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(57) Abstract: In one aspect, methods of treating hyperinsulinemic hypoglycemia comprising administration of an effective amount of a derivative of an exendin-4 peptide are provided. In some embodiments, the method comprises subcutaneously administering to a patient having hyperinsulinemic hypoglycemia a therapeutically effective amount of exendin(5-39).



TREATMENT OF HYPERINSULINEMIC HYPOGLYCEMIA WITH EXENDIN-4 DERIVATIVES

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/303,983, filed March 4, 2016, the entire content of which is incorporated by reference herein.

10

FIELD OF INVENTION

[0002] The present invention provides methods and compositions for the treatment of hypoglycemia, particularly post-bariatric hyperinsulinemia and more generally hyperinsulinemic hypoglycemia of any origin, and so relates to the fields of biology, chemistry, medicinal chemistry, medicine, molecular biology, and pharmacology.

15

BACKGROUND OF THE INVENTION

[0003] Roux-en-Y gastric bypass (RYGB) is a form of bariatric surgery that is widely performed for medically complicated obesity and that cures type 2 diabetes in 85% of cases. The physiologic mechanisms mediating diabetes resolution are controversial, but it is
20 believed that the incretin hormone glucagon-like peptide-1 (GLP-1) may play an important role. GLP-1 stimulates the secretion of insulin by pancreatic beta cells and is responsible for the "incretin" effect: incretin hormones enhance the glucose-dependent secretion of insulin, such that pancreatic beta cells will secrete more insulin after an oral glucose load than after an isoglycemic IV glucose load. Enhanced secretion of GLP-1 after RYGB, and a
25 resultant elevation in insulin secretion, may play a primary role in the resolution of diabetes after RYGB.

[0004] However, as the use of bariatric surgical procedures continues to increase worldwide, a severe complication — hyperinsulinemic hypoglycemia — is increasingly reported. This disorder manifests in 1-6% of RYGB patients, and leads to severe

symptomatic hypoglycemia, often multiple times daily, characterized by glucose concentrations low enough (20-40 mg/dL) to cause seizures, altered mental status, loss of consciousness, cognitive dysfunction, disability, and death. Quality of life is severely diminished, and many patients cannot care for themselves or others, work, drive, or be left
5 unaccompanied. Currently there is no satisfactory treatment for hyperinsulinemic hypoglycemia. Severe cases have been managed with near-total to total pancreatectomy, which results in insulin-dependent diabetes and is associated with a 6% surgical mortality risk. There continues to be a need for a therapy that safely and effectively mitigates hyperinsulinemic hypoglycemia.

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BRIEF SUMMARY OF THE INVENTION

[0005] In one aspect, methods of preventing or treating hyperinsulinemic hypoglycemia or associated acute or chronic symptoms or outcomes thereof are provided. In some embodiments, the method comprises administering an exendin-4 derivative to a patient in
15 need thereof, wherein the exendin-4 derivative is selected from the group consisting of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), and exendin(8-39).

[0006] In some embodiments, the exendin-4 derivative is pegylated (e.g., pegylated exendin(3-39), pegylated exendin(4-39), pegylated exendin(5-39), pegylated exendin(6-39),
20 pegylated exendin(7-39), or pegylated exendin(8-39)). In some embodiments, the exendin-4 derivative is pegylated exendin(5-39). In some embodiments, the exendin-4 derivative is not pegylated.

[0007] In some embodiments, the exendin-4 derivative is subcutaneously administered. In some embodiments, the exendin-4 derivative is subcutaneously administered as an
25 immediate release formulation. In some embodiments, the exendin-4 derivative is subcutaneously administered as an extended release formulation.

[0008] In some embodiments, the patient has previously had gastrointestinal surgery. In some embodiments, the patient has previously had bariatric surgery. In some embodiments, the patient has previously had a non-bariatric gastrointestinal surgical procedure. In some
30 embodiments, the patient has congenital hyperinsulinemic hypoglycemia.

[0009] In some embodiments, the exendin-4 derivative is administered (e.g., subcutaneously administered) at a dose of about 0.01 mg to about 50 mg. In some embodiments, the exendin-4 derivative is administered (e.g., subcutaneously administered) at a dose in the range of 0.01 mg to 1 mg, e.g., about 0.01 mg to about 10 mg, about 0.5 mg to about 30 mg, about 0.5 mg to about 20 mg, or about 0.5 mg to about 10 mg. In some embodiments, the exendin-4 derivative is administered at a dose in the range of 0.1 mg to 1 mg. In some embodiments, the exendin-4 derivative is administered (e.g., subcutaneously administered) once per day (QD) or twice per day (BID). In some embodiments, the exendin-4 derivative is administered (e.g., subcutaneously administered) once per week (QW) or twice per week (BIW). In some embodiments, the exendin-4 derivative is administered at a total daily dose of about 0.01 mg to about 50 mg, e.g., about 0.5 mg to about 30 mg, about 0.5 mg to about 20 mg, or about 0.5 mg to about 10 mg.

[0010] In some embodiments, the exendin-4 derivative is a non-pegylated exendin-4 derivative and the non-pegylated exendin-4 derivative is administered at a dose in the range of about 0.5 mg to about 30 mg. In some embodiments, the non-pegylated exendin-4 derivative is administered QD or BID. In some embodiments, the exendin-4 derivative is a non-pegylated exendin-4 derivative and the non-pegylated exendin-4 derivative is administered at a dose in the range of about 0.5 mg to about 30 mg BID (e.g., about 0.5 mg to about 20 mg BID, about 0.5 mg to about 15 mg BID, or about 0.5 mg to about 10 mg BID). In some embodiments, the exendin-4 derivative is exendin(5-39) and the exendin(5-39) is administered (e.g., subcutaneously administered) at a dose in the range of about 0.5 mg to about 30 mg BID (e.g., about 0.5 mg to about 20 mg BID, about 0.5 mg to about 15 mg BID, or about 0.5 mg to about 10 mg BID).

[0011] In some embodiments, the exendin-4 derivative is a pegylated exendin-4 derivative and the pegylated exendin-4 derivative is administered at a dose in the range of about 0.5 mg to about 30 mg. In some embodiments, the non-pegylated exendin-4 derivative is administered QW or BIW. In some embodiments, the exendin-4 derivative is a pegylated exendin-4 derivative and the pegylated exendin-4 derivative is administered at a dose in the range of 0.5 mg to 30 mg once per week (QW) or twice per week (BIW) (e.g., about 0.5 mg to about 20 mg BID, about 0.5 mg to about 15 mg BID, or about 0.5 mg to about 10 mg QW or BIW). In some embodiments, the exendin-4 derivative is pegylated exendin(5-39) and the

pegylated exendin(5-39) is administered at a dose in the range of about 0.5 mg to about 30 mg QW or BIW (e.g., about 0.5 mg to about 20 mg BID, about 0.5 mg to about 15 mg BID, or about 0.5 mg to about 10 mg QW or BIW).

5 [0012] In some embodiments, the exendin-4 derivative is a non-pegylated exendin-4 derivative and the non-pegylated exendin-4 derivative is administered at a dose in the range of about 0.01 mg to about 10 mg. In some embodiments, the non-pegylated exendin-4 derivative is administered QD or BID. In some embodiments, the exendin-4 derivative is a non-pegylated exendin-4 derivative and the non-pegylated exendin-4 derivative is administered at a dose in the range of 0.1 mg to 1 mg BID. In some embodiments, the
10 exendin-4 derivative is exendin(5-39) and the exendin(5-39) is administered (e.g., subcutaneously administered) at a dose in the range of 0.1 mg to 1 mg BID.

[0013] In some embodiments, the exendin-4 derivative is a pegylated exendin-4 derivative and the pegylated exendin-4 derivative is administered at a dose in the range of about 0.01 mg to about 10 mg. In some embodiments, the non-pegylated exendin-4 derivative is
15 administered QW or BIW. In some embodiments, the exendin-4 derivative is a pegylated exendin-4 derivative and the pegylated exendin-4 derivative is administered at a dose in the range of 0.1 mg to 1 mg once per week (QW) or twice per week (BIW). In some embodiments, the exendin-4 derivative is pegylated exendin(5-39) and the pegylated exendin(5-39) is administered at a dose in the range of 0.1 mg to 1 mg QW or BIW.

20 [0014] These and other aspects and embodiments of the invention are described in more detail below.

DETAILED DESCRIPTION OF THE INVENTION

I. INTRODUCTION

[0015] In one aspect, the present invention relates to exendin-4 derivatives that act as an
25 antagonist of the GLP-1 receptor. Exendin-4, a 39-amino acid peptide, is a hormone that was originally isolated from Gila monster venom and which is a GLP-1 receptor agonist. N-terminal truncation of exendin-4 by 8 amino acids resulted in a GLP-1 receptor antagonist, exendin(9-39). See, Montrose-Rafizadeh et al., *Journal of Biological Chemistry*, 272:21201-21206 (1997).

[0016] As described herein, shorter deletions of N-terminal amino acids from exendin-4 are expected to retain antagonistic activity for the GLP-1 receptor, or even show improved antagonistic activity for the GLP-1 receptor, as compared to exendin(9-39). In some embodiments, the exendin-4 derivative comprising an N-terminal deletion is selected from the group consisting of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), and exendin(8-39). In some embodiments, a pegylated or unpegylated form of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39) exhibits improved antagonistic activity without agonistic activity for the GLP-1 receptor as compared to exendin(9-39). Thus, in some embodiments, a lower dose and/or less frequent dosing can be used for an exendin-4 derivative as described herein as compared to dosing regimens that are used for exendin(9-39).

II. DEFINITIONS

[0017] The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, because the scope of the present invention will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not be construed as representing a substantial difference over the definition of the term as generally understood in the art.

[0018] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0019] All numerical designations, e.g., pH, temperature, time, concentration, and molecular weight, including ranges, are approximations which are varied (+) or (-) by increments of 0.1 or 1.0, as appropriate. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term “about.”

5 [0020] The singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a compound” includes a plurality of compounds.

[0021] The terms “administer,” “administering,” and “administration” refer to introducing a compound, a composition, or an agent of the present disclosure into a subject, such as a
10 human. In the context of the present invention, one preferred route of administration of the agents is subcutaneous administration. Other routes are intravenous administration and oral administration.

[0022] The term “comprising” is intended to mean that the compounds, compositions and methods include the recited elements, but does not exclude others. “Consisting essentially
15 of” when used to define compounds, compositions and methods, shall mean excluding other elements that would materially affect the basic and novel characteristics of the claimed invention. Embodiments defined by each of these transition terms are within the scope of this invention.

[0023] As used herein, the terms “patient” and “subject” interchangeably refer to an
20 individual (e.g., a human or a non-human mammal) having or prone to having a condition that can be treated or prevented by administration of an exendin-4 derivative as described herein. In some embodiments, a patient or subject has hyperinsulinemic hypoglycemia. In some embodiments, a patient or subject has previously had a bariatric procedure (e.g., gastric bypass surgery).

25 [0024] The term “pharmaceutical composition” is meant to encompass a composition suitable for administration to a subject. In general a “pharmaceutical composition” is sterile, and preferably free of contaminants that are capable of eliciting an undesirable response within the subject (e.g., the compound(s) in the pharmaceutical composition is pharmaceutical grade). Pharmaceutical compositions can be designed for administration to
30 subjects or patients in need thereof via a number of different routes of administration

including oral, intravenous, buccal, rectal, parenteral, intraperitoneal, intradermal, intratracheal, intramuscular, subcutaneous, inhalational, and the like.

[0025] The terms “QD” and “BID” have their usual meanings of, respectively, administration of a composition (e.g., a composition comprising an exendin-4 derivative as described herein) once per day or twice per day. In some embodiments, administration once per day (QD) means that at least 20 hours, at least 22 hours, or about 24 hours elapse between administrations. In some embodiments, administration once per day means administration about every 24 hours. In some embodiments, administration twice per day (BID) means that at least 6 hours, at least 8 hours, at least 10 hours, at least 11 hours, or about 12 hours elapse between administrations. In some embodiments, administration twice per day means administration about every 12 hours.

[0026] The terms “QW” and “BIW” have their usual meanings of, respectively, administration of a composition (e.g., a composition comprising an exendin-4 derivative as described herein) once per week or twice per week. In some embodiments, administration once per week (QW) means that at least 5 days, at least 6 days, or about 7 days elapse between administrations. In some embodiments, administration once per day means administration about every 7 days. In some embodiments, administration twice per week (BIW) means that at least 2 days, about 3 days, or about 4 days elapse between administrations. In some embodiments, administration once per day means administration two times in a 7-day period (e.g., on days 1 and 4 of a 7-day period).

[0027] The term “therapeutically effective amount” as used herein refers to that amount of a compound, agent, or drug (e.g., an exendin-4 derivative as disclosed herein) being administered that will treat to some extent a disease, disorder, or condition, e.g., relieve one or more of the symptoms of the disease, i.e., infection, being treated, and/or that amount that will prevent, to some extent, one or more of the symptoms of the disease that the subject being treated has or is at risk of developing.

[0028] The terms “treatment,” “treating,” or “treat,” as used herein in reference to administering an exendin-4 derivative to treat hyperinsulinemic hypoglycemia, covers any treatment of the disease in a human subject, and includes: (a) reducing the risk, frequency, or severity of hypoglycemic episodes in patients with a history of hyperinsulinemic

hypoglycemia; (b) reducing the risk of occurrence of hypoglycemia in a subject determined to be predisposed to the disease, such as a person who has received post-bariatric surgery, but not yet diagnosed as having the disease; (c) impeding the development of the disease; and/or (d) relieving the disease, i.e., causing regression of the disease and/or relieving one or more disease symptoms.

III. METHODS FOR THE TREATMENT OF HYPERINSULINEMIC HYPOGLYCEMIA

[0029] In one aspect, methods for the treatment and prevention of hyperinsulinemic hypoglycemia or associated acute or chronic symptoms or outcomes thereof are provided.

10 In some embodiments, the method comprises the subcutaneous administration of a GLP-1 receptor antagonist that is an exendin-4 derivative to a patient in need thereof. In some embodiments, the exendin-4 derivative that is subcutaneously delivered is exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39). In some

15 embodiments, the exendin-4 derivative that is subcutaneously delivered is a pegylated form of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39). In some embodiments, a patient in need thereof is a patient having hyperinsulinemic hypoglycemia post bariatric surgery. In some embodiments, a patient in need thereof is a patient having hyperinsulinemic hypoglycemia post gastrointestinal surgery (e.g., post non-bariatric gastrointestinal surgery). In some embodiments, a patient in need thereof is a

20 patient having congenital hyperinsulinemic hypoglycemia.

Patient Population

[0030] In some embodiments, a patient to be treated is a patient having hyperinsulinemic hypoglycemia. "Hyperinsulinemic hypoglycemia," as used herein, encompasses the conditions dumping syndrome, nesidioblastosis, noninsulinoma pancreatogenous

25 hypoglycemia syndrome (NIPHS), and/or post-prandial reactive hypoglycemia. Hyperinsulinemic hypoglycemia may result from a gastric or bariatric procedure, or may have a congenital, acquired, or induced origin.

[0031] In some embodiments, a patient to be treated has previously had a bariatric and/or related metabolic procedure, such as but not limited to Roux-en-Y Gastric Bypass.

30 Bariatric and/or related metabolic procedures include, but are not limited to, Roux-en-Y

Gastric Bypass, Vertical Sleeve Gastrectomy, placement of an endosleeve device, such as the EndoBarrier Gastrointestinal Liner System, also called an "endoluminal liner," duodenal mucosal resurfacing, also referred to as duodenal ablation, partial bypass of the duodenum, involving duodeno-ileal or duodeno-jejunal anastomosis, vagal nerve blockade, and/or
5 pyloroplasty.

[0032] A bariatric procedure (i.e., bariatric surgery) typically involves any of the foregoing: partially or completely bypassing the duodenum and/or decreasing nutrient exposure to the duodenum, increasing the rapidity of nutrient transit to the lower part of the intestines (often specifically the ileum), and/or otherwise increasing ileal nutrient exposure. Bariatric
10 surgery may be intended for weight loss or metabolic benefit (such as resolution of diabetes), or both. Such weight loss or metabolic procedures, referred to herein as "bariatric procedures" may enhance secretion of GLP-1 from the distal small intestine, especially the ileum, leading to elevated insulin secretion, and in some patients hypoglycemia. The patient may be referred to as a "post bariatric surgery" patient or "post-RYGB." In a preferred
15 embodiment, the patient has had bariatric surgery to aid in weight loss and/or metabolic control and has suffered hypoglycemic excursions requiring urgent medical attention.

[0033] In some embodiments, the patient treated has previously had a non-bariatric surgical procedure involving the gastrointestinal system (including but not limited to esophagectomy, for example for treatment of esophageal cancer, Nissen fundoplication, for
20 example gastroesophageal reflux, or gastrectomy, for example for treatment of gastric cancer) and so may be referred to herein as "post gastrointestinal surgery."

[0034] In some embodiments, the patient treated is prediabetic and/or insulin resistant and may benefit from prevention of pancreatic hyperstimulation from oral carbohydrate ingestion leading to post-prandial hypoglycemia. In some embodiments, a treated patient
25 has a congenital, acquired, or induced form of hyperinsulinemic hypoglycemia, such as congenital hyperinsulinism or sometimes referred to as congenital nesidioblastosis. Acquired hyperinsulinism may result from insulinomas, autoimmune syndromes, reactive hypoglycemia, adult nesidioblastosis, or gastric dumping syndrome (not due to bariatric or GI surgery). Congenital hyperinsulinism may manifest in the newborn period, or many years

later. Accordingly, the compositions and methods disclosed herein encompass the treatment of such conditions.

[0035] In some embodiments, the patient is an adult patient with hyperinsulinemic hypoglycemia. In some embodiments, a patient is diagnosed as having hyperinsulinemic hypoglycemia according to the diagnostic criteria described in De Leon and Stanley, *Best Pract Res Clin Endocrinol Metab*, 2013, 27:763-769, which is incorporated by reference herein. A typical adult patient with hyperinsulinemic hypoglycemia will present within 10 years of bariatric and/or other gastrointestinal surgery with one or more symptoms of hypoglycemia (e.g. palpitations, tremor, weakness, sweating, confusion, fatigue, blurred vision,) within 5 hours of eating that are associated with a plasma glucose of ≤ 60 mg/dL and immediate resolution with carbohydrate intake. In some embodiments, the patient exhibits one or more neuroglycopenic symptoms, such as altered mental status, loss of consciousness, or seizures. Hyperinsulinemia (>2 μ U/mL or 13.9 pmol/L) may be documented in the proper laboratory setting at the time of the hypoglycemic event. However, documentation of hyperinsulinemia is not always possible due to logistical challenges associated with this testing (which involves induced hypoglycemia) and concerns over patient safety.

[0036] With the increasing incidence of obesity in children and adolescents, and the consequent increasing use of bariatric surgery in the pediatric and adolescent population, hyperinsulinemic hypoglycemia is anticipated in this cohort, and will likely present similarly to the typical adult patient. Thus, in some embodiments, the compositions and methods disclosed herein encompass the treatment of such patients.

Exendin-4 Derivatives

[0037] The present disclosure relates to compositions comprising exendin-4 derivatives and methods for the treatment of hyperinsulinemic hypoglycemia comprising the administration of an exendin-4 derivative to a subject in need thereof. In some embodiments, the exendin-4 derivative is selected from the group consisting of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), and exendin(8-39). As used herein, the term "exendin-4 derivative" (e.g., "exendin(3-39)", "exendin(4-39)", "exendin(5-39)", "exendin(6-39)", "exendin(7-39)", and "exendin(8-39)") encompass pharmaceutically

acceptable salts of the exendin-4 derivative, including but not limited to sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate salts.

5 **[0038]** In some embodiments, the exendin-4 derivative is exendin(3-39), which is a peptide having the amino acid sequence EGTFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS (SEQ ID NO:1).

[0039] In some embodiments, the exendin-4 derivative is exendin(4-39), which is a peptide having the amino acid sequence GTFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS
10 (SEQ ID NO:2).

[0040] In some embodiments, the exendin-4 derivative is exendin(5-39), which is a peptide having the amino acid sequence TFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS (SEQ ID NO:3).

[0041] In some embodiments, the exendin-4 derivative is exendin(6-39), which is a peptide having the amino acid sequence FTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS (SEQ
15 ID NO:4).

[0042] In some embodiments, the exendin-4 derivative is exendin(7-39), which is a peptide having the amino acid sequence TSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS (SEQ ID NO:5).

20 **[0043]** In some embodiments, the exendin-4 derivative is exendin(8-39), which is a peptide having the amino acid sequence SDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS (SEQ ID NO:6).

[0044] In some embodiments, the exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39)) is pegylated. In some
25 embodiments, the PEG group has a size of about 5 kD to about 40 kD, e.g., about 20 kD. In some embodiments, the exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39)) is pegylated at the N-terminus. In some embodiments, the exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39)) is pegylated at the C-terminus. In some

embodiments, the PEG is coupled to the exendin-4 derivative via a linker (e.g., a cysteine). Without being bound to a particular theory, it is believed that adding PEG at the N-terminus or C-terminus of an exendin-4 derivative as described herein will not destabilize the alpha helix structure of the exendin-4 derivative or negatively affect binding affinity of the exendin-4 derivative to the GLP-1 receptor. Thus, in some embodiments, pegylation of
5 exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39) can improve the pharmacokinetic profile of the exendin-4 derivative, reducing the dosing frequency in patients, and/or reduce the amount of exendin-4 derivative that is needed for the treatment and prevention of hyperinsulinemic hypoglycemia.

10 Dosages and Administration

[0045] An exendin-4 derivative as described herein (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) may be administered at any therapeutically appropriate dose. In some embodiments, the exendin-4 derivative is administered at a dose of about 0.01 mg, about 0.05 mg, about 0.1
15 mg, about 0.5 mg, about 1 mg, about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg. In some embodiments, the exendin-4 derivative is administered at a dose in one of the following ranges (all inclusive of the lower and upper values): 0.01-50 mg, 0.01-10 mg, 0.1-50 mg, 0.1-10 mg, 0.1-1 mg, 0.5-50 mg, 0.5-10 mg, 0.5-5 mg, 1-10 mg, 1-20
20 mg, 2-20 mg, 4-40 mg, 10-75 mg, 20-50 mg, or 20-40 mg. In some embodiments, a therapeutically effective dose of an exendin-4 derivative or range of doses will vary depending upon the needs and physical attributes of the patient. It will be understood by a person of ordinary skill in the art that the doses described herein can be administered at varying concentrations.

25 [0046] In some embodiments, an exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) is administered at a dosage or range of doses as described herein twice a day (BID). In some embodiments, the exendin-4 derivative is administered BID at a dose in the range of about 0.01-50 mg, 0.01-10 mg, 0.1-50 mg, 0.1-10 mg, 0.1-1 mg, 0.5-50 mg, 0.5-10 mg, 0.5-5 mg, 1-
30 10 mg, 1-20 mg, 2-20 mg, 4-40 mg, 10-75 mg, 20-50 mg, or 20-40 mg. In some embodiments, the exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39),

exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) is administered at a dosage or range of doses as described herein once a day (QD). In some embodiments, the exendin-4 derivative is administered QD at a dose in the range of about 0.01-50 mg, 0.01-10 mg, 0.1-50 mg, 0.1-10 mg, 0.1-1 mg, 0.5-50 mg, 0.5-10 mg, 0.5-5 mg, 1-10 mg, 1-20 mg, 2-20 mg, 4-40 mg, 10-75 mg, 20-50 mg, or 20-40 mg. The exendin-4 derivative can be administered more often or less often, as appropriate. In some embodiments, the exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) is administered once per week (QW) or twice per week (BIW) at a dose in the range of about 0.01-50 mg, 0.01-10 mg, 0.1-50 mg, 0.1-10 mg, 0.1-1 mg, 0.5-50 mg, 0.5-10 mg, 0.5-5 mg, 1-10 mg, 1-20 mg, 2-20 mg, 4-40 mg, 10-75 mg, 20-50 mg, or 20-40 mg.

[0047] In some embodiments, the exendin-4 derivative as described herein (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) is administered at a total daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1 mg, about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg. In some embodiments, the exendin-4 derivative is administered at a total daily dose in the range of about 0.01-50 mg, about 0.01-10 mg, about 0.1-50 mg, about 0.1-10 mg, about 0.1-1 mg, about 0.5-50 mg, about 0.5-10 mg, about 0.5-5 mg, about 1-10 mg, about 1-20 mg, about 2-20 mg, about 4-40 mg, about 10-75 mg, about 20-50 mg, or about 20-40 mg.

[0048] In some embodiments, an exendin-4 derivative (e.g., exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39), or a pegylated form thereof) is administered prior to the administration of a meal. For example, in some embodiments, an exendin-4 derivative is administered within 60-150 minutes (e.g., within 90-120 minutes) prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). In some embodiments, an exendin-4 derivative is administered at least one hour prior to the morning meal. In some embodiments, the dosing schedule is semi-independent of mealtimes. For example, the morning dose can be administered on a predetermined schedule relative to the morning meal and the evening dose can be scheduled at a time independent of the time of the evening meal (e.g., about 12

hours after the morning administration without regard to the time of the evening meal). In some embodiments, the dosing schedule is independent of (i.e., not based on, or dictated by) the timing of meals.

[0049] In some embodiments, an exendin-4 derivative as described herein is administered via subcutaneous administration (e.g., subcutaneous injection). Sites of injection, include, but are not limited to, injection in the thigh, abdomen, upper arm region, or upper buttock region. In some embodiments, the exendin-4 derivative is subcutaneously administered twice a day (BID). In some embodiments, the exendin-4 derivative is subcutaneously administered once a day (QD). The exendin-4 derivative can be administered more often or less often, as appropriate. In some embodiments, the exendin-4 derivative is subcutaneously administered once per week (QW) or twice per week (BIW).

[0050] In some embodiments, an exendin-4 derivative as described herein is administered at a concentration of about 4-50 mg/mL, about 4-40 mg/mL, about 4-35 mg/mL, about 10-50 mg/mL, about 10-40 mg/mL, about 15-50 mg/mL, about 4-25 mg/mL, about 4-20 mg/mL, about 10-25 mg/mL, about 10-20 mg/mL, about 10-18 mg/mL, about 8-16 mg/mL, about 12-20 mg/mL, about 10-15 mg/mL, or about 13-16 mg/mL (e.g., about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 11 mg/mL, about 12 mg/mL, about 13 mg/mL, about 14 mg/mL, about 15 mg/mL, about 16 mg/mL, about 17 mg/mL, about 18 mg/mL, about 19 mg/mL, about 20 mg/mL, about 21 mg/mL, about 22 mg/mL, about 23 mg/mL, about 24 mg/mL, about 25 mg/mL, about 26 mg/mL, about 27 mg/mL, about 28 mg/mL, about 29 mg/mL, about 30 mg/mL, about 31 mg/mL, about 32 mg/mL, about 33 mg/mL, about 34 mg/mL, about 35 mg/mL, about 36 mg/mL, about 37 mg/mL, about 38 mg/mL, about 39 mg/mL, about 40 mg/mL, about 41 mg/mL, about 42 mg/mL, about 43 mg/mL, about 44 mg/mL, about 45 mg/mL, about 46 mg/mL, about 47 mg/mL, about 48 mg/mL, about 49 mg/mL, or about 50 mg/mL).

[0051] In some embodiments, the dose is administered in a total volume ranging from 0.25-2 ml injectate, e.g., an injection volume ranging from 0.5-1.5 ml or 0.7-1 ml. In some embodiments, the patient self-administers such a dose at least once a day (QD), and often twice a day (BID). In some embodiments, the patients administers such a dose with each meal, it being understood that "with each meal" typically refers to a set period (at least 60

minutes, for example) before a meal, e.g., the first or last meal of the day. In some embodiments, the patient self-administers such a dose once per week (QW) or twice per week (BIW).

Duration of Treatment and Treatment Outcomes

5 [0052] Patients may receive therapy for a predetermined time, an indefinite time, or until an endpoint is reached. Treatment may be continued on a continuous daily or weekly basis for at least two to three months. In some embodiments, therapy is for at least 30 days, at least 60 days, at least 90 days, at least 120 days, at least 150 days, or at least 180 days. In some embodiments, treatment is continued for at least 6 months, at least 7 months, at least 10 8 months, at least 9 months, at least 10 months, at least 11 months, or at least one year. In other embodiments, treatment is continued for the rest of the patient's life or until administration is no longer effective in maintaining normal plasma glucose levels to provide meaningful therapeutic benefit.

[0053] In some embodiments, patients treated according to the methods of the invention 15 exhibit an improvement in one or more symptoms of hypoglycemia, including but not limited to neuroglycopenic symptoms, beta-adrenergic symptoms, or plasma glucose levels.

[0054] In some embodiments, treatment in a patient refers to treatment such that the postprandial plasma glucose nadir is maintained above a concentration of approximately 55 mg/dl (3.0 mmol/liter) based upon the Endocrine Society's Clinical Guidelines (*Journal of 20 Clinical Endocrinology & Metabolism*, March 2009, 94(3): 709-728), and symptoms of hypoglycemia are reduced. Ideally, normal plasma glucose concentrations are maintained, with those skilled in the art recognizing that in humans a plasma glucose level of 65 mg/dl or greater is preferred.

[0055] In some embodiments, treatment in a patient refers to treatment such that at least 25 a 15% increase in postprandial plasma glucose nadir is achieved relative to baseline (e.g., before the onset of treatment). In some embodiments, treatment in a patient refers to treatment such that for a patient having a postprandial plasma glucose nadir ≤ 50 mg/dl at baseline (e.g., before the onset of treatment), an increase in postprandial plasma glucose nadir to ≥ 55 mg/dl is achieved relative to baseline.

[0056] Plasma glucose nadir can be measured, for example, by oral glucose tolerance test (OGTT), by meal tolerance test (MTT), or by continuous glucose monitoring (CGM). In some embodiments, treatment in a patient refers to treatment such that a statistically significant decrease in the severity of one or more symptoms of hypoglycemia overall during OGTT, MTT, or CGM and/or of neuroglycopenic symptoms elicited during the glucose "fall" period of OGTT, MTT, or CGM is achieved relative to baseline (e.g., before the onset of treatment).

IV. COMPOSITIONS AND KITS

[0057] In another aspect, pharmaceutical compositions for the treatment or prevention of hyperinsulinemic hypoglycemia are provided. In some embodiments, the pharmaceutical composition comprises exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39). In some embodiments, the pharmaceutical composition comprises a pegylated form of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39).

[0058] In some embodiments, the present disclosure provides for pharmaceutical compositions in which the exendin-4 derivative is formulated (e.g., into a preparation for injection) by dissolving, suspending or emulsifying the exendin-4 derivative in an aqueous or non-aqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and optionally, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. In some embodiments, an exendin-4 derivative (e.g., pegylated or unpegylated exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), or exendin(8-39)) is formulated with a pharmaceutically acceptable diluent or carrier that is suitable for subcutaneous administration. Examples of pharmaceutically acceptable diluents or carriers include, but are not limited to, water, saline, and isotonic buffer solutions. In some embodiments the pharmaceutical composition further comprises one or more additional excipients such as preservatives, tonicity-modifying agents, and pH adjustment agents. In some embodiments, the exendin-4 derivative is formulated in normal saline (0.9% saline), and optionally further comprises one or more preservatives, tonicity-modifying agents, and/or pH adjustment agents.

[0059] In some embodiments, an exendin-4 derivative as described herein is formulated for immediate release (e.g., immediate subcutaneous release) using art-known methods. In some embodiment, an exendin-4 derivative as described herein is formulated for extended release (e.g., extended subcutaneous release) using art-known methods.

5 [0060] In some embodiments, a pharmaceutical composition comprising an exendin-4 derivative as disclosed herein is formulated as a sterile, preserved isotonic solution in a unit or multi-dose glass vial or ampule for administration with the use of a syringe, similar to the glucagon emergency kit. In some embodiments, a pharmaceutical composition comprising an exendin-4 derivative as disclosed herein is formulated as a sterile, preserved isotonic
10 solution in a glass cartridge pen-injector device. In some embodiments, a pharmaceutical composition comprising an exendin-4 derivative as disclosed herein is formulated as an injectable suspension in a single-dose pen containing exendin(9-39), a diluent, and one or more needles.

[0061] In some embodiments, a pharmaceutical composition comprising an exendin-4
15 derivative as disclosed herein is conveniently packaged, for example, in the form of the dual-chamber pen device provided by the invention, for patients or their care providers to administer therapeutically effective amounts in doses ranging from 0.01-50 mg, e.g., 0.01-10 mg, 0.01-1 mg, 0.1-10 mg, or 0.1-1 mg. In some embodiments, an exendin-4 derivative as described herein is formulated and administered in an injectable pen device that may be
20 pre-programmed to deliver a fixed dosage amount ranging from 0.01-50 mg, e.g., 0.01-10 mg, 0.01-1 mg, 0.1-10 mg, or 0.1-1 mg, depending upon the needs and physical attributes of the patient. Typically, most adult patients (60-100 kg or more) will receive therapeutic benefit from a single dose in the range of 0.01-10 mg, with some achieving full therapeutic effect with 0.1-1 mg. If necessary, dosing may be initiated at lower doses, and maintained if
25 efficacious or alternatively increased stepwise if an enhanced dose response is desired. For especially small patients, for example in the case of children or infants, a dose as low as 0.05 mg or less might be employed. In some instances, for example in the case of altered subcutaneous absorption or metabolism, doses outside of this range may be warranted.

[0062] In another aspect, kits for the treatment or prevention of hyperinsulinemic
30 hypoglycemia are provided. In some embodiments, the kit comprises unit dose forms of the

exendin-4 derivative, e.g., a sterile, preserved isotonic solution comprising a unit dose of the exendin-4 derivative (e.g., a dose in the range of 0.01 mg to 50 mg, e.g., 0.01-10 mg, 0.01-1 mg, 0.1-10 mg, or 0.1-1 mg). In some embodiments, the kit further comprises one or more delivery devices, e.g., a syringe or an injectable pen device. In some embodiments, a kit
 5 comprises a plurality of individual injectable pen devices (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pens in a kit). In some embodiments, the kit comprises two or more individual injectable pen devices that are pre-programmed to deliver a fixed dosage amount of an exendin-4 derivative as disclosed herein (e.g., a dose in the range of 0.01 mg to 50 mg, e.g., 0.01-10 mg, 0.01-1 mg, 0.1-10 mg, or 0.1-1 mg). In some embodiments, the kit further
 10 comprises instructions for use (e.g., for administering according to a method as described herein).

EXAMPLES

[0063] The following examples are provided to illustrate, but not to limit, the claimed invention.

15 Example 1. Evaluation of Exendin(5-39) and Pegylated Exendin(5-39)

[0064] This prophetic example describes a protocol for evaluating the agonistic and antagonistic activities and pharmacokinetic profiles of exendin(5-39) and pegylated exendin(5-39) for human GLP-1 receptor. The exendin(5-39) peptides to be evaluated are as follows:

20 Pegylated Exendin 5-39: (PEG)-TFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS
 Exendin 5-39: TFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS

[0065] The exendin(5-39) and pegylated exendin(5-39) peptides are tested for agonistic and antagonistic activities for human GLP-1 receptor in cell culture. Exendin-4 and
 25 exendin(9-39) are used as control compounds in the cell culture studies. GLP-1 receptor binding affinity is tested in *in vitro* assays using cell lines that express human GLP-1 receptor.

[0066] The improvement in pharmacokinetic parameters for exendin(5-39) and pegylated exendin(5-39) is tested in one or more animal models (e.g., in rat). Exendin-4 and exendin(9-39) are used as control compounds.

[0067] In some embodiments, exendin(5-39) and pegylated exendin(5-39) exhibits better antagonistic activity without agonistic activity for GLP-1 receptor as compared to exendin(9-39). In some embodiments, the pharmacokinetic profiles that are obtained for exendin(5-39) and pegylated exendin(5-39) support the use of a lower dose as compared to exendin(9-39) (e.g., a dose that is 10x lower than is used for exendin(9-39), and/or support the use of less frequent dosing as compared to exendin(9-39) (e.g., once weekly or twice weekly dosing) in a patient in need thereof.

Example 2. *In Vitro* Pharmacology Study of Exendin(5-39), Pegylated Exendin(5-39), Exendin(9-39), and Pegylated Exendin(9-39)

[0068] This example describes a study that tested the peptides exendin(5-39), pegylated exendin(5-39), exendin(9-39), and pegylated exendin(9-39) in *in vitro* cellular functional assays.

[0069] The agonistic and antagonistic effects of each of the four peptides on the receptor GLP-1 was tested in β TC6 cells, which are cells that endogenously express the mouse GLP-1 receptor, in a cAMP functional assay.

[0070] For the agonist assay, exendin(5-39), pegylated exendin(5-39), exendin(9-39), and pegylated exendin(9-39) were dissolved at a concentration of 10 mM in PBS. Cells were incubated with exendin(5-39), pegylated exendin(5-39), exendin(9-39), or pegylated exendin(9-39) for 10 minutes at room temperature. Following the incubation period, the resulting intracellular level of cAMP was measured by homogenous time resolved fluorescence (HTRF). None of the four peptides exhibited agonistic activity on the human GLP-1 receptor.

[0071] For the antagonist assay, exendin(5-39), pegylated exendin(5-39), exendin(9-39), and pegylated exendin(9-39) were dissolved at a concentration of 10 mM in PBS; exendin(5-39) and exendin(9-39) were also dissolved at a concentration of 1 mM in DMSO. Cells were stimulated with 0.3 nM glucagon-like peptide 1 (7-37) [GLP-1 (7-37)], a ligand of the GLP-1 receptor, and incubated with exendin(5-39), pegylated exendin(5-39), exendin(9-39), or pegylated exendin(9-39) for 10 minutes at room temperature. Following the incubation period, the resulting intracellular level of cAMP was measured by HTRF. Overall, exendin(5-39) and exendin(9-39) were found to have comparable antagonistic activity on the human

GLP-1 receptor. When exendin(5-39) and exendin(9-39) were dissolved in PBS, exendin(5-39) was about 3 times more potent than exendin(9-39) at blocking the human GLP-1 receptor. When exendin(5-39) and exendin(9-39) were dissolved in DMSO, exendin(9-39) was about four times more potent than exendin(5-39) at blocking the human GLP-1 receptor. See Table 1 below. Pegylated exendin(5-39) and pegylated exendin(9-39) did not exhibit significant antagonistic activity on the human GLP-1 receptor.

Table 1. IC₅₀ results for GLP-1 antagonist assay

Peptide	IC ₅₀	K _B
Exendin(9-39) in PBS	8.9E-08 M	1.7E-08 M
Exendin(9-39) in DMSO	1.5E-09 M	2.9E-10 M
Exendin(5-39) in PBS	3.1E-08 M	6.1E-09 M
Exendin(5-39) in DMSO	6.3E-09 M	1.2E-09 M

[0072] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0073] It should be understood that although the present invention has been specifically disclosed by certain aspects, embodiments, and optional features, modification, improvement and variation of such aspects, embodiments, and optional features can be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this disclosure.

[0074] The inventions have been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

WHAT IS CLAIMED IS:

1. A method of preventing or treating hyperinsulinemic hypoglycemia or associated acute or chronic symptoms or outcomes thereof, the method comprising administering an exendin-4 derivative to a patient in need thereof, wherein the exendin-4 derivative is selected from the group consisting of exendin(3-39), exendin(4-39), exendin(5-39), exendin(6-39), exendin(7-39), and exendin(8-39).
2. The method of claim 1, wherein the exendin-4 derivative is exendin(5-39).
3. The method of claim 1 or 2, wherein the exendin-4 derivative is pegylated.
4. The method of any of claims 1 to 3, wherein the exendin-4 derivative is subcutaneously administered.
5. The method of any of claims 1 to 4, wherein the patient has previously had bariatric surgery.
6. The method of claim 5, wherein the patient has previously had a surgery selected from the group consisting of Roux-en-Y Gastric Bypass, Vertical Sleeve Gastrectomy, placement of an endosleeve device, duodenal mucosal resurfacing, partial bypass of the duodenum, vagal nerve blockade, and pyloroplasty.
7. The method of any of claims 1 to 4, wherein the patient has previously had gastrointestinal surgery.
8. The method of any of claims 1 to 4, wherein the patient has congenital hyperinsulinemic hypoglycemia.
9. The method of any of claims 1 to 8, wherein the exendin-4 derivative is administered at a dose of about 0.01 mg to about 50 mg.
10. The method of claim 9, wherein the exendin-4 derivative is administered at a dose of about 0.5 mg to about 30 mg.

11. The method of claim 9, wherein the exendin-4 derivative is administered at a dose of about 0.01 mg to about 1 mg.
12. The method of any of claims 1 to 11, wherein the exendin-4 derivative is administered once per day.
13. The method of any of claims 1 to 11, wherein the exendin-4 derivative is administered twice per day.
14. The method of any of claims 1 to 11, wherein the exendin-4 derivative is administered once per week or twice per week.
15. The method of claim 1, wherein the exendin-4 derivative is exendin(5-39) and wherein the exendin(5-39) is subcutaneously administered at a dose of 0.5 mg to 30 mg BID.
16. The method of claim 1, wherein the exendin-4 derivative is exendin(5-39) and wherein the exendin(5-39) is subcutaneously administered at a dose of 0.1 mg to 1 mg BID.
17. The method of claim 1, wherein the exendin-4 derivative is pegylated exendin(5-39) and wherein the pegylated exendin(5-39) is subcutaneously administered at a dose of 0.5 mg to 30 mg once per week (QW) or twice per week (BIW).
18. The method of claim 1, wherein the exendin-4 derivative is pegylated exendin(5-39) and wherein the pegylated exendin(5-39) is subcutaneously administered at a dose of 0.1 mg to 1 mg once per week (QW) or twice per week (BIW).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/20596

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 38/16, A61P 11/00, A61P 19/02 (2017.01)
 CPC - C07K 14/57563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/0368311 A1 (SANOFI) 24 December 2015 (24.12.2015); para [0001], [0137], [0142], [0241], claim 1, claim 15	1-3 and 15-18
Y	THANTHAN et al, Glucagon-like peptide-1 inhibits insulinotropic effects of oxyntomodulin and glucagon in cattle, Domestic Animal Endocrinology, 2012, Vol. 42, pages 155-164; Abstract; p.163, col 2, para 1	1-3 and 15-18
Y	US 2015/0274800 A1 (AMUNIX OPERATING INC.) 1 October 2015 (01.10.2015); para [0124]	3, 17, 18

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
 2 May 2017

Date of mailing of the international search report

26 MAY 2017

Name and mailing address of the ISA/US
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 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/20596

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-14
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.