

INSULIN RECEPTOR MODULATION FOR TUMOR ASSOCIATED HYPERINSULINISM**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] The present application claims the priority benefit of US Provisional Patent Application No. 63/552,089, filed February 9, 2024, hereby incorporated by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE DISCLOSURE

[0002] The Sequence Listing, which is a part of the present disclosure, is submitted concurrently with the specification as a computer readable file. The name of the file containing the Sequence Listing is "59732_SeqListing.xml", which was created on February 4, 2025, and is 9,868 bytes in size. The subject matter of the Sequence Listing is incorporated herein in its entirety by reference.

FIELD

[0003] The present disclosure, relates, in general, to the treatment of hypoglycemia and hyperinsulinism associated with cancers using antagonists or allosteric antagonists, such as antibodies, against the insulin receptor.

BACKGROUND

[0004] Insulin receptor isoform A (INSR-A) and insulin receptor isoform B (INSR-B) involved signaling is involved in cellular metabolism and cellular proliferation via insulin, proinsulin, as well as insulin like growth factor 1 (IGF-1) or insulin like growth factor 2 (IGF-2) signaling. Insulin, proinsulin, IGF-1, IGF-2 (e.g., big IGF-2 and other IGF-2 variants), or prohormone precursors (or variants) of IGF-1 or IGF-2 induce cellular metabolism and growth intracellular signaling pathways by binding to homodimers and heterodimers of the INSR-A, INSR-B and Insulin growth factor 1 receptor (IGFR-1) receptors. When insulin binds to the INSR -A or INSR -B, the receptor is activated by tyrosine autophosphorylation and the INSR tyrosine kinase phosphorylates various effector molecules leading to impacts on glucose metabolism and cellular survival and proliferation (Ullrich et al, Nature 313: 756-761, 1985; Goldfine et al, Endocrine Reviews 8: 235-255, 1987; White and Kahn, Journal Biol. Chem. 269: 1-4, 1994).

SUMMARY

[0005] The present disclosure describes the use of an anti-insulin receptor antagonists, such as an antibody (anti INSR-A and INSR-B) to prevent or decrease INSR-A or INSR-B involved signaling by insulin, proinsulin, autoantibodies against the INSR, IGF-1, IGF-2 or prohormone precursors (variants) of IGF-1 or IGF-2. The disclosure is useful for a variety of applications including the treatment of benign or malignant neoplasms associated with

hyperinsulinism and hypoglycemia, either as a stand-alone anti-neoplastic or as an adjuvant therapy, or the anti-insulin receptor antibody may also be used as a treatment for associated metabolic consequences of excessive INSR signaling (tumor associated hyperinsulinism), such as hypoglycemia, resulting from the neoplastic production and secretion of insulin, proinsulin, IGF-1, IGF-2, or prohormone precursor variants of any of these peptide hormones.

[0006] Provided herein is a method of treating benign or malignant neoplasms comprising administering an antibody to a subject in need thereof that specifically binds insulin receptor (INSR) or another antagonist of insulin receptor signaling.

[0007] In various embodiments, the antibody or other antagonist of insulin receptor signaling is administered to a subject in need thereof in combination with anti-neoplastic therapies or other therapeutics used to treat hypoglycemia or hyperinsulinism.

[0008] In various embodiments, the neoplasm is associated with a solid tumor. In various embodiments, the neoplasm is selected from the group consisting of adrenal gland cancer, AIDS-associated cancer, alveolar soft part sarcoma, anal cancer, bladder cancer, bone cancer, brain and spinal cord cancer, breast cancer, carotid body tumor, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, desmoplastic small round cell tumor, ependymoma, endometrial cancer (including, unselected endometrial cancer, MSI-high endometrial cancer, dMMR endometrial cancer, and/or POLE exonuclease domain mutation positive endometrial cancer), Ewing's sarcoma, extraskeletal myxoid chondrosarcoma, gallbladder or bile duct cancer (including, cholangiocarcinoma bile duct cancer), gastric cancer, gastroesophageal junction (GEJ) cancer, gestational trophoblastic disease, germ cell tumor, glioblastoma, head and neck cancer, a hematological malignancy, a hepatocellular carcinoma, islet cell tumor, insulinoma, Kaposi's Sarcoma, kidney cancer, leukemia, liposarcoma/malignant lipomatous tumor, liver cancer, lymphoma, lung cancer, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesothelioma, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancer, papillary thyroid carcinoma, parathyroid tumor, pediatric cancer, peripheral nerve sheath tumor, pharyngeal cancer, pheochromocytoma, pituitary tumor, prostate cancer, posterior uveal melanoma, renal metastatic cancer, rhabdoid tumor, rhabdomyosarcoma, sarcoma, skin cancer, a small round blue cell tumor of childhood, soft-tissue sarcoma, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, and uterine cancer.

[0009] In various embodiments, the benign or malignant neoplasm results in tumor associated hyperinsulinism and hypoglycemia that is mediated through excess INSR signaling by an insulin-like substance. In various embodiments, the insulin-like substance is insulin, proinsulin, INSR autoantibodies, other insulin-like peptides, hormones, or effector substances. In various embodiments, the other insulin-like peptides, hormones or effector substances are selected from the group consisting of insulin-like growth hormone 1 (IGF-1) or its precursors, IGF-1 prohormones, IGF-1 variants, insulin-like growth hormone-2 (IGF-2) or its precursors, IGF-2 prohormones, and IGF-2 variants. In certain embodiments, the IGF-2 variant is Big IGF.

[0010] Also provided is a method of treating tumor-associated hyperinsulinism and hypoglycemia induced by benign or malignant neoplasms comprising administering to a subject in need thereof an antibody that specifically binds insulin receptor (INSR).

[0011] Further contemplated is a method of treating tumor-associated hyperinsulinism and hypoglycemia induced by benign or malignant neoplasms comprising administering to a subject in need thereof a compound that specifically binds insulin receptor (INSR).

[0012] In various embodiments, the antibody or compound that binds the insulin receptor inhibits or alters signaling through the insulin receptor.

[0013] In various embodiments, the benign or malignant neoplasm is selected from the group consisting of: non-islet cell tumor hypoglycemia (NICTH), non-islet cell tumor hyperinsulinism (NICTHI), Doege-Potter syndrome, insulinoma, ectopic insulinoma, IGF2-oma, pro-insulinoma, pancreatic neuroendocrine tumors, non-pancreatic neuroendocrine tumors, mesenchymal tumors, adrenal carcinoma, hepatocellular carcinoma, gastrointestinal carcinoma, ovarian carcinoma, pheochromocytoma, sarcomas, lymphomas, leukemias, and small-cell lung carcinomas.

[0014] In various embodiments, the neoplasm is a primary tumor or is metastatic. In various embodiments, the neoplasm is a metastatic neoplasm.

[0015] In various embodiments, the neoplasm exhibits an overproduction of insulin, proinsulin, IGF2, big IGF2, or IGF2 variants. In various embodiments, the tumor associated hyperinsulinism and resulting hypoglycemia are mediated through excess INSR signaling by an insulin-like substance. In various embodiments, the insulin-like substance is insulin, proinsulin, INSR autoantibodies, other insulin-like peptides, hormones, or effector substances. In various embodiments, the other insulin-like peptides, hormones or effector substances are selected from the group consisting of insulin-like growth hormone 1 (IGF-1) or its precursors, IGF-1 prohormones, IGF-1 variants, insulin-like growth hormone-2 (IGF-2)

or its precursors, IGF-2 prohormones, and IGF-2 variants. In certain embodiments, the IGF-2 variant is Big IGF-2.

[0016] In various embodiments, the anti-INSR antibody comprises: (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

[0017] In various embodiments, the anti-INSR antibody comprises, a. a light chain variable domain comprising a sequence of amino acids at least 80% identical to SEQ ID NO: 2; or b. a heavy chain variable domain comprising a sequence of amino acids that is at least 80% identical to SEQ ID NO: 1; or, c. a light chain variable domain of (A) and a heavy chain variable domain of (B).

[0018] In various embodiments, the anti-INSR antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

[0019] In various embodiments, the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0020] In various embodiments, the anti-INSR antibody is an IgG2 antibody.

[0021] In various embodiments, the anti-INSR antibody is RZ358. In various embodiments, RZ358 comprises (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2; or a

heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0022] The antibody as used in the methods herein in some embodiments comprises or consists of two heavy chains and two light chains connected by disulfide bonds, wherein each heavy chain comprises the heavy chain constant region, heavy chain variable region or CDR sequences mentioned above, and each light chain comprises the light chain constant region, light chain variable region or CDR sequences mentioned above, wherein the C-terminus of the heavy chain variable region is linked to the N-terminus of the heavy chain constant region, and the C-terminus of the light chain variable region is linked to the N-terminus of the light chain constant region, wherein the antibody binds to insulin receptor isoform A or insulin receptor isoform B. The antibody of the disclosure can be a full-length antibody, for example, of an IgG1, IgG2 or IgG4 isotype. The antibody disclosed herein for use in the methods, in other embodiments, may be a single chain antibody, or consists of antibody fragments, such as an individual Fab or two conjugated Fab fragments.

[0023] In various embodiments, the present disclosure provides a method for treating a subject suffering from a disease or condition as described herein. The method comprises administering to the subject the compound described herein. Also contemplated is a method for treating a condition of tumor-associated hyperinsulinism and resulting hypoglycemia due to the production of insulin or other insulin-like substances from the tumor that act on the INSR in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition comprising the anti-INSR antibody as described herein.

[0024] In various embodiments, the composition is administered daily, every 2 days, every 3 days, weekly, every 2 weeks, every 3 weeks, twice monthly, every 4 weeks, monthly, every 5 weeks, every 6 weeks, every 2 months, every 3 months or every 6 months. In various embodiments, the composition is administered for a period of at least 4 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 9 months, 1 year or more. In various embodiments, the composition is administered intravenously. In various embodiments, the composition is administered subcutaneously.

[0025] In various embodiments, from 3-12 mg/kg anti-INSR antibody is administered to the subject. In various embodiments, the subject is administered 9 mg/kg anti-INSR antibody weekly, bi-weekly, every 3 weeks or every 4 weeks.

[0026] In various embodiments, the antagonist of INSR signaling, e.g., an anti-INSR antibody, alleviates one or more symptoms associated with hypoglycemia or hyperinsulinism resulting from cancer in a subject. In various embodiments the symptoms are selected from the group consisting of anxiety, abnormal hunger, abnormal fatigue, overeating, psychiatric

symptoms associated with low blood sugar, lack of coordination, sweating, fatigue, weakness, headache, palpitations, confusion, somnolence, loss of consciousness, seizures, and coma.

[0027] In various embodiments, the subject is still receiving a standard of care therapy for treating hypoglycemia. In various embodiments, the standard of care therapy is selected from the group consisting of intravenous dextrose, parenteral nutrition, short-acting glucagon injections, continuous glucagon infusions, diazoxide, SSAs, corticosteroids, mTOR inhibitors, supplemental enteral carbohydrates (tube feeding), and uncooked corn starch.

[0028] In various embodiments, the administration results in a decrease in need for or use of standard of care therapies. In various embodiments, the administration eliminates need for or use of standard of care therapies.

[0029] It is contemplated that the methods herein reduce tumor size, or tumor burden in the subject, and/or reduce metastasis in the subject. In various embodiments, the methods reduce the tumor size by 10%, 20%, 30% or more. In various embodiments, the methods reduce tumor size by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100%.

[0030] It is further provided that the methods herein reduce tumor burden, and also reduce or prevent the recurrence of tumors once the cancer has gone into remission.

[0031] In various embodiments, the administration results in a decrease from baseline in overall hypoglycemia events compared to the rate of hypoglycemia episodes experienced prior to administration of therapy.

[0032] In various embodiments, the administration results in a decrease from baseline in Level 2 and/or Level 3 hypoglycemia events compared to the administration of standard of care therapy.

[0033] Use of any of the foregoing antibodies or compounds described herein that bind the insulin-INSR signaling interaction in preparation of a medicament for treatment of any of the disorders described herein (e.g., a benign or malignant neoplasm that results in tumor associated hyperinsulinism and hypoglycemia) is also contemplated. Also contemplated is a composition comprising antibodies or compounds described herein that bind the insulin-INSR for use in treatment of any of the disorders described herein. Syringes, e.g., single use or pre-filled syringes, sterile sealed containers, e.g., vials, bottle, vessel, and/or kits or packages comprising any of the foregoing antibodies or polypeptides, optionally with suitable instructions for use, are also provided.

[0034] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the invention and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as “one embodiment”, “some embodiments”, “certain embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of embodiments is a nonlimiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the invention. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned. The headings herein are for the convenience of the reader and not intended to be limiting. Additional aspects, embodiments, and variations of the invention will be apparent from the Detailed Description and/or Drawings and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] Figure 1 shows the amino acid sequence of the RZ358 antibody CDRs, variable regions, and full length heavy and light chain.

[0036] Figure 2 shows the effect of RZ358 on IGF2 signaling through the insulin receptor.

[0037] Figure 3 illustrates a phase 3 protocol for treating tumor associated hyperinsulinemia.

DETAILED DESCRIPTION

[0038] The present disclosure provides for the use of antibodies specific for the insulin receptor, e.g., RZ358, to treat neoplastic growth and tumor-associated hyperinsulinism or hypoglycemia associated with excessive insulin receptor signaling.

[0039] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure include, but are not limited to: Singleton et al., *DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY* (2d Ed. 1994); *THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY* (Walker Ed., 1988); *THE GLOSSARY OF GENETICS*, 5th Ed., R. Rieger et al. (Eds.), Springer Verlag (1991); and Hale & Marham, *THE HARPER COLLINS DICTIONARY OF BIOLOGY* (1991).

[0040] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth.

[0041] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range.

[0042] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0043] The terms "treat", "treating" and "treatment" refer to the amelioration or eradication of a disease or symptoms associated with a disease. In various embodiments, the terms refer to minimizing or slowing the spread, progression, or worsening of the disease resulting from the administration of one or more prophylactic or therapeutic compounds described herein to a patient with such a disease.

[0044] The terms "prevent," "preventing," and "prevention" refer to the prevention of the onset, recurrence, or spread of the disease in a patient resulting from the administration of a compound described herein.

[0045] The term "effective amount" refers to an amount of a compound as described herein or other active ingredient sufficient to provide a therapeutic or prophylactic benefit in the treatment or prevention of a disease or to delay or minimize symptoms associated with a disease. Further, a therapeutically effective amount with respect to a compound as described herein means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or prevention of a disease. Used in connection with a compound as described herein, the term can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease, or enhances the therapeutic efficacy of or is synergistic with another therapeutic agent.

[0046] A "patient" or "subject" includes an animal, such as a human, monkey, cow, horse, sheep, lamb, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig. In

accordance with some embodiments, the animal is a mammal such as a non-primate and a primate (e.g., monkey and human). In one embodiment, a patient is a human, such as a human infant, child, adolescent or adult. In the present disclosure, the terms “patient” and “subject” are used interchangeably.

[0047] The term “antibody” is used in the broadest sense and includes fully assembled antibodies, tetrameric antibodies, monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), antibody fragments that can bind an antigen (e.g., Fab', F(ab)2, Fv, single chain antibodies, diabodies), and recombinant peptides comprising the foregoing as long as they exhibit the desired biological activity. An “immunoglobulin” or “tetrameric antibody” is a tetrameric glycoprotein that consists of two heavy chains and two light chains, each comprising a variable region and a constant region. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antibody fragments or antigen-binding portions include, inter alia, Fab, Fab', F(ab')2, Fv, domain antibody (dAb), complementarity determining region (CDR) fragments, CDR-grafted antibodies, single-chain antibodies (scFv), single chain antibody fragments, chimeric antibodies, diabodies, triabodies, tetrabodies, minibody, linear antibody; chelating recombinant antibody, a tribody or bibody, an intrabody, a nanobody, a small modular immune pharmaceutical (SMIP), an antigen-binding-domain immunoglobulin fusion protein, a camelized antibody, a VHH containing antibody, or a variant or a derivative thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as one, two, three, four, five or six CDR sequences, as long as the antibody retains the desired biological activity. “Monoclonal antibody” refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. “Antibody variant” as used herein refers to an antibody polypeptide sequence that contains at least one amino acid substitution, deletion, or insertion in the variable region of the natural antibody variable region domains. Variants may be substantially homologous or substantially identical to the unmodified antibody.

[0048] A “chimeric antibody,” as used herein, refers to an antibody containing sequence derived from two different antibodies (see, e.g., U.S. Patent No. 4,816,567) which typically originate from different species. Most typically, chimeric antibodies comprise human and rodent antibody fragments, generally human constant and mouse variable regions. A “neutralizing antibody” is an antibody molecule which is able to eliminate or significantly reduce a biological function of an antigen to which it binds. Accordingly, a “neutralizing” antibody is capable of eliminating or significantly reducing a biological function, such as

enzyme activity, ligand binding, or intracellular signaling. "Heavy chain variable region" as used herein refers to the region of the antibody molecule comprising at least one complementarity determining region (CDR) of said antibody heavy chain variable domain. The heavy chain variable region may contain one, two, or three CDR(s) of said antibody heavy chain. "Light chain variable region" as used herein refers to the region of an antibody molecule, comprising at least one complementarity determining region (CDR) of said antibody light chain variable domain. The light chain variable region may contain one, two, or three CDR(s) of said antibody light chain, which may be either a kappa or lambda light chain depending on the antibody.

[0049] As used herein, an antibody that "specifically binds" is "antigen specific", is "specific for" antigen target or is "immunoreactive" with an antigen refers to an antibody or polypeptide binding agent used herein that binds an antigen with greater affinity than other antigens of similar sequence. In one aspect, the antibody, or fragments, variants, or derivatives thereof, will bind with a greater affinity to human antigen as compared to its binding affinity to similar antigens of other, i.e., non-human, species, but polypeptide binding agents that recognize and bind orthologs of the target are within the scope of the methods. For example, a polypeptide binding agent that is an antibody or fragment thereof "specific for" its cognate antigen indicates that the variable regions of the antibodies recognize and bind the desired antigen with a detectable preference (e.g., where the desired antigen is a polypeptide, the variable regions of the antibodies are able to distinguish the antigen polypeptide from other known polypeptides of the same family, by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between family members). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule.

[0050] Screening assays to determine binding specificity of a polypeptide binding agent, e.g., antibody, for use in the methods herein are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies for use in the methods can be produced using any method known in the art. The term "epitope" refers to that portion of any molecule capable of being recognized by and bound by a selective binding agent at one or more of the antigen binding regions. Epitopes usually consist of chemically active surface groupings of molecules, such as, amino acids or carbohydrate side chains, and have specific three-dimensional structural characteristics as

well as specific charge characteristics. Epitopes as used herein may be contiguous or noncontiguous.

[0051] Monoclonal antibodies may be modified for use as therapeutics or diagnostics. One embodiment is a "chimeric" antibody in which a portion of the heavy (H) and/or light (L) chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies, so long as they exhibit the desired biological activity. See U.S. Pat. No. 4,816,567; Morrison et al., 1985, Proc. Natl. Acad. Sci. 81:6851-55.

[0052] In another embodiment, a monoclonal antibody is a "humanized" antibody. Methods for humanizing non-human antibodies are well known in the art. See U.S. Pat. Nos. 5,585,089 and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. Humanization can be performed, for example, using methods described in the art (Jones et al., 1986, Nature 321:522-25; Riechmann et al., 1998, Nature 332:323-27; Verhoeyen et al., 1988, Science 239:1534-36), by substituting at least a portion of a rodent complementarity-determining region for the corresponding regions of a human antibody.

[0053] Chimeric, CDR grafted, and humanized antibodies and/or antibody variants are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (e.g., human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

[0054] The term "insulin-like substance" as used herein refers to molecules that signal through the insulin receptor such as insulin, proinsulin, INSR autoantibodies, other insulin-like peptides, hormones, or effector substances. Other insulin-like peptides, hormones or effector substances include insulin-like growth hormone 1 (IGF-1) or its precursors, IGF-1 prohormones, IGF-1 variants, insulin-like growth hormone-2 (IGF-2) or its precursors, IGF-2 prohormones, and IGF-2 variants.

Anti-INSR Antibodies

[0055] Provided herein are methods of use of anti-INSR antibodies that negatively modulate insulin receptor activity as disclosed in U.S. Patents 9,944,698, 10,253,101 and 11,261,247, incorporated herein by reference. These negative modulator antibodies

allosterically bind to the insulin receptor at a site that does not interfere with insulin binding, but that weakens the binding and signaling of effector substances such as insulin or insulin-like substances through the insulin receptor. Accordingly, in one aspect, the disclosure pertains to use of an isolated antibody or an antigen-binding portion thereof binding to the extracellular portion of either insulin receptor isoform A or insulin receptor isoform B.

[0056] RZ358 is a monoclonal antibody specific for insulin receptor (INSR) that binds allosterically to INSR and modulates binding of insulin or insulin-like substances to the insulin receptor without blocking the binding of insulin to the insulin receptor. In a Phase 1 trial, RZ358 was shown to reduce glucose levels in healthy volunteers (Johnson et al., J Clin Endocrinol Metab. 2017 102(8):3021-3028), and in a later study shown to reduced daily periods of hypoglycemia and correct nighttime hypoglycemia in Post Gastric Bypass Hypoglycemia (PGBH) Patients (Hu et al., Journal of the Endocrine Society, Volume 5, Issue Supplement 1, April-May 2021, Pages A328–A329). A recent Phase 2b trial demonstrated improvements in hypoglycemia in congenital hyperinsulinism (CHI) patients receiving antibody therapy (Thornton et al., *RZ358 in Congenital Hyperinsulinism: Results from a Multi-Center, Global, Phase 2b Study (RIZE)*, Pediatric Endocrine Society Annual Meeting 2022).

[0057] In various embodiments, the disclosure provides an antibody or fragment thereof comprising three heavy chain CDRs having the amino acid sequence set out in SEQ ID NOs: 3-5 and three light chain CDRs have the amino acid sequences set out in SEQ ID NOs: 6-8. In various embodiments, the antibody or fragment thereof binds to i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or (iii) a complex comprising insulin-like substances such as IGF-1, IGF-2 or variants and the insulin receptor, both (i) and (ii), or both (i) and (iii).

[0058] In various embodiments, the antibody comprises a polypeptide having an amino acid sequence at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain variable region set out in SEQ ID NO: 1 and an amino acid sequence at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain variable region set out in SEQ ID NO: 2, the antibody further comprising at least one, two, three, four, five or all of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3 set out in SEQ ID NOs: 3-8, respectively.

[0059] In various embodiments, the anti-INSR antibody or fragment thereof comprises a heavy chain variable region amino acid sequence is set out in SEQ ID NO: 1, and a light chain variable region amino acid sequence is set out in SEQ ID NO: 2.

[0060] In exemplary instances, the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0061] Also contemplated is an antibody or antibody variant that binds INSR comprising (A) a heavy chain variable domain selected from the group consisting of: (i) a sequence of amino acids at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:1; (ii) a sequence of amino acids encoded by a polynucleotide sequence encoding a polypeptide that is at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:1; (iii) a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide encoding a polypeptide consisting of SEQ ID NO:1; and (B) a light chain variable domain selected from the group consisting of: (i) a sequence of amino acids at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:2; (ii) a sequence of amino acids encoded by a polynucleotide sequence encoding a polypeptide that is at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO: 2; (iii) a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide encoding a polypeptide consisting of SEQ ID NO: 2; or (C) a light chain variable domain of (A) and a heavy chain variable domain of (A), wherein the antibody or antibody variant specifically binds to i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or (iii) a complex comprising insulin-like substances such as IGF-1, IGF-2 or variants and the insulin receptor, both (i) and (ii), or both (i) and (iii).

[0062] In various embodiments, the antibody or fragment thereof is a Fab fragment.

[0063] In a related embodiment, the residues of the framework are altered. The heavy chain framework regions which can be altered lie within regions designated H-FR1, H-FR2, H-FR3 and H-FR4, which surround the heavy chain CDR residues, and the residues of the light chain framework regions which can be altered lie within the regions designated L-FR1, L-FR2, L-FR3 and L-FR4, which surround the light chain CDR residues. An amino acid within the framework region may be replaced, for example, with any suitable amino acid identified in a human framework or human consensus framework.

[0064] In various embodiments, the antibody or antibody variant thereof is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody,

a Fab fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody. In various embodiments, the anti-INSR antibody is an IgG2 antibody.

[0065] Exemplary sequences for a human IgG2 constant region are available from the Uniprot database as Uniprot number P01859, incorporated herein by reference. Information, including sequence information for other antibody heavy and light chain constant regions is also publicly available through the Uniprot database as well as other databases well-known to those in the field of antibody engineering and production.

[0066] In various embodiments, the antibody, antibody variant or fragment thereof binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or (iii) a complex comprising insulin-like substances such as IGF-1, IGF-2 or variants and the insulin receptor, both (i) and (ii), or both (i) and (iii). In various embodiments, the antibody increases the EC₅₀ of insulin receptor signaling activity by effector substances such as insulin, IGF-2, or variants by about 2-fold to 1000-fold, optionally in a pAKT assay or other related assays measuring insulin receptor signaling that are known in the art.

[0067] Additional antibodies binding to human INSR have been reported in Soos et al, Biochem. J. 235: 199-208, 1986; Taylor et al, Biochem. J. 242: 123-129, 1987; Prigent et al, J. Biol. Chem. 265(17):9970-9977, 1990; Brindle et al, Biochem. J. 268: 615-620, 1990; Steele-Perkins and Roth, J. Biol. Chem. 265(16): 9458-9463, 1990; McKern et al, Nature 443(14): 218-221; Boado et al, Biotech and BioEng. 96(2): 381-391; WO04/050016; Roth et al, Proc. Natl. Acad. Sci. USA 79: 7312-7316, 1982; Morgan et al, Proc. Natl. Acad. Sci. USA 83: 328-332, 1986; Lebrun et al, J. Bl. Chem. 268(15): 11272-11277, 1993; Forsayeth et al, Proc. Natl. Acad. Sci. USA 84: 3448-3451, 1987; Forsayeth et al, J. Biol. Chem. 262(9): 4134-4140, Goodman et al, J. Receptor Res. 14(6-8), 381-398, 1994; Ganderton et al, Biochem J. 288: 195-205, 1992; Spasov et al, Bull. of Exp. Biol. and Med. 144(1): 46-48, 2007; EP 2 036 574 A1.

[0068] In various embodiments, the RZ358 antibody has the CDR sequences set out in SEQ ID NOs: 3-8; a heavy chain variable region amino acid sequence set out in SEQ ID NO: 1, and a light chain variable region amino acid sequence set out in SEQ ID NO: 2; and a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

Methods of Making

[0069] Methods of making the composition of the present disclosure are further provided herein. Using transgenic animals (e.g., mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production such antibodies are produced by immunization with a polypeptide antigen (i.e., having at least 6 contiguous

amino acids), optionally conjugated to a carrier. See, e.g., Jakobovits et al., 1993, Proc. Natl. Acad. Sci. 90:2551-55; Jakobovits et al., 1993, Nature 362:255-58; Bruggermann et al., 1993, Year in Immuno. 7:33. See also PCT App. Nos. PCT/US96/05928 and PCT/US93/06926. Additional methods are described in U.S. Pat. No. 5,545,807, PCT App. Nos. PCT/US91/245 and PCT/GB89/01207, and in European Patent Nos. 546073B1 and 546073A1. Human antibodies can also be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

[0070] Chimeric, CDR grafted, and humanized antibodies and/or antibody variants are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (e.g., human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells.

[0071] For recombinant production of the antibody or antibody fragment, the nucleic acid encoding it is isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the monoclonal antibody is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more selective marker genes, an enhancer element, a promoter, and a transcription termination sequence.

[0072] Suitable host cells for cloning or expressing the DNA in the vectors herein are prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, *Enterobacteriaceae* such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41 P disclosed in DD 266,710 published Apr. 12, 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. One preferred *E. coli* cloning host is *E. coli* 294 (ATCC 31,446), although other strains such as *E. coli* B, *E. coli* X1776 (ATCC 31,537), and *E. coli* W3110 (ATCC 27,325) are suitable. These examples are illustrative rather than limiting.

[0073] Eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms.

However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastors* (EP 183,070); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[0074] Suitable host cells for the expression of glycosylated antibody are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present disclosure, particularly for transfection of *Spodoptera frugiperda* cells.

[0075] Examples of useful mammalian host cell lines are Chinese hamster ovary cells, including CHOK1 cells (ATCC CCL61), DXB-11, DG-44, and Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77: 4216 (1980)); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, (Graham et al., *J. Gen Virol.* 36: 59, 1977); baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, (*Biol. Reprod.* 23: 243-251, 1980); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., *Annals N.Y Acad. Sci.* 383: 44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0076] Host cells are transformed or transfected with expression or cloning vectors for antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In addition, novel vectors and transfected cell lines with multiple copies of transcription units separated by a selective marker are particularly useful and preferred for the expression of antibodies that bind the desired antigen.

Methods of Use

[0077] Provided herein is use of antagonists of the insulin receptor, e.g., anti-INSR antibodies, for example, RZ358, or other antagonist compounds, in the treatment of neoplasms (benign or malignant neoplasms), and/or tumor-associated hyperinsulinism or hypoglycemia that results from excessive INSR signaling caused by the production of insulin or insulin-like effector substances by the neoplasm.

[0078] Neoplastic proliferation often involves autocrine, or paracrine signaling of growth stimulating factors such as insulin, proinsulin, insulin growth factor-1, or insulin growth factor-2, which may induce cellular proliferation through cellular signaling involving insulin receptor homodimers or insulin receptor-insulin growth factor heterodimeric receptors. Subsequent to binding to a receptor, intracellular signaling pathways involving ERK or Akt intracellular signaling pathways are activated. Cell survival and proliferation may be positively impacted by activation of these pathways and inhibition or slowing of insulin receptor associated intracellular signaling pathway may inhibit neoplastic cell survival or growth.

[0079] Hypoglycemia describes the condition and effects of low blood glucose, which may be caused by INSR-mediated cellular signaling induced by insulin, proinsulin, insulin growth factor-1, insulin growth factor-2 or their variants or precursor prohormones, autoantibodies to the INSR, or exogenous medications that act like insulin, such as native or synthetic insulin analogs, or that stimulate the secretion of insulin, such as sulfonylureas.

[0080] Typical symptoms associated with hypoglycemia that patients complain about include tiredness, weakness, tremulous and hunger. Many patients have to eat frequently to prevent symptoms from the low blood sugar. Some patients may develop psychiatric symptoms because of the low blood sugar. Hypoglycemia may result in a variety of symptoms including but not limited to, lack of coordination, sweating, fatigue, weakness, headache, palpitations, confusion, somnolence, loss of consciousness, seizures, coma, and even death.

[0081] Most episodes of mild and acute hypoglycemia are effectively self-treated by ingestion of glucose tablets or other carbohydrate containing drinks or snacks. More severe acute symptomatic hypoglycemia also can be treated with oral carbohydrate ingestion. However, when the hypoglycemic patient cannot take oral glucose supplements, because of confusion, unconsciousness or other reasons, parenteral therapy is required for acute or emergent management of hypoglycemia. As a non-hospital rescue procedure, injection of the hyperglycemic hormone, glucagon, is sometimes employed, either subcutaneously or intramuscularly by the patient himself or an associate of the patient who has been trained to recognize and treat severe hypoglycemia. In a medical setting, intravenous glucose is the

standard parenteral therapy for the management of acute or emergent hypoglycemia. When hypoglycemia is persistent, chronic, and/or pervasive and is due to hyperinsulinism caused by congenital or acquired factors such as congenital hyperinsulinism, gastric bypass surgery, pancreatic neuroendocrine tumors (e.g., insulinoma), or tumor-associated hyperinsulinism due to non-islet cell tumor hyperinsulinism, chronic medical therapies directed at controlling hyperinsulinism and hypoglycemia may be required. These may include but not necessarily limited to diazoxide, short-acting somatostatin analog therapies (e.g., octreotide), long-acting somatostatin analog therapies (e.g., lanreotide, pasireotide, or octreotide long-acting), continuous infusion of glucagon, mTOR inhibitors (e.g., everolimus), calcium channel blockers (e.g., verapamil), or systemic glucocorticoids. Bolus, semi-continuous, or continuous intravenous or enteral carbohydrate administration may also be employed.

[0082] Antagonists and/or negative modulators of insulin binding to INSR may be useful for treating and/or reducing the likelihood of the onset of disorders and symptoms related to hypoglycemia in a subject, such as reducing anxiety, abnormal hunger, abnormal fatigue, overeating, psychiatric symptoms associated with low blood sugar, hypoglycemia-related seizure, coma, and death. In various embodiments, the antagonist of INSR signaling, e.g., an anti-INSR antibody, alleviates one or more symptom associated with hypoglycemia or hyperinsulinism resulting from a neoplasm as described herein. In various embodiments the symptoms are selected from the group consisting of anxiety, abnormal hunger, abnormal fatigue, overeating, psychiatric symptoms associated with low blood sugar, lack of coordination, sweating, fatigue, weakness, headache, palpitations, confusion, somnolence, loss of consciousness, seizures, and coma.

[0083] Tumor induced hypoglycemia (TIH) and non-islet cell tumor hypoglycemia (NICTH) cause life-threatening low blood glucose due to secretion of excess amounts of insulin or aberrant signaling through IGF2. It is contemplated that IGF2-associated hypoglycemia and TIH or NICTH are treated with negative modulators of or antagonists to insulin receptor interacting with insulin-like substances such as IGF-1, IGF-2 or variants, thereby preventing aberrant signaling through the INSR pathway. See e.g., Bodnar et al., J Clin Endocrinol Metab. 2014 Mar;99(3):713-22.

[0084] A predominant cause of NICTH is abnormal IGF2 protein. IGF2 is produced initially pre-pro peptide of 180-amino acid peptide (prepro-IGF2), comprising a 24-amino acid signal peptide, a 67-amino acid mature IGF-II, and an 89-amino acid C-terminus sequence. All pro-IGF-II-related molecules are designated as “big” IGF-II. In NICTH circulating IGF2 is often found as a high molecular weight form in the 10- to 20-kDa range. This big IGF2 is formed due to abnormal processing of an IGF-II precursor in tumors, typically with aberrant

IGF2 gene transcription. Big IGF-II includes, but is not limited to, IGF2 peptides having amino acid residues 1–87 or residues 1–104 (Bodnar et al., *supra*).

[0085] It is contemplated that the methods herein reduce tumor size or tumor burden in the subject, and/or reduce metastasis in the subject. In various embodiments, the methods reduce the tumor size by 10%, 20%, 30% or more. In various embodiments, the methods reduce tumor size by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100%.

[0086] It is further contemplated that the methods herein reduce or prevent the recurrence of tumors in subjects exhibiting neoplasms as described herein.

[0087] In various embodiments, the subject is still receiving a standard of care therapy for treating hypoglycemia. Exemplary standard of care therapy includes intravenous dextrose, parenteral nutrition, short-acting glucagon injections, continuous glucagon infusions, diazoxide, SSAs, corticosteroids, mTOR inhibitors, supplemental enteral carbohydrates (tube feeding), and uncooked corn starch.

[0088] In various embodiments, the administration of the antibody or compound results in a decrease in need for or use of standard of care therapies, or results in elimination of need for or use of standard of care therapies.

[0089] In various embodiments, the administration of the antibody or compound results in a decrease from baseline in overall hypoglycemia events. Baseline refers to the rate of hypoglycemia episodes experienced by a subject prior to administration of therapy.

[0090] For example, the administration results in change from baseline in average weekly count of aggregate Level 2 (<54 mg/dL [<3 mmol/L] by SMBG) and/or Level 3 hypoglycemia events. A Level 2 hypoglycemia event refers to blood glucose <54 mg/dL [<3 mmol/L] by self-monitored blood glucose [SMBG]). A Level 3 hypoglycemia event is characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia, even if blood glucose is not documented. In various embodiments, the treatment is more effective in subject with Level 2 hypoglycemic events. In various embodiments, the treatment is more effective in a subject with Level 3 hypoglycemic events. In some embodiments, the treatment is effective in subjects with both Level 2 and Level 3 hypoglycemic events.

[0091] In another embodiment, the administration results in a change from baseline in average weekly count of overall hypoglycemia events (<70 mg/dL [<3.9 mmol/L]) by SMBG by at least 10%, 20%, 30%, 40%, 50%, 60% or more. In various embodiments, the

administration results in a decrease from baseline in overall hypoglycemia events, and optionally compared to the administration of standard of care therapy.

[0092] In another embodiments, the administration results in a change from baseline in average daily IV glucose/dextrose infusion rate (GIR, mg/kg/min) and/or change from baseline in average daily total IV glucose delivery (mg or g) during the entire treatment period in a subject receiving treatment as described herein.

[0093] Additional effects of the administration of the antibody or compound described herein are set out in the endpoints in the Examples. For example, it is contemplated that administration as described herein results in one or more of a change from baseline in daily percent time with overall hypoglycemia, average daily duration (min) with overall hypoglycemia, average 8-hour overnight percent time with overall hypoglycemia, need for rescue medication, time in Level 2 hypoglycemia, time in a glucose target range, weekly count of hyperglycemia events by SMBG (e.g., at thresholds of >250 mg/dL and >400 mg/dL), change in biomarker levels, or overall survival.

[0094] In various embodiments, the tumor associated hyperinsulinism and resulting hypoglycemia in a neoplasm are mediated through excess INSR signaling by an insulin-like substance. In various embodiments, the insulin-like substance is insulin, proinsulin, INSR autoantibodies, other insulin-like peptides, hormones, or effector substances. In various embodiments, the other insulin-like peptides, hormones or effector substances are selected from the group consisting of insulin-like growth hormone 1 (IGF-1) or its precursors, IGF-1 prohormones, IGF-1 variants, insulin-like growth hormone-2 (IGF-2) or its precursors, IGF-2 prohormones, and IGF-2 variants. In certain embodiments, the IGF-2 variant is Big IGF.

[0095] In various embodiments, the neoplasm is selected from the group consisting of adrenal gland cancer, AIDS-associated cancer, alveolar soft part sarcoma, anal cancer, bladder cancer, bone cancer, brain and spinal cord cancer, breast cancer, carotid body tumor, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, desmoplastic small round cell tumor, ependymoma, endometrial cancer (including, unselected endometrial cancer, MSI-high endometrial cancer, dMMR endometrial cancer, and/or POLE exonuclease domain mutation positive endometrial cancer), Ewing's sarcoma, extraskeletal myxoid chondrosarcoma, gallbladder or bile duct cancer (including, cholangiocarcinoma bile duct cancer), gastric cancer, gastroesophageal junction (GEJ) cancer, gestational trophoblastic disease, germ cell tumor, glioblastoma, head and neck cancer, a hematological malignancy, a hepatocellular carcinoma, islet cell tumor, insulinoma, Kaposi's Sarcoma, kidney cancer, leukemia, liposarcoma/malignant lipomatous tumor, liver cancer, lymphoma, lung cancer,

medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesothelioma, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancer, papillary thyroid carcinoma, parathyroid tumor, pediatric cancer, peripheral nerve sheath tumor, pharyngeal cancer, pheochromocytoma, pituitary tumor, prostate cancer, posterior uveal melanoma, renal metastatic cancer, rhabdoid tumor, rhabdomyosarcoma, sarcoma, skin cancer, a small round blue cell tumor of childhood, soft-tissue sarcoma, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, and uterine cancer.

[0096] In various embodiments, the benign or malignant neoplasm is selected from the group consisting of: non-islet cell tumor hypoglycemia (NICTH), non-islet cell tumor hyperinsulinism (NICTHI), Doege-Potter syndrome, insulinoma, ectopic insulinoma, IGF2-oma, pro-insulinoma, pancreatic neuroendocrine tumors, non-pancreatic neuroendocrine tumors, mesenchymal tumors, adrenal carcinoma, hepatocellular carcinoma, gastrointestinal carcinoma, ovarian carcinoma, pheochromocytoma, sarcomas, lymphomas, leukemias, and small-cell lung carcinomas.

[0097] In various embodiments, the neoplasm is a primary tumor or is metastatic.

Administration and Dosing

[0098] Also contemplated by the disclosure are methods of administering an antagonist of insulin receptor (INSR), e.g., an antibody composition, as described herein to treat neoplasm and/or tumor associated hyperinsulinism with resulting hypoglycemia or hyperinsulinism.

[0099] Methods of the disclosure are performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian subject, including but not limited to injections, infusions, oral ingestion, intranasal, topical, transdermal, parenteral, inhalation spray, vaginal, or rectal administration. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, and intracisternal injections, as well as catheter or infusion techniques. Administration by, intradermal, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Suitable delivery devices may include those developed for the delivery of insulin (see, e.g., Owens et al *Diabetic Med.* 20(11):886-898, 2003; US20140128803; and Peyser et al. *Annals NY Acad Sci*, 1311:102-123, 2014).

[0100] An antibody composition as described herein may be administered daily, every 2 days, every 3 days, weekly, every 2 weeks, every 3 weeks, twice monthly, every 4 weeks, monthly, every 2 months, every 3 months or every 6 months. In various embodiments, the

composition is administered for a period of at least 4 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 9 months, 1 year or more.

[0101] In one embodiment, administration is performed at the site of an affected tissue needing treatment by direct injection into the site or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally. For example, biodegradable microspheres or capsules or other biodegradable polymer configurations capable of sustained delivery of a composition (e.g., a soluble polypeptide, antibody, or small molecule) can be included in the formulations useful in the disclosure implanted at the site.

[0102] Therapeutic compositions may also be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of time. In certain cases it is beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, hourly, daily, weekly, every 2 weeks, every 3 weeks, every 4 weeks, monthly, every 5 weeks, or every 6 weeks.

[0103] The amounts of antibody composition in a given dosage will vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated. In exemplary treatments, it may be necessary to administer about 0.1 to about 25 mg/kg per dose or per day, or from about 0.05 mg/kg to about 10 mg/kg, from about 0.3 mg/kg to about 6 mg/kg, or from about 0.1 mg/kg to about 3 mg/kg. Exemplary doses include, 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 1 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, or 25 mg/kg. Other doses include 1 mg/day, 2.5 mg/day, 5 mg/day, 10 mg/day, 20 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 500 mg/day or 1000 mg/day. These dose amounts may be administered as a single dosage form or as multiple doses or continuously.

[0104] In various embodiments, from 3-12 mg/kg anti-INSR antibody is administered to the subject. In various embodiments, 9 mg/kg anti-INSR antibody weekly, bi-weekly, every 3 weeks, or every 4 weeks.

[0105] In various embodiments, the anti-INSR antibody is the RZ358 antibody, which is in a formulation comprising at least one amino acid or a salt thereof, a surfactant, and a sugar alcohol. Exemplary formulations are described in International Patent Publication WO 2023/225657, incorporated herein by reference. It is contemplated that the formulation

comprises the anti-INSR antibody at a concentration from about 20 mg/mL to about 200 mg/mL, from about 50 mg/mL to about 150 mg/mL, or from about 80 mg/mL to about 120 mg/mL. The formulation may comprise the anti-INSR antibody (e.g., RZ358) at a concentration of about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, about 100 mg/mL, about 110 mg/mL, about 120 mg/mL, about 130 mg/mL, about 140 mg/mL, about 150 mg/mL, about 160 mg/mL, about 170 mg/mL, about 180 mg/mL, about 190 mg/mL, or about 200 mg/mL.

[0106] In various embodiments, an RZ358 composition for administration contains 80 mg/ml (80 mg per approximately 1 ml) RZ358 with inactive ingredients L-histidine hydrochloride, L-histidine, L-methionine, sorbitol, polysorbate and water for injection, with no preservatives, at a pH of 5.8.

[0107] Also contemplated in the present methods is the administration of multiple agents, such as an antibody composition described herein in conjunction with a second agent as described herein. Compositions comprising an antibody described herein may be administered to persons or mammals suffering from, or predisposed to suffer from, a condition or disorder, e.g., cancer, to be treated.

[0108] Concurrent administration of two or more therapeutic agents does not require that the agents be administered at the same time or by the same route, as long as there is an overlap in the time period during which the agents are exerting their therapeutic effect. Simultaneous or sequential administration is contemplated, as is administration on different days or weeks.

[0109] A second agent may be other therapeutic agents, such as anti-neoplastic agents, chemotherapy, hormone therapy, hyperthermia, immunotherapy, radiation therapy, targeted radiolabeled delivery, stem cell transplant, gene therapy, surgery, embolization, targeted anti-neoplastic therapies, or photodynamic therapy where appropriate.

[0110] Exemplary agents include, but are not limited to, bevacizumab, nivolumab, pembrolizumab, palbociclib, atezolizumab, lutetium Lu 177 Dotatate, and other agents useful to treat neoplasms or side effects associated with neoplasms. In various embodiments, an antibody described herein is administered in a delivery device, e.g., a smart delivery device (see, e.g., US20140128803) or dual sensor/pump (e.g., a bionic pancreas system).

[0111] A second agent may be other therapeutic agents, such as anti-diabetic agents, anti-inflammatory agents, or agents used to treat hyperinsulinemia or hyperinsulinism including agents that promote glucagon release or have glucagon-activity, agents that promote release of hepatic glucose, agents that suppress insulin production or release,

agents that inhibit insulin action, agents that prevent peripheral glucose uptake, carbohydrate supplementation, and anti-neoplastic drugs or molecules.

[0112] Exemplary second agents for the treatment of hyperinsulinemia or hyperinsulinism include, but are not limited to, glucagon or synthetic forms of glucagon, octreotide, long-acting release octreotide, lanreotide, pasireotide, verapamil, diazoxide, everolimus, sirolimus, glucocorticoids, glucagon-like peptides, parenteral carbohydrates, enteral carbohydrates, and other agents useful to treat hypoglycemia or side effects associated with hypoglycemia.

[0113] A number of exemplary second agents for the treatment of diabetes mellitus targeting replacement of insulin, promotion of insulin secretion, or enhancement of insulin action, are known in the art, and may result in unintended or excessive hyperinsulinemia, insulin sensitivity or responsiveness, hyperinsulinism and/or hypoglycemia. These include but may not be limited to: sulfonylureas (e.g., glimepiride, glisentide, sulfonylurea, AY31637); biguanides (e.g., metformin); alpha-glucosidase inhibitors (e.g., acarbose, miglitol); thiazolidinediones (e.g., troglitazone, pioglitazone, rosiglitazone, glipizide, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, AD 5075, T 174, YM 268, R 102380, NC 2100, NIP 223, NIP 221, MK 0767, ciglitazone, adaglitazone, CLX 0921, darglitazone, CP 92768, BM 152054); glucagon-like-peptides (GLP) and GLP analogs or agonists of GLP-1 receptor (e.g., exendin) or stabilizers thereof (e.g., DPP4 inhibitors, such as sitagliptin); insulin or analogues or mimetics thereof (e.g., lispro, aspart, glulisine, detemir insulin, egludec insulin, insulin glargine, LANTUS®); and sodium-glucose Cotransporter-2 (SGLT2) inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin).

[0114] Chemotherapeutic agents contemplated for use with the antagonists/antibodies of described herein include, but are not limited to, those listed in Table I, including combinations of the various agents as known in the art to treat neoplasms and solid tumors.

TABLE I

<u>Alkylating agents</u> <u>Nitrogen mustards</u> mechlorethamine cyclophosphamide ifosfamide melphalan chlorambucil <u>Nitrosoureas</u> carmustine (BCNU) lomustine (CCNU) semustine (methyl-CCNU)	<u>Natural products</u> <u>Antimitotic drugs</u> <u>Taxanes</u> paclitaxel Vinca alkaloids vinblastine (VLB) vincristine vinorelbine Taxotere® (docetaxel) estramustine
--	---

<u>Ethylenimine/Methyl-melamine</u> triethylenemelamine (TEM) triethylene thiophosphoramidate (thiotepa) hexamethylmelamine (HMM, altretamine) <u>Alkyl sulfonates</u> busulfan <u>Triazines</u> dacarbazine (DTIC) <u>Antimetabolites</u> <u>Folic Acid analogs</u> methotrexate Trimetrexate Pemetrexed (Multi-targeted antifolate) <u>Pyrimidine analogs</u> 5-fluorouracil fluorodeoxyuridine gemcitabine cytosine arabinoside (AraC, cytarabine) 5-azacytidine 2,2'-difluorodeoxy-cytidine <u>Purine analogs</u> 6-mercaptopurine 6-thioguanine azathioprine 2'-deoxycoformycin (pentostatin) erythrohydroxynonyl-adenine (EHNA) fludarabine phosphate 2-chlorodeoxyadenosine (cladribine, 2-CdA) <u>Type I Topoisomerase Inhibitors</u> camptothecin topotecan irinotecan <u>Biological response modifiers</u> G-CSF GM-CSF <u>Differentiation Agents</u> retinoic acid derivatives <u>Hormones and antagonists</u> Adrenocorticosteroids/ antagonists prednisone and equivalents	estramustine phosphate <u>Epipodophylotoxins</u> etoposide teniposide <u>Antibiotics</u> actinomycin D daunomycin (rubido-mycin) doxorubicin (adria-mycin) mitoxantroneidarubicin bleomycin splicamycin (mithramycin) mitomycinC dactinomycin aphidicolin <u>Enzymes</u> L-asparaginase L-arginase <u>Radiosensitizers</u> metronidazole misonidazole desmethylmisonidazole pimonidazole etanidazole nimorazole RSU 1069 EO9 RB 6145 SR4233 nicotinamide 5-bromodeoxyuridine 5-iododeoxyuridine bromodeoxycytidine <u>Miscellaneous agents</u> <u>Platinum coordination complexes</u> cisplatin Carboplatin oxaliplatin Anthracenedione mitoxantrone <u>Substituted urea</u> hydroxyurea <u>Methylhydrazine derivatives</u> N-methylhydrazine (MIH) procabazine <u>Adrenocortical suppressant</u> mitotane (o,p'-DDD) ainoglutethimide
--	--

dexamethasone ainoglutethimide	
<u>Progestins</u> hydroxyprogesterone caproate medroxyprogesterone acetate megestrol acetate	<u>Cytokines</u> interferon (α , β , γ) interleukin-2
<u>Estrogens</u> diethylstilbestrol ethynyl estradiol/ equivalents	<u>Photosensitizers</u> hematoporphyrin derivatives Photofrin® benzoporphyrin derivatives Npe6 tin etioporphyrin (SnET2) pheoboride-a bacteriochlorophyll-a naphthalocyanines phthalocyanines zinc phthalocyanines
<u>Antiestrogen</u> tamoxifen	
<u>Androgens</u> testosterone propionate fluoxymesterone/equivalents	<u>Radiation</u> X-ray ultraviolet light gamma radiation visible light infrared radiation microwave radiation
<u>Antiandrogens</u> flutamide gonadotropin-releasing hormone analogs leuprolide	
<u>Nonsteroidal antiandrogens</u> flutamide	

[0115] CAPTEM regimen is a chemotherapy treatment for neuroendocrine tumors (NETs) that uses the drugs capecitabine and temozolomide. The regimen is used to treat metastatic NETs, including those in the pancreas, liver, gastrointestinal tract, pituitary gland, and medullary thyroid.

[0116] Any of the antibodies or fragments thereof described herein may be concurrently administered with one or more second agent known in the art or described herein.

[0117] It is contemplated that the antibody and a second agent may be given simultaneously, in the same formulation. It is further contemplated that the agents are administered in a separate formulation and administered concurrently, with concurrently referring to agents given within 30 minutes of each other.

[0118] In another aspect, the second agent is administered prior to administration of the antibody composition. Prior administration refers to administration of the second agent within the range of four weeks (e.g., four, three, two or one week, or days, prior to treatment with the antibody), up to 30 minutes before administration of the antibody. It is further contemplated that the second agent is administered subsequent to administration of the

antibody composition. Subsequent administration is meant to describe administration from 30 minutes after antibody treatment up to four weeks after antibody administration.

[0119] It is further contemplated that other adjunct therapies may be administered, where appropriate. For example, the patient may also be administered a diet or food plan designed for a hypoglycemic patient, surgical therapy, or radiation therapy where appropriate.

[0120] It will also be apparent that dosing may be modified if traditional therapeutics are administered in combination with antibody formulations described herein.

Kits

[0121] The present disclosure also provides a kit including a composition described herein together with a package insert, package label, instructions, or other labeling directing or disclosing any of the methods or embodiments disclosed herein. In certain embodiments, the present disclosure provides kits for producing a single-dose administration unit. In certain embodiments of this disclosure, kits containing single and multi-chambered prefilled syringes (e.g., liquid syringes) are included.

[0122] Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting

EXAMPLES

Example 1-Treatment of Tumor Associated Hyperinsulinism with Anti-INSR Antibody

[0123] RZ358 has been shown to counteract excessive insulin action downstream, at the insulin-receptor on target organs. It is hypothesized herein that the unique mechanism of action of RZ358 makes this therapy, and other antagonists to insulin receptor signaling, a potential universal treatment for any form of hyperinsulinism, including tumor-associated hyperinsulinism resulting from pancreatic neuroendocrine tumors, i.e., insulinomas.

[0124] In an initial experiment, the inhibition of ligand-mediated signaling with RZ358 antibody molecule is quantified using PH Insulin Bioassay when stimulated either with insulin or IGF-2 (Eurofins DiscoverX EFC assay). In the assay, β -galactosidase (β -gal) enzyme split into two fragments, Prolink (PK) and Enzyme acceptor (EA) is used. Independently these fragments have no β -gal activity; however when forced to complement via protein-protein interactions, they form an active β -gal enzyme. An EA-tagged SH2 domain protein is recruited to the ligand activated PK-tagged INSRb, forcing the complementation of β -gal subunits (EA and PK) that leads to production of signal and is a measure of receptor-ligand binding. β -gal enzymatic activity is quantitatively measured using a chemiluminescent substrate in the PathHunter Bioassay Detection Kit.

[0125] A recent study published in the New England Journal of Medicine reported that the anti-INSR antibody RZ358 successfully treated symptoms of a metastatic insulinoma that resulted in severe hypoglycemia in the subject (Ostaphan et al., N Engl J Med 2023 389(8):767-769). Other patients with tumor-associated hyperinsulinism and refractory hypoglycemia resulting from pancreatic and extra-pancreatic (cervical cancer) metastatic insulinoma have been treated with RZ358 at doses ranging from 3-12 mg/kg every 1 to 4 weeks.

[0126] These patients were receiving, but refractory to, usual standard of care therapies for chronic management of hypoglycemia and were requiring continuous high volume/concentration intravenous dextrose or nutritional infusion and were hospitalized and in life-threatening or hospice-bound condition because of uncontrollable hypoglycemia. Further treatment with tumor-directed therapies (e.g., embolization, radiotherapy, chemotherapy) were being deferred for these reasons.

[0127] RZ358, because of its mechanism of action as an anti-insulin receptor modulator, led to substantial improvement in hypoglycemia in these patients with tumor-associated hyperinsulinism caused by metastatic insulinomas. RZ358 was initially used in conjunction with other therapies to control hypoglycemia, but continuous carbohydrate administration and other background medical therapies were frequently able to be weaned or stopped. In some cases, as appropriate, patients were able to resume tumor-directed therapies for treatment of underlying cancer. This exemplifies the potential use of RZ358, a negative allosteric modulator of the insulin receptor, to treat tumor-associated hyperinsulinism and resulting hypoglycemia alone or in combination with second agents that are utilized to treat the underlying malignancy (cancer-directed therapies) or with second agents that are utilized to directly treat the hypoglycemia resulting from tumor-mediated hyperinsulinism.

[0128] The clinical safety, PK, PD, and glycemic efficacy of RZ358 have been investigated in clinical studies, including two single-dose Phase 1 studies in adult healthy volunteers, a combined single- and repeat-dose Phase 2 study in adult subjects with post gastric bypass hypoglycemia (PGBH), two single-dose Phase 2 studies in adult and teenage subjects with congenital HI, and a repeat-dose Phase 2b study (RZ358-606; RIZE)

[0129] RZ358 has been administered in completed trials as an IV infusion at single doses ranging from 0.1 mg/kg to 9 mg/kg (healthy volunteers), repeat once weekly doses of 3 mg/kg for 4 weeks (PGBH) and single and repeat bi-weekly doses ranging from 1 to 9 mg/kg (congenital HI). Studies in congenital HI demonstrated improvement of hypoglycemia time and events across pooled doses, and up to ~75% improvement in hypoglycemia ($P \leq 0.05$) at the top doses (Demirbilek et al., *ESPE Abstracts* (2022) **95** FC3.2).

[0130] Based on previously observed and modeled concentrations, the projected repeat-dose maximum concentrations (C_{max}) and exposures at 9 mg/kg administered on a weekly to bi-weekly basis in the present study are expected to be ~400 µg/mL (C_{max}) and ~2000 µg*day/mL (Area under the concentration-time curve [AUC_{0-7d}]). Furthermore, the projected accumulated C_{max} and AUC exposures at longer treatment durations (e.g. >8 weeks) is comparable to what is being assessed at a 10 mg/kg dose regimen in a cHI Phase 3 study with a 26-week pivotal treatment period. RZ358 was administered as a repeat IV infusion every 1-4 weeks at doses of 6 or 9 mg/kg.

[0131] RZ358 was initiated in three insulinoma (pancreatic neuroendocrine tumor) patients at 6 mg/kg every two weeks and titrated up. In four patients, RZ358 was initiated with 9 mg/kg weekly (by 30-min intravenous infusion) resulting in satisfactory glycemic control within several weeks of treatment. Blood glucose was monitored via continuous glucose monitoring (CGM) for all patients to evaluate glycemic efficacy.

[0132] Five patients with insulinoma achieved significant resolution of hypoglycemia which resulted in discontinuation of intravenous glucose infusion/TPN average within two weeks of starting treatment with 9 mg/kg weekly dosing regimen. Time to response was somewhat longer in those patients who initially received RZ358 at a lower dose or frequency. Hospitalized patients were able to be discharged when normoglycemia was achieved without recurrent hypoglycemia events and receive maintenance RZ358 at reduced frequency (usually 2-4 weekly regimen) on an outpatient basis, with durable benefit. Background therapies for hypoglycemia, which are often associated with significant side effects (e.g., diazoxide, systemic steroids) were able to be reduced or even discontinued in some cases. In several instances, patients were able to resume/initiate targeted anticancer therapies for treatment of underlying cancer. The duration of treatment with RZ358 has ranged from approximately 4 months to 13 months.

[0133] Patient Outcomes

- Patients treated with RZ358 have achieved greater overall survival than patients reported in the literature who have not received RZ358
 - ≥3 months OS is 100% for RZ358 patients compared to 14% for the natural history cohort
 - ≥6 months OS is 71% for RZ358 patients compared to 14% for the natural history cohort
 - ≥6 months OS is 29% for RZ358 patients compared to 14% for the natural history
 - Survival of patients receiving RZ358 and literature cases are 57% and 33%, respectively

- All patients receiving IV dextrose/TPN (6) who received RZ358 were able to reduce or completely stop infusion
 - For patients with an initial dose of RZ358 at 6 mg/kg, time to reduce/wean off was 79 days after first dose
 - For patients with an initial dose of RZ358 at 9 mg/kg, time to wean off was 3.7 days after first dose
- 71% of Expanded Access Program (EAP) patients (5 of 7) were able to reduce/wean off background SOC therapy after receiving RZ358
- 43% of EAP patients (3 of 7) were able to continue with tumor-directed therapy after receiving RZ358.

[0134] A patient diagnosed with a pro-insulinoma, in which pro-insulin levels were increased compared to normal, was also treated with RZ358. The pro-insulin secreting tumor showed a positive response to treatment with RZ358.

[0135] Because other insulin-like effector substances produced and secreted by islet or non-islet cell tumors mediate hyperinsulinism and resulting hypoglycemia via the insulin receptor or hybrid insulin/insulin-like growth factor receptors, RZ358 or other antagonists to insulin receptor signaling, would also be expected to prevent hyperinsulinism and resulting hypoglycemia caused by over-production and over-secretion of paraneoplastic insulin-like effector substances (e.g. IGF-2 or its variants) from non-islet cell tumors. Since the mechanism of action of RZ358 as a negative allosteric modulator of insulin receptor binding and signaling has been characterized, it is expected to the same mechanism of action and pharmacologic effect when other insulin-like effector substances (e.g., IGF-2) mediate excess insulin-receptor binding and activity (hyperinsulinism).

Example 2-Anti-INSR Antibody Attenuates IGF-2 Signaling Through Insulin Receptor

[0136] RZ358 attenuates IGF-2 mediated INSR α signaling in a dose-dependent manner as determined in a cell-based assay. When insulin receptor-expressing cells were stimulated with an EC₅₀ of IGF-2 (comparable to disease-relevant concentration in human), inhibition by RZ358 was observed with an IC₅₀ of 1.916 μ g/mL (13 nM). As shown in Figure 2, RZ358 attenuates both IGF-2 and insulin-mediated INSR α signaling in a concentration-dependent manner and to a comparable degree, at equivalent and disease-relevant concentrations (EC₈₀) for each respective ligand. When stimulated with an EC₈₀ of insulin, INSR α signaling was inhibited by RZ358 with an IC₅₀ of 0.977 μ g/mL and a S/B of 5.6. Similarly, when stimulated with an EC₈₀ of IGF-2, inhibition by RZ358 was observed with an IC₅₀ of 1.916 μ g/mL and S/B of 5.3.

[0137] These results suggest that agents that block insulin receptor, such as an anti-INSR antibody, would be useful to treat tumors resulting in hypoglycemia as a result of IGF-2 stimulation of the insulin receptor.

Example 3-Phase 3 Study to Treat Tumor Associated Hyperinsulinism

[0138] Approximately 24, and up to 48, eligible ambulatory participants with inadequately controlled hypoglycemia due to hyperinsulinism caused by islet cell tumors (ICTs) and NICT/paraneoplastic secreting tumors will be enrolled in randomized, double-blind fashion to receive RZ358 or placebo control as add-on to applicable background SOC anti-hypoglycemic therapies for a period of 8 weeks (pivotal treatment period). Participants enrolled into the double-blind study will be randomized in a 1:1 ratio to receive 9 mg/kg/week of either RZ358 (n=12) or matched placebo (n=12) as add on to applicable background SOC over a 8-week pivotal treatment period (8 weekly doses – at Day 1 (Week 0), Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, and Week 7).

[0139] Both RZ358 drug product (DP) and its matched placebo are sterile, clear aqueous solutions supplied in 2.0 mL single-use glass vials of 1.24 mL solution. Each vial of RZ358 or placebo is filled with a usable volume of 1.0 mL of 80 mg/mL RZ358 or placebo, in a pH 5.8 formulation buffer.

[0140] To meet glycemic qualification criteria, ambulatory participants must be experiencing Level 2 hypoglycemia (blood glucose <54 mg/dL [<3 mmol/L] by self-monitored blood glucose [SMBG]) and/or Level 3 hypoglycemia (events characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia, even if a blood glucose is not documented) at an average weekly rate of ≥ 3 events per week during the 2-week period before randomization.

[0141] Upon completion of all screening procedures, eligible participants will be randomized into the double-blind pivotal treatment period in 1:1 ratio to receive 9 mg/kg/week of either RZ358 or matched placebo as add on to SOC therapy for a period of 8 weeks.

[0142] Beginning at Day 1 of the pivotal treatment period, all enrolled participants will receive study drug at 9 mg/kg as an IV infusion over at least 30 min (<60 min) every week for a total of 8 doses (Week 0 [Day 1], Week 1 [Day 8], Week 2 [Day 15], Week 3 [Day 22], Week 4 [Day 29], Week 5 [Day 36]), Week 6 [Day 43]) and Week 7 [Day 50]). At the Week 8 (Day 57) end of treatment (EoT) visit, participants who continue in the Open Label Extension (OLE) phase of the study will receive RZ358 in open label fashion after completion of all scheduled procedures, whereas those that do not continue into the OLE will complete a 4-week safety follow up period.

[0143] During the pivotal treatment period study drug dosing regimen should remain fixed; however, the dose may be modified for any potential safety concerns (e.g. possible toxicities of RZ358 in combination with chemotherapy).

[0144] Applicable Standard of Care (SOC) anti-hypoglycemic therapies could include current or prior use of one or more of the following treatments, as appropriate for the individual patient circumstances: IV dextrose, short-acting glucagon injections, continuous glucagon infusions, diazoxide, SSAs, corticosteroids, mTOR inhibitors, and/or supplemental enteral carbohydrates (tube feeding) or parenteral nutrition, and/or uncooked corn starch.

[0145] Inclusion Criteria

[0146] Each double-blind participant must meet all of the following criteria to be enrolled in this study:

[0147] 1. The eligibility criteria of all participants must be evaluated by a multidisciplinary team led by the PI, which must include an oncologist to ensure the participant is appropriate for this clinical trial.

[0148] 2. Male or female participants of ≥ 18 years of age who provide written informed consent as per regulations.

[0149] 3. Participants with a clinical diagnosis and laboratory confirmation of tHI due to an ICT (e.g. insulinoma/pro-insulinoma) or NICT, with associated hypoglycemia that is considered refractory to surgery (surgically unresectable, as indicated and appropriate) and to usual SOC anti-hypoglycemia therapies, per investigator judgement.

[0150] 4. Experiencing an average of ≥ 3 hypoglycemia events per week that meet Level 2 criteria (blood glucose < 54 mg/dL [< 3 mmol/L] by SMBG) and/or Level 3 criteria (events characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia, even if a blood glucose is not documented) during the two weeks before randomization.

[0151] 5. Must have an estimated minimum life expectancy of ≥ 3 months.

[0152] 6. ECOG performance status ≤ 2 .

[0153] 7. Female participants of childbearing potential must not be pregnant or breast feeding, and willing to use effective contraceptive measures* to prevent pregnancy for the duration of the study AND including for at least 3 months after receiving the last dose of study drug.

[0154] 8. Male participants with female partner of childbearing potential must be willing to use effective contraceptive measures* to prevent pregnancy for the duration of the study AND including for at least 3 months after receiving the last dose of study drug.

[0155] Exclusion Criteria:

[0156] Participants meeting any of the following criteria will be excluded from the study:

[0157] 1. Participants who require and are eligible and appropriate for tumor-directed therapies in lieu of trial enrollment for an investigational anti-hypoglycemia therapy, but who are not currently receiving and/or have not previously received tumor-directed therapy (including at least one course/trial of systemic tumor-directed therapy, as appropriate), as reviewed by and at the discretion of the investigator in conjunction with expert input from an oncologist and/or a multi-disciplinary oncology care team.

[0158] 2. Initiation of, or changes to tumor directed therapies (e.g. surgery, radiation therapy, chemotherapy or PRRT) within 8 weeks prior to initiation of study drug, or expected initiation or significant changes to these therapies over the course of the pivotal treatment period.

[0159] 3. Initiation of, or significant changes to, SOC medical (e.g. diazoxide, SSAs, continuous glucagon, mTOR-Inhibitors, etc.) or supplemental enteral treatments (e.g. continuous tube feeds) used for the chronic management of hypoglycemia within 4 weeks of screening (per investigator's discretion), or expected changes to SOC medical therapies over the course of the pivotal treatment period.

[0160] 4. Any out-of-range laboratory value at screening (other than glucose) that is assessed as clinically significant by the investigator. Laboratory or radiographic abnormalities that are considered related to the underlying disease under study or associated therapies and do not pose additional safety risk for study participation per investigator and Medical Monitor may be allowed.

[0161] 5. A history of insulin or other anti-hyperglycemic agent for diabetes mellitus within 4 weeks of screening.

[0162] 6. Active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ (metastasis to other organs is not exclusionary).

[0163] 7. Seropositivity, indicative of active infection for human immunodeficiency virus, hepatitis B, or hepatitis C (excluding immunization patterns).

- [0164]** 8. Major surgery within 1 month before screening or anticipated during the study period (gastrostomy or other enteral catheter insertions, central or peripheral catheter insertion, or similar procedures are acceptable).
- [0165]** 9. Symptomatic brain metastasis requiring active treatment (stable participants with radiation and/or steroid therapy may be allowed, per investigator).
- [0166]** 10. Participants with active, uncontrolled seizure disorder (stable participants with antiepileptic medication may be allowed, per investigator).
- [0167]** 11. Treatment with an investigational drug or device within 30 days or 5 half-lives of the investigational drug (whichever is longer), however, if the treating physician and Medical Monitor consider no significant risk of drug-drug interaction and potential benefit outweigh the risk then the participant may be allowed to participate. Participation in registries and purely diagnostic studies is allowed.
- [0168]** 12. Known allergy or sensitivity to RZ358 or any component of the drug.
- [0169]** 13. History of a significant cardio-vascular or cerebrovascular event within last six months (e.g. Class III or IV congestive heart failure, unstable angina, myocardial infarction [MI], stroke etc.).
- [0170]** 14. Any organ condition, concomitant disease (e.g., psychiatric illness, severe alcoholism, or drug abuse, cardiac, hepatic, or kidney disease), or other abnormality that itself, or the treatment of which, could interfere with the conduct of the study or that, in the opinion of the investigator and/or Sponsor's Medical Monitor would pose an unacceptable risk to the participant in the study.
- [0171]** Primary efficacy endpoints include:
- [0172]** • Percent change from baseline in average weekly count of aggregate Level 2 (<54 mg/dL [<3 mmol/L] by SMBG) and adjudicated Level 3 hypoglycemia events during the entire pivotal treatment period.
- [0173]** Secondary efficacy endpoints include:
- [0174]** • Change from baseline in average weekly count of aggregate Level 2 (<54 mg/dL [<3 mmol/L] by SMBG) and adjudicated Level 3 hypoglycemia events during the entire pivotal treatment period.
- [0175]** • Percent change from baseline in average weekly count of Level 2 hypoglycemia (glucose <54 mg/dL [<3 mmol/L] by SMBG) events.
- [0176]** • Percent change from baseline in average weekly count of Level 3 (adjudicated) hypoglycemia events

- [0177]** • Percent change from baseline in average daily percent time with Level 2 hypoglycemia (glucose <54 mg/dL [<3 mmol/L]) by CGM during Weeks 1-8 of the pivotal treatment period.
- [0178]** • Percent change from baseline in average weekly count of overall hypoglycemia events (<70 mg/dL [<3.9 mmol/L]) by SMBG.
- [0179]** Secondary endpoints for those patients in a later open label trial include change from baseline in average daily IV glucose/dextrose infusion rate (GIR) and change from baseline in average daily total IV glucose delivery (mg) during the entire treatment period.
- [0180]** Other endpoints include:
- [0181]** • Percent change from baseline in average weekly count of overall hypoglycemia events (<70 mg/dL [<3.9 mmol/L]) by SMBG.
- [0182]** • Percent change from baseline in average daily percent time with overall hypoglycemia (glucose <70 mg/dL [<3.9 mmol/L]) by CGM.
- [0183]** • Change from baseline in average daily duration (min) with overall hypoglycemia (<70 mg/dL [<3.9 mmol/L]); and separately Level 2 (<54 mg/dL [<3 mmol/L]) hypoglycemia by CGM.
- [0184]** • Change from baseline in average 8-hour overnight percent time with overall hypoglycemia (<70 mg/dL [<3.9 mmol/L]); and separately Level 2 hypoglycemia (<54 mg/dL [<3 mmol/L]) by CGM.
- [0185]** • Proportion of participants requiring acute rescue medication use for Level 2 or 3 hypoglycemia meeting rescue criteria.
- [0186]** • Proportion of participants requiring rescue medications for hypoglycemia with documented blood glucose <54 mg/dL [<3 mmol/L] via SMBG.
- [0187]** • Proportion of participants achieving <4% average daily time in Level 2 hypoglycemia (blood glucose <54 mg/dL [<3 mmol/L]) by CGM.
- [0188]** • Change from baseline in average daily area under and area over the glucose curve (AOC, AUC) for Level 2 hypoglycemia threshold (<54 mg/dL [<3 mmol/L]) by CGM.
- [0189]** • Occurrence of in-patient hospitalization for hypoglycemia and/or related events.
- [0190]** • Change from baseline in average daily percentage time in a glucose target range of 70 to 180 mg/dL (3.9 to 10 mmol/L) by CGM.
- [0191]** Open-Label Arm efficacy endpoints include:
- [0192]** • Clinically meaningful reduction ($\geq 50\%$) in glucose infusion rate from baseline

- [0193]** • Change from baseline in average daily IV glucose/dextrose infusion rate (GIR)
- [0194]** • Change from baseline in average daily total IV glucose delivery (mg or g) during the treatment period.
- [0195]** • Time to complete weaning off IV glucose administration after initiating RZ358
- [0196]** Occurrence of in-patient hospitalization for hypoglycemia and/or related events.
- [0197]** Change from baseline in average daily percentage time in a glucose target range of 70 to 180 mg/dL (3.9 to 10 mmol/L) by CGM.
- [0198]** Proportion of participants achieving no Level 2 (by SMBG) or Level 3 hypoglycemia events, in aggregate and separately at each threshold.
- [0199]** Percent change from baseline in average weekly count of hyperglycemia events by SMBG at thresholds of >250 mg/dL and >400 mg/dL.
- [0200]** Change from baseline in PD biomarkers (e.g., levels of insulin, c-peptide).
- [0201]** Changes from baseline in ECOG and HRQoL assessments (SF-36 v2, HFS-II Worry Subscale Only).
- [0202]** Overall survival (OS).
- [0203]** Any changes in background SOC medications for hypoglycemia will be evaluated, such as the occurrence of overall use, de-escalation, and escalation of SOC regimen may also be assessed.
- [0204]** Efficacy evaluation
- [0205]** The glycemic efficacy of RZ358 will be assessed by SMBG via POC glucometer (primary), adjudicated Level 3 hypoglycemia events, CGM, patient reported outcomes (e.g., HRQoL, ECOG), and use of acute treatments meeting rescue criteria during the endpoint-specific efficacy evaluable periods, compared to baseline and/or the placebo-controlled group (SOC alone).
- [0206]** Self-monitoring of blood glucose by POC glucometer will be used as the primary tool to evaluate glycemic eligibility and efficacy endpoints. Self-monitored blood glucose readings should be performed by the participant at least 4 times per day (e.g. morning [pre-feed], mid-day [pre-feed], evening [pre-feed] and at bedtime) throughout the study. Several criteria for evaluation of glycemic control by SMBG (event based) will be evaluated over the 8-week efficacy evaluable period after the last dose in the pivotal treatment period, including the average weekly count (rate) of hypoglycemia and hyperglycemia events at different thresholds (including the primary efficacy endpoint).

[0207] Several criteria for evaluation of glycemic control by CGM (time-based criteria) will be evaluated over the 8-week efficacy evaluable period after the last dose in the pivotal treatment period, concluding with the Week 8 EoT visit. Criteria for evaluation based on CGM will include the average time in hypoglycemia, target range, or hypoglycemia at different thresholds and time periods (daily and overnight).

[0208] Participant-Reported Quality of Life (QoL) Assessments: At screening and prior to dosing on Week 4 and Week 8 participants will be asked to complete 2 QoL surveys: HFS-II-W (worry subscale) and Short-Form 36 version 2 (SF-36-v2) to assess ancillary clinical outcomes related to hypoglycemia. The criteria for evaluation of these participant-reported outcomes include change in QoL (SF-36-v2), health-related Hypoglycemia-relevant questionnaire (HFS-II).

[0209] Eastern Cooperative Oncology Group (ECOG): These scales and criteria are used by doctors and researchers to assess how a participant's disease is progressing, to discuss how the disease affects the daily living abilities of the participant, and to determine appropriate treatment and prognosis (Oken, 1982). The ECOG performance scale will be used to evaluate participant performance status during screening, Week 4 and at the end of the pivotal treatment period (Week 8).

[0210] Participant-Reported Assessments (eDiary/ Concomitant Therapeutic Interventions): During screening and the pivotal treatment period, the participants will be asked to use an eDiary, to capture and characterize clinically apparent hypoglycemia events (symptomatic or requiring 3rdparty intervention, or meeting and requiring rescue), including associated SMBG values, if available. All acute therapeutic rescue interventions including acute enteral (tube) interventions e.g. dextrose used for these events, are also to be recorded in the eDiary

[0211] Statistical Analysis Method

[0212] For the primary endpoint, the mixed model for repeated measure (MMRM) model will be used to handle the missing data. Missing data caused by treatment discontinuation will be imputed using control-based pattern imputation assuming missing not at random (MNAR). Multiple imputed datasets will be created. Each dataset will be analyzed using an MMRM with treatment, week, treatment by week interaction as fixed effects and baseline average weekly count of aggregate Level 2 (SMBG) and Level 3 hypoglycemia events as a covariate. Rubin's method will be used to pool model results from all imputed datasets. The 95% confidence intervals (CIs) will be calculated.

[0213] It is hypothesized that the administration of RZ358 anti-INSR antibody will improve insulin signaling (as measured by hypoglycemia endpoints), and reduce hypoglycemic events in treated subjects.

[0214] It is provided herein that anti-insulin receptor antibodies or other agents that block signaling through the insulin receptor by insulin or insulin-like substances are useful to treat hypoglycemia or hyperinsulinism associated with non-islet cell tumors and other neoplasms that are not insulinomas.

What is claimed is:

1. A method of treating benign or malignant neoplasms comprising administering to a subject in need thereof an antibody that specifically binds insulin receptor (INSR) or another antagonist of insulin receptor signaling.
2. The method of claim 1, wherein the antibody or another antagonist of insulin receptor signaling is administered in combination with other anti-neoplastic therapies or other therapeutics used to treat hypoglycemia or hyperinsulinism.
3. The method of claim 1 or 2, wherein the neoplasm is associated with a solid tumor.
4. The method of any one of claims 1 to 3, wherein the neoplasm is selected from the group consisting of adrenal gland cancer, AIDS-associated cancer, alveolar soft part sarcoma, anal cancer, bladder cancer, bone cancer, brain and spinal cord cancer, breast cancer, carotid body tumor, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, desmoplastic small round cell tumor, ependymoma, endometrial cancer (including, unselected endometrial cancer, MSI-high endometrial cancer, dMMR endometrial cancer, and/or POLE exonuclease domain mutation positive endometrial cancer), Ewing's sarcoma, extraskeletal myxoid chondrosarcoma, gallbladder or bile duct cancer (including, cholangiocarcinoma bile duct cancer), gastric cancer, gastroesophageal junction (GEJ) cancer, gestational trophoblastic disease, germ cell tumor, glioblastoma, head and neck cancer, a hematological malignancy, a hepatocellular carcinoma, islet cell tumor, insulinoma, Kaposi's Sarcoma, kidney cancer, leukemia, liposarcoma/malignant lipomatous tumor, liver cancer, lymphoma, lung cancer, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesothelioma, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancer, papillary thyroid carcinoma, parathyroid tumor, pediatric cancer, peripheral nerve sheath tumor, pharyngeal cancer, pheochromocytoma, pituitary tumor, prostate cancer, posterior uveal melanoma, renal metastatic cancer, rhabdoid tumor, rhabdomyosarcoma, sarcoma, skin cancer, a small round blue cell tumor of childhood, soft-tissue sarcoma, squamous cell cancer, stomach cancer, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, and uterine cancer.
5. The method of any one of claims 1-4, wherein the neoplasm exhibits an overproduction of insulin, pro-insulin, IGF2, big IGF2, or IGF2 variants.
6. The method of any one of claims 1-5, wherein the neoplasm is a metastatic neoplasm.

7. A method of treating tumor-associated hyperinsulinism and hypoglycemia induced by benign or malignant neoplasms comprising administering to a subject in need thereof an antibody that specifically binds insulin receptor (INSR).

8. A method of treating tumor-associated hyperinsulinism and hypoglycemia induced by benign or malignant neoplasms comprising administering to a subject in need thereof a compound that specifically binds insulin receptor (INSR).

9. The method of claim 7 or claim 8, wherein the benign or malignant neoplasm is selected from the group consisting of: non-islet cell tumor hypoglycemia (NICTH), non-islet cell tumor hyperinsulinism (NICTHI), Doege-Potter syndrome, insulinoma, ectopic insulinoma, IGF2-oma, pro-insulinoma, pancreatic neuroendocrine tumors, non-pancreatic neuroendocrine tumors, mesenchymal tumors, adrenal carcinoma, hepatocellular carcinoma, gastrointestinal carcinoma, ovarian carcinoma, pheochromocytoma, sarcomas, lymphomas, leukemias, and small-cell lung carcinomas.

10. The method of any one of claims 7 to 9, wherein the tumor associated hyperinsulinism and resulting hypoglycemia are mediated through excess INSR signaling of an insulin-like substance.

11. The method of claim 10, wherein the insulin-like substance is insulin, proinsulin, INSR autoantibodies, other insulin-like peptides, hormones, or effector substances.

12. The method of claim 11, wherein the other insulin-like peptides, hormones or effector substances are selected from the group consisting of insulin-like growth hormone 1 (IGF-1) or its precursors, IGF-1 prohormones, IGF-1 variants, insulin-like growth hormone-2 (IGF-2) or its precursors, IGF-2 prohormones, and IGF-2 variants.

13. The method of claim 12, wherein the IGF-2 variant is Big IGF-2.

14. The method of any one of claims 1 to 13, wherein the anti-INSR antibody comprises

(A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and

(B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

15. The method of any one of claims 1 to 14, wherein the anti-INSR antibody comprises
- a. a light chain variable domain comprising a sequence of amino acids at least 80% identical to SEQ ID NO: 2; or
 - b. a heavy chain variable domain comprising a sequence of amino acids that is at least 80% identical to SEQ ID NO: 1; or
 - c. a light chain variable domain of (A) and a heavy chain variable domain of (B).
16. The method of any one of claims 1 to 15, wherein the anti-INSR antibody is an IgG2 antibody.
17. The method of any one of claims 1 to 16, wherein the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.
18. The method of any one of claims 1 to 17, wherein the composition is administered daily, every 2 days, every 3 days, weekly, every 2 weeks, every 3 weeks, twice monthly, every 4 weeks, monthly, every 2 months, every 3 months or every 6 months.
19. The method of any one of claims 1 to 18, wherein the composition is administered intravenously.
20. The method of any one of claims 1 to 18, wherein the composition is administered subcutaneously.
21. The method of any one of the preceding claims wherein the subject is administered from 3-12 mg/kg anti-INSR antibody.
22. The method of any one of the preceding claims, wherein the subject is administered 9 mg/kg anti-INSR antibody weekly, bi-weekly, every 3 weeks, or every 4 weeks.
23. The method of any one of the preceding claims, wherein the subject is still receiving a standard of care therapy for treating hypoglycemia.
24. The method of claim 23, wherein the standard of care therapy is selected from the group consisting of intravenous dextrose, short-acting glucagon injections, continuous glucagon infusions, parenteral nutrition, diazoxide, SSAs, corticosteroids, mTOR inhibitors, supplemental enteral carbohydrates, and uncooked corn starch.
25. The method of any one of the preceding claims, wherein the administration results in a decrease in need for or use of standard of care therapies.

26. The method of any one of the preceding claims, wherein the administration results in a decrease from baseline in Level 2 and/or Level 3 hypoglycemia events.

27. The method of any one of the preceding claims, wherein the administration results in a decrease from baseline in overall hypoglycemia events.