fragment thereof further comprises a LCVR

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 ~~invention~~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 ~~invention~~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 ~~a third aspect~~one embodiment, the ~~invention~~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 ~~invention~~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).

[0047] In ~~a fourth aspect~~one embodiment, the ~~invention~~disclosure features a pharmaceutical composition comprising a

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

[0047a] In one aspect, there is provided a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as defined above and a pharmaceutically acceptable carrier or diluent.

[0047b] In one aspect, there is provided a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof as defined above, and a second therapeutic agent comprising an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to PCSK9, and a pharmaceutically acceptable carrier or diluent.

[0048] In one embodiment, the ~~invention~~disclosure features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the ~~invention~~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 ~~invention~~disclosure.

[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 ~~invention~~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 ~~invention~~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 ~~invention~~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).

[0054] In certain embodiments, the composition may include a second agent selected from the group consisting of non-sulfonylurea secretagogues, insulin, insulin analogs, exendin-4 polypeptides, beta 3 adrenoceptor agonists, PPAR agonists, dipeptidyl peptidase IV inhibitors, statins and statin-containing combinations, inhibitors of cholesterol uptake and/or bile acid re-absorption, LDL-cholesterol antagonists, cholesteryl ester transfer protein antagonists, endothelin receptor antagonists, growth hormone antagonists, insulin sensitizers, amylin mimetics or agonists, cannabinoid receptor antagonists, glucagon-like peptide-1 agonists, melanocortins, melanin-concentrating hormone receptor agonists, SNRIs, a fibroblast growth factor 21 (FGF21) mimetic (See, for example, US20110002845 and US20080261236), a fibroblast growth factor receptor 1c (FGFR1c) agonist (See, for example, US20110150901), an inhibitor of advanced glycation endproduct formation, such as, but not limited to, aminoguanidine, and protein tyrosine phosphatase inhibitors.

[0055] In certain embodiments, the composition may include a second agent to help lower lipid or cholesterol levels and may include an agent such as a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (for example, a statin such as atorvastatin, (LIPITOR®), fluvastatin (LESCOL®), lovastatin (MEVACOR®), pitavastatin (LIVALO®), pravastatin (PRAVACHOL®), rosuvastatin (CRESTOR®) and simvastatin (ZOCOR®) and the like.

[0056] In certain embodiments, it may be beneficial to administer the antibodies of the ~~invention~~disclosure in combination with any one or more of the following: (1) niacin, which increases lipoprotein catabolism; (2) fibrates or amphipathic carboxylic acids, which reduce low-density lipoprotein (LDL) level, improve high-density lipoprotein (HDL) and TG levels, and reduce the number of non-fatal heart attacks; and (3) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol, or fixed combinations such as VYTORIN®) (ezetimibe plus simvastatin); a statin with a bile resin (*e.g.*, cholestyramine, colestipol, colesevelam), a fixed combination of niacin plus a statin (*e.g.*, niacin with lovastatin); or with other lipid lowering agents such as omega-3-fatty acid ethyl esters (for example, omacor). Furthermore, the second therapeutic agent can be one or more other inhibitors of glucagon or GCGR, as well as inhibitors of other molecules, such as angiopoietin-like protein 3 (ANGPTL3), angiopoietin-like protein 4 (ANGPTL4), angiopoietin-like protein 5 (ANGPTL5), angiopoietin-like protein 6 (ANGPTL6), which are involved in lipid metabolism, in particular, cholesterol and/or triglyceride homeostasis. Inhibitors of these molecules include small molecules and antibodies that specifically bind to these molecules and block their activity.

[0057] In certain embodiments, it may be beneficial to administer the anti-GCGR antibodies of the ~~invention~~disclosure in combination with a nucleic acid that inhibits the activity of hPCSK9, such as an antisense molecule, a double stranded RNA, or a siRNA molecule. Exemplary nucleic acid molecules that inhibit the activity of PCSK9 are described in US2011/0065644, US2011/0039914,US2008/0015162 and US2007/0173473.

[0058] *In certain embodiments, it may be beneficial to administer the anti-hGCGR antibodies of*

the ~~invention~~disclosure in combination with an antibody that specifically binds to and inhibits the activity of hPCSK9, thereby inhibiting its activity, wherein such antibody acts to lower lipid or cholesterol levels. Exemplary anti-hPCSK9 antibodies are described in US2010/0166768. The isolated antibody that specifically binds to human PCSK9, or an antigen-binding fragment thereof, may be administered at a dose ranging from about 0.01 mg/kg to about 30 mg/kg. It may be administered as a single dose or as multiple doses. The anti-hPCSK9 antibody may be administered concurrently with the anti-GCGR antibody, or it may be administered prior to or after the anti-GCGR antibody.

[0059] In one embodiment, the second therapeutic agent to be used in combination with an antibody of the ~~invention~~disclosure comprises an isolated antibody that specifically binds to human PCSK9, or an antigen-binding fragment thereof, wherein the anti-hPCSK9 antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within any one of the HCVR sequences selected from the group consisting of SEQ ID NOs: 173 and 177; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the LCVR sequences selected from the group consisting of SEQ ID NOs: 175 and 185.

[0060] In one embodiment, the isolated antibody that specifically binds to human PCSK9, or antigen-binding fragment thereof, comprises a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO: 173 and 177.

[0061] In one embodiment, the isolated antibody that specifically binds to human PCSK9, or antigen-binding fragment thereof, comprises a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO: 175 and 185.

[0062] In one embodiment, the isolated antibody that specifically binds to human PCSK9, or antigen-binding fragment thereof, comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 173 and 177 and a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 175 and 185.

[0063] In one embodiment, the isolated antibody that specifically binds to human PCSK9, or antigen-binding fragment thereof, comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein the HCVR/ LCVR sequence pairs are selected from the group consisting of SEQ ID NO: 173/175; and SEQ ID NO: 177/185.

[0064] In one embodiment, the isolated antibody that specifically binds to human PCSK9, or antigen-binding fragment thereof, comprises: a HCDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 161 and 179; a HCDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 163 and 181; a HCDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 165 and 183; a LCDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 167 and 187; a LCDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 169 and 189 and a LCDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 171 and 191.

[0065] In certain embodiments, the hPCSK9 antibodies to be used in combination with the anti-GCGR antibodies of the ~~invention~~disclosure are encoded by nucleic acid molecules as described herein. For example, in one embodiment, the ~~invention~~disclosure provides an anti-hPCSK9 antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 172 and 176, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof, and a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 174 and 184, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0066] In one embodiment, the ~~invention~~disclosure provides an anti-hPCSK9 antibody to be used in combination with the anti-GCGR antibodies of the ~~invention~~disclosure, wherein the anti-PCSK9 antibody or fragment thereof comprises a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 160 and 178, 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: 162 and 180, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 164 and 182, 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: 166 and 186, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 168 and 188, 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: 170 and 190, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0067] When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art.

[0068] In ~~a fifth aspect~~one embodiment, the ~~invention~~disclosure features methods for inhibiting hGCGR activity using the anti-hGCGR antibody or antigen-binding portion of the antibody of the ~~invention~~disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof. The antibodies of the ~~invention~~disclosure may be used to treat any condition or disorder, which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of hGCGR activity. It is envisioned that the antibodies of the ~~invention~~disclosure may be used alone, or as adjunct therapy with other agents or methods known to be standard care for treating patients suffering from diseases

or conditions characterized in part by elevated blood glucose or ketone levels, such as, but not limited to, diabetes. Such standard therapy may include fluid administration, or administration of any other pharmaceutical agents useful for lowering blood glucose, ketones, or lipids, or for weight reduction.

[0069] The anti-hGCGR antibodies of the ~~invention~~disclosure may function to block the interaction between glucagon and its receptor, thereby inhibiting the glucose elevating effects of glucagon. The use of glucagon receptor antagonists, such as the antibodies described herein, may be an effective means of achieving normal levels of glucose, thereby ameliorating, or preventing one or more symptoms of, or long term complications associated with, for example, diabetes. The use of glucagon receptor antagonists, such as the antibodies described herein, may also be an effective means of achieving normal levels of glucose in non-diabetic patients, who experience hyperglycemia as a result of conditions or disorders not related to diabetes, such as perioperative hyperglycemia (hyperglycemia observed in patients just prior to surgery, or after surgery). In certain embodiments, methods of lowering blood glucose levels or ketone levels in diabetic ketoacidosis are envisioned using the antibodies of the ~~invention~~disclosure. In certain embodiments, methods of treating patients to achieve a reduction in body weight, or to prevent weight gain, or to maintain a normal body weight, are also envisioned using the antibodies of the ~~invention~~disclosure.

[0070] The antibodies of the present ~~invention~~disclosure may also be useful for ameliorating conditions such as, for example, impaired glucose tolerance, obesity, or for treating diabetic conditions, or for preventing or reducing the severity of any one or more of the long-term complications associated with diabetes, such as nephropathy, neuropathy, retinopathy, cataracts, stroke, atherosclerosis, impaired wound healing and other complications associated with diabetes, known to those skilled in the art.

[0071] Other conditions or disorders treatable by the therapeutic methods of the ~~invention~~disclosure include diabetic ketoacidosis, hyperglycemia (including perioperative hyperglycemia, hyperglycemia in the intensive care unit patient, and hyperosmolar hyperglycemia syndrome), hyperinsulinemia, the metabolic syndrome, insulin resistance syndrome, impaired fasting glucose, or hyperglycemia associated with hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, and general dyslipidemias. In certain embodiments, the ~~invention~~disclosure provides for an isolated antibody or antigen-binding fragment thereof specific for GCGR, s described 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 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. In certain

embodiments, use of the isolated antibody or antigen-binding fragment of the ~~invention~~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.

[0072] The antibodies may also be useful for treating patients with inoperable glucagonoma (pancreatic endocrine tumor with or without necrolytic migratory erythema and hyperglycemia).

[0073] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0074] Fig. 1 shows the percent change in blood glucose levels in C57BL6 mice after administration of H4H1327P (anti-GCGR antibody), and/or H1H316P (anti-PCSK9 antibody) when given alone or in combination. Control (X with solid line); H4H1327P at 3 mg/kg (■ with solid line); H4H1327P at 10 mg/kg (▲with solid line); H1H316P at 10 mg/kg (▼ with solid line); H4H1327P at 3 mg/kg + H1H316P at 10 mg/kg (◆ with dashed line); H4H1327P at 10 mg/kg + H1H316P at 10 mg/kg (O with dashed lines).

[0075] Fig. 2 shows plasma LDL-C levels in C57BL6 mice after administration of H4H1327P, and/or H1H316P when given alone or in combination. Control (X with solid line); H4H1327P at 3 mg/kg (■ with solid line); H4H1327P at 10 mg/kg (▲with solid line); H1H316P at 10 mg/kg (▼ with solid line); H4H1327P at 3 mg/kg + H1H316P at 10 mg/kg (◆ with dashed line); H4H1327P at 10 mg/kg + H1H316P at 10 mg/kg (O with dashed lines).

[0076] Fig. 3 shows plasma HDL-C levels in C57BL6 mice after administration of H4H1327P, and/or H1H316P when given alone or in combination. Control (X with solid line); H4H1327P at 3 mg/kg (■ with solid line); H4H1327P at 10 mg/kg (▲with solid line); H1H316P at 10 mg/kg (▼ with solid line); H4H1327P at 3 mg/kg + H1H316P at 10 mg/kg (◆ with dashed line); H4H1327P at 10 mg/kg + H1H316P at 10 mg/kg (O with dashed lines).

[0077] Fig. 4 shows total plasma cholesterol levels in C57BL6 mice after administration of H4H1327P, and/or H1H316P when given alone or in combination. Control (X with solid line); H4H1327P at 3 mg/kg (■ with solid line); H4H1327P at 10 mg/kg (▲with solid line); H1H316P at 10 mg/kg (▼ with solid line); H4H1327P at 3 mg/kg + H1H316P at 10 mg/kg (◆ with dashed line); H4H1327P at 10 mg/kg + H1H316P at 10 mg/kg (O with dashed lines).

[0078] Fig. 5 shows plasma triglyceride levels in C57BL6 mice after administration of H4H1327P, and/or H1H316P when given alone or in combination. Control (X with solid line); H4H1327P at 3 mg/kg (■ with solid line); H4H1327P at 10 mg/kg (▲with solid line); H1H316P at 10 mg/kg (▼ with solid line); H4H1327P at 3 mg/kg + H1H316P at 10 mg/kg (◆ with dashed line); H4H1327P at 10 mg/kg + H1H316P at 10 mg/kg (O with dashed lines).

[0079] Fig. 6 shows hepatic triglyceride levels in C57BL6 mice after administration of

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.

What is claimed is:

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: 86; and the CDRs of a light chain variable region (LCVR), wherein the LCVR has an amino acid sequence as set forth in SEQ ID NO: 88.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain variable region (HCVR) having an amino acid sequence as set forth in SEQ ID NO: 86.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, comprising a light chain variable region (LCVR) having an amino acid sequence as set forth in SEQ ID NO: 88.

4. The isolated human antibody or antigen-binding fragment thereof of claim 1, comprising: (a) a HCVR having an amino acid sequence as set forth in SEQ ID NO: 86; and (b) a LCVR having an amino acid sequence as set forth in SEQ ID NO: 88.

5. An isolated 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: 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;

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

(g) a LCDR3 domain having an amino acid sequence as set forth in SEQ ID NO: 84.

6. The isolated antibody or antigen-binding fragment of claim 1, comprising a HCVR/LCVR sequence pair as set forth in SEQ ID NOs: 86/88.

7. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof of claim 1, and a second therapeutic agent comprising an isolated antibody, or an antigen-binding fragment thereof, that specifically binds to PCSK9, and a pharmaceutically acceptable carrier or diluent.

8. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 5 and a pharmaceutically acceptable carrier or diluent.

9. A pharmaceutical composition comprising an antibody or antigen-binding fragment thereof of claim 5, and a second therapeutic agent comprising an isolated antibody, or an antigen-binding

fragment thereof, that specifically binds to PCSK9, and a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of claim 1 and a pharmaceutically acceptable carrier or diluent.