binding to extracellular regions of the INSR uncomplexed to inslin, to the INSR complexed with insulin, or to both. INSR is a membrane-bound cell surface receptor.

[0011] In one example, the disclosure provides an antibody that binds to insulin receptor and/or a complex comprising insulin and insulin receptor with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of strengthening binding affinity or binding rate parameter between insulin and insulin receptor (INSR) by about 5-fold to 200-fold. In one embodiment, the antibody is capable of strengthening the binding affinity or binding rate parameter between insulin and insulin receptor by about 1.5-fold to about 100-fold, or about 2-fold to 25-fold. It is further contemplated that the modulation is about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g., at least 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to 100-fold, or up to 90-fold, or up to 80-fold, or up to 70-fold, or up to 60-fold, or up to 50-fold, or up to 40-fold, or up to 30-fold, or up to 20-fold, or up to 10-fold. In a further example, the antibody strengthens binding affinity or binding rate parameter by 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 fold or more, or any range between any of these values. In some examples, the binding affinity is any one of K_A, K_D, the ratio of on rate divided by off rate, or the ratio of off rate divided by on rate. In specific examples, the antibody increases K_A by the desired fold, or decreases K_D by the desired fold, or increases the ratio of on rate to off rate by the desired fold, or decreases the ratio of off rate to on rate by the desired fold. In some examples, the binding rate parameter is the on rate or off rate. In specific examples, the antibody increases the on rate or decreases the off rate. Alternatively, in some examples where the binding affinity does not change detectably or significantly, increasing the on rate and increasing the off rate may shift the signaling pathway away from mitogenic signaling towards metabolic signaling (glucose uptake).

[0012] In one example, an antibody that strengthens the binding affinity between insulin and INSR is a positive modulator.

[0013] In another example, the antibody is an agonist.

[0014] In a related example, an antibody that activates the INSR without dependence on insulin is an allosteric agonist. In certain examples, the disclosure provides an allosteric agonist antibody that binds to insulin receptor with an affinity of at least 10^{-5},10^{-6}, 10^{-7}, 10^{-8},

10^{-9} M and (a) exhibits maximal agonist activity that is 20%-80% that of insulin's maximal agonist activity when measured in a pAKT assay, (b) when present does not alter the EC50 of insulin for INSR by more than 2-fold, and (c) when present does not alter the K_D of insulin for INSR by more than 2-fold .

[0015] In a related example, the allosteric agonist exhibits a maximal agonist response that is 80% or less of the maximal agonist response of insulin, for example 15%-80%, 20-60%, 20%-40% or 15%-30%. In certain examples, the antibodies constitutively activate INSR with a maximal agonist response that is at least about 15%, 20%, 25%, 30%, 35%, 40%; and up to 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% of the maximal agonist response of insulin. It is understood that any combination of any of these range endpoints is contemplated without having to recite each possible combination.

[0016] In another example, the disclosure provides an antibody that binds to insulin receptor and/or a complex comprising insulin and insulin receptor with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of weakening the binding affinity or binding rate parameter between insulin and insulin receptor by about 1.5-fold to 100-fold. In one example, the antibody is capable of weakening the binding affinity or binding rate parameter between insulin and insulin receptor by about 2-fold to 25-fold, or 1.5-fold to 25 fold, or 2-fold to 50-fold. It is further contemplated that the modulation is about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g. at least 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to 100-fold, or up to 90-fold, or up to 80-fold, or up to 70-fold, or up to 60-fold, or up to 50-fold, or up to 40-fold, or up to 30-fold, or up to 20-fold, or up to 10-fold. In a further example, the antibody weakens binding affinity or binding rate parameter by 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 fold or more, or any range between any of these values. In some example, the binding affinity is any one of K_A, K_D, the ratio of on rate divided by off rate, or the ratio of off rate divided by on rate. In specific examples, the antibody decreases K_A by the desired fold, or increases K_D by the desired fold, or decreases the ratio of on rate to off rate by the desired fold, or increases the ratio of off rate to on rate by the desired fold. In some examples, the binding rate parameter is the on rate or off rate. In specific examples, the antibody decreases the on rate or increases the off rate.

[0017] In one example, an antibody that weakens the binding affinity between insulin and INSR is a negative modulator. In some specific examples, an antibody that weakens the binding affinity between insulin and INSR is an antagonist.

[0018] In still another example, an antibody that strengthens or weakens binding affinity or binding rate parameter between insulin and insulin receptor comprises at least one heavy chain CDR (HCDR1, HCDR2 and HCDR3) set out in SEQ ID NOS: 151-303. In a related example, the antibody comprises a mature heavy chain variable region of SEQ ID NO: 151-303. It is contemplated that any of the above antibodies further comprises a suitable human or human consensus or human-derived constant region, e.g. IgG1, IgG2, IgG3, or IgG4 or a hybrid thereof.

[0019] In a further example, the antibody that strengthens or weakens binding affinity or binding rate parameter between insulin and insulin receptor comprises at least one light chain CDR (LCDR1, LCDR2, or LCDR3) set out in SEQ ID NOS: 1-150. In still another example, the antibody comprises a mature light chain variable region of SEQ ID NO: 1- 150. It is contemplated that any of the above antibodies further comprises a human kappa or lambda light chain constant region.

[0020] In one example, the antibody binds insulin receptor. In a related example, the antibody binds the α subunit of INSR. In a further example, the antibody binds the β subunit of INSR. In yet another example, the antibody binds the α and β subunit of the receptor. In a related example, the antibody binds an insulin/ insulin receptor complex. In another example, the antibody that binds the insulin/INSR complex does not detectably bind insulin receptor alone, e.g., in the absence of insulin, or insulin alone.

[0021] In another example, the disclosure provides an antibody that specifically binds insulin receptor and/or a complex comprising insulin and insulin receptor with an equilibrium dissociation constant K_D of 10^{-5}M or less, comprising at least one heavy chain CDR (HCDR1, HCDR2 and HCDR3) of SEQ ID NOS: 151-303. In a related example, the antibody comprises a heavy chain variable region of SEQ ID NO: 151-303. It is contemplated that any of the above antibodies further comprises a suitable human or human consensus or human-derived constant region, e.g. IgG1, IgG2, IgG3, or IgG4 or a hybrid thereof.

[0022] In a further example, the antibody that specifically binds insulin receptor and/or a complex comprising insulin and insulin receptor with an equilibrium dissociation constant

K_D of 10^{-5}M or less, comprises at least one light chain CDR (LCDR1, LCDR2, or LCDR3) set out in SEQ ID NOS: 1-150. In still another example, the antibody comprises a light chain variable region of SEQ ID NO: 1-150. It is contemplated that any of the above antibodies further comprises a human kappa or lambda light chain constant region.

[0023] It is further contemplated that any of the antibodies described above comprises one, two, three, four, five or six CDRs. In one example, the antibody comprises one, two or three heavy chain CDRs set out in SEQ ID NO: 151-303. In another example, the antibody comprises one, two or three light chain CDRs set out in SEQ ID NO: 1-150.

[0024] In one example, the antibody binds insulin receptor. In a related example, the antibody binds an insulin/INSR complex. In another example, the antibody that binds the insulin/INSR complex does not detectably bind insulin receptor alone or insulin alone.

[0025] It is further contemplated that an antibody that strengthens binding affinity or binding rate parameter of insulin and insulin receptor activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay. In a related example, the INSR is activated by at least 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, or 80% of the maximal signal of insulin. In another example, the antibody that strengthens binding affinity or binding rate parameter of insulin/INSR activates less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay. In a related example, the INSR is activated by less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% of the maximal signal of insulin. In some examples, the INSR is not detectably activated by the antibody.

[0026] It is further contemplated that the antibody reduces fasting blood glucose levels, in a subject having elevated blood glucose, hyperglycemia or disorder associated with insulin resistance, toward the normal range of glucose levels. In one example, the positive modulating antibody or agonist reduces fasting blood glucose levels in the subject by approximately 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more.

[0027] In one example, antibody refers to an antibody or fragment thereof, or a polypeptide comprising an antigen binding domain of an antibody. Exemplary antibodies or antibody fragments include polyclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, multispecific antibodies, 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 immunopharmaceutical (SMIP), a 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. In one example, the antibody is a monoclonal antibody. In a related example, the antibody is a human antibody.

[0028] In some specific examples, the disclosure excludes rodent antibodies, i.e. antibodies produced by a hybridoma of rodent (e.g. murine, rat) cells. Such antibodies, whether produced by the hybridoma or recombinantly, would have rodent framework amino acid sequence and be immunogenic if administered to humans. In some specific examples, the disclosure excludes the rodent antibodies disclosed in any one of the following references, hereby incorporated by reference in their entirety: 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. However, the disclosure may include humanized versions of such rodent antibodies, treatment methods using such humanized antibodies, and sterile pharmaceutical compositions comprising such humanized antibodies. In some specific examples, the disclosure excludes the humanized antibody 83-14 reported in Boado et al, Biotech and BioEng. 96(2): 381-391 or WO04/050016.

[0029] In some examples, the disclosure contemplates:

[0030] a monoclonal antibody that retains any one, two, three, four, five, or six of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, or LCDR3 of any one of SEQ ID NOs: 151-303 and SEQ ID NOs: 1-150, respectively, optionally including one or two mutations in such CDR(s),

e.g., a conservative or non-conservative substitution, and optionally paired as set forth in Table 3;

[0031] a monoclonal antibody that retains all of HCDR1, HCDR2, HCDR3, or the heavy chain variable region of any one of SEQ ID NOs: 151-303, optionally including one or two mutations in any of such CDR(s), optionally further comprising any suitable heavy chain constant region, e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, or IgE or hybrid thereof;

[0032] a monoclonal antibody that retains all of LCDR1, LCDR2, LCDR3, or the light chain variable region of any one SEQ ID NOs: 1-150, optionally including one or two mutations in any of such CDR(s), optionally further comprising to any suitable light chain constant region, e.g. a kappa or lambda light chain constant region;

[0033] a purified preparation of a monoclonal antibody, comprising the light chain variable region and heavy chain variable regions as set forth in SEQ ID NOs: 1-303 and paired as set forth in Table 3;

[0034] a monoclonal antibody that binds to the same linear or three-dimensional epitope of INSR as an antibody comprising a variable region set out in SEQ ID NO: 1-303 a, e.g., as determined through X-ray crystallography or other biophysical or biochemical techniques such as deuterium exchange mass spectrometry, alanine scanning and peptide fragment ELISA;

[0035] a monoclonal antibody that competes with an antibody comprising a variable region set out in SEQ ID NO: 1-303, optionally paired as in Table 3, for binding to human INSR by more than about 75%, more than about 80%, or more than about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94% or 95%.

[0036] In some examples, the antibody comprises all three light chain CDRs, all three heavy chain CDRs, or all six CDRs of an antibody comprising a variable region set out in SEQ ID NO: 1-303. In some examples, two light chain CDRs from an antibody may be combined with a third light chain CDR from a different antibody. Alternatively, a LCDR1 from one antibody can be combined with a LCDR2 from a different antibody and a LCDR3 from yet another antibody, particularly where the CDRs are highly homologous. Similarly, two heavy chain CDRs from an antibody may be combined with a third heavy chain CDR from a different antibody; or a HCDR1 from one antibody can be combined with a HCDR2 from a different antibody and a HCDR3 from yet another antibody, particularly where the CDRs are highly homologous.

[0037] Consensus CDRs may also be used. Any one of the consensus CDRs derived herein may be combined with two other CDRs from the same chain (e.g., heavy or light) of any of the antibodies described herein, e.g. to form a suitable heavy or light chain variable region.

[0038] In another example, the disclosure provides variants or derivatives of the antibodies described herein. For example, in one example the antibody is labeled with a detectable moiety as described herein. In a further example, the antibody is conjugated to a hydrophobic moiety described herein.

[0039] Variants of the antibodies include antibodies having a mutation or alteration in an amino acid sequence provided herein, including an amino acid insertion, deletion or substitution, e.g., a conservative or non-conservative substitution.

[0040] In some examples, an antibody is provided that comprises a polypeptide having an amino acid sequence at least about 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 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: 151-303 and/or an amino acid sequence an amino acid sequence at least about 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 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: 1-150, the antibody further comprising at least one, two, three, four, five or all of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3. In some examples, the amino acid sequence with percentage identity to the light chain variable region may comprise one, two or three of the light chain CDRs. In other examples, the amino acid sequence with percentage identity to the heavy chain variable region may comprise one, two, or three of the heavy chain CDRs.

[0041] It is contemplated that the antibodies of the disclosure may have one, or two or more amino acid substitutions in the CDR regions of the antibody, e.g. conservative substitutions.

[0042] In a related example, 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.

[0043] It is further contemplated that the disclosure provides a purified polypeptide comprising any one of the amino acid sequences of SEQ ID NO: 1-150 fused to any one of the amino acid sequences of SEQ ID NO: 151-303, optionally paired as the heavy/light chain variable regions set forth in Table 3, or fragments thereof that include at least a portion of SEQ ID NO: 1-150 and SEQ ID NO: 151-303, optionally paired as set forth in Table 3, wherein the polypeptide binds insulin receptor, insulin or the insulin/insulin receptor complex.

[0044] It is contemplated that antibodies of the disclosure, including polypeptides comprising all or a portion of an antigen binding fragment in any one of SEQ ID NOs: 1-303, retain binding affinity, e.g. as measured by K_D, to insulin receptor, insulin or a complex of insulin/INSR of 10^{-5},10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} M or less (wherein a lower value indicates a higher binding affinity), optionally as measured by surface plasmon resonance.

[0045] In some of the preceding examples, the disclosure contemplates an antibody that binds to insulin receptor and/or a complex comprising insulin and insulin receptor, with an equilibrium dissociation constant K_D of 10^{-5}M or less, that is capable of strengthening the binding affinity between insulin and insulin receptor by about 5-fold to 500-fold. In one example, the antibody is characterized by the following equilibrium dissociation constant K_D binding properties: (i) said antibody binds with an equilibrium dissociation constant K_D of about 10^{-5}M, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} 10^{-10} , 10^{-11} M or less, to a complex comprising insulin (C1) and insulin receptor (C2); and (ii) any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$ is at least about 5-fold lower than any of K_{AC2} or K_{AC1}. In a related example, any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$ is about 5-fold to 200-fold lower than any of K_{AC2} or K_{AC1}.

[0046] In some examples, the antibody binds an insulin/ insulin receptor complex. In further examples, the antibody binds insulin receptor alone, in an uncomplexed form. In a related example, the antibody does not detectably bind insulin receptor alone, e.g., in the absence of insulin. In certain examples, the antibody is capable of strengthening the binding affinity between insulin and insulin receptor by at least about 5-fold, optionally to about 200-fold, optionally to about 100-fold. It is further provided that in some examples, the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

[0047] In some examples, for any of the antibodies described herein, the difference in binding affinity or binding rate parameter ranges from about 1.5-fold to about 1000-fold, or

about 1.5-fold to about 500-fold, about1.5-fold to about 100-fold, or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, about 5-fold to about 500-fold, or about 5-fold to about 200-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to 500-fold, or up to 200-fold, or up to 150-fold, or up to 100-fold, or up to 90-fold, or up to 80-fold, or up to 70-fold, or up to 60-fold, or up to 50-fold, or up to 40-fold, up to 30-fold, up to 20-fold, or up to 10-fold, or up to 5-fold or up to 3-fold.

[0048] In some examples, the disclosure provides an agonist antibody that binds to insulin receptor with an affinity, e.g. K_D, of 10^{-5},10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} 10^{-10} , 10^{-11} M or less, optionally that exhibits maximal agonist activity that is 20%-100% that of insulin's maximal agonist activity when measured in pAKT assay. In a related example, the disclosure contemplates an allosteric agonist antibody that binds to insulin receptor with an affinity, e.g., K_D of 10^{-5},10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} 10^{-10} , 10^{-11} M or less and (a) exhibits maximal agonist activity that is 20%-80% that of insulin's maximal agonist activity when measured in pAKT assay, (b) when present does not alter the EC50 of insulin for INSR by more than 2-fold or 3-fold, and (c) when present does not alter the K_D of insulin for INSR by more than 2-fold or 3-fold. It is further provided that in some examples, the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

[0049] It is contemplated, in certain examples, that any of the above antibodies may also exhibit weak agonist activity, e.g., activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay. In a further example, the antibody activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

[0050] In some examples, the antibody comprises a heavy chain variable region selected from the group consisting of the mature heavy chain variable region sequences set forth in SEQ ID NOs:, 281, 278, 277, 209, 275, 223, 284, 276, and 236 and a light chain variable region selected from the group consisting of the mature light chain variable sequences set forth in SEQ ID NOs: 141, 138, 137, 35, 135, 57, 144, 136, and 98, optionally paired as set forth in Table 3.

[0051] In another example, the antibody comprises (a) the heavy chain variable region of any of Ab006, Ab030, Ab004, Ab013, Ab009, Ab007, Ab011, Ab001, Ab012, Ab010,

Ab003, Ab008, Ab002, Ab005, Ab076, Ab077, Ab079, Ab080, Ab083, Ab059, Ab078, Ab085 or set out in SEQ ID NO: 291, 196, 239, 267 and 271 and the light chain variable region of any of Ab006, Ab030, Ab004, Ab013, Ab009, Ab007, Ab011, Ab001, Ab012, Ab010, Ab003, Ab008, Ab002, Ab005, Ab076, Ab077, Ab079, Ab080, Ab083, Ab059, Ab078, Ab085 or set out in SEQ ID NO: 76, 80, 101, 128, and 132, optionally paired as set forth in Table 3 and preferably the mature portions thereof, or (b) one, two or three heavy chain CDRs of any of Ab006, Ab030, Ab004, Ab013, Ab009, Ab007, Ab011, Ab001, Ab012, Ab010, Ab003, Ab008, Ab002, Ab005, Ab076, Ab077, Ab079, Ab080, Ab083, Ab059, Ab078, Ab085 or set out in SEQ ID NO: 291, 196, 239, 267 and 271 and/or one, two or three light chain CDRs of any of Ab006, Ab030, Ab004, Ab013, Ab009, Ab007, Ab011, Ab001, Ab012, Ab010, Ab003, Ab008, Ab002, Ab005, Ab076, Ab077, Ab079, Ab080, Ab083, Ab059, Ab078, Ab085 or set out in SEQ ID NO: 76, 80, 101, 128, and 132, optionally including one or two mutations in any one, two or three of such heavy or light chain CDRs, e.g., a conservative or non-conservative substitution, optinoally paired as set forth in Table 3; or (c) all six CDRs of any of Ab006, Ab030, Ab004, Ab013, Ab009, Ab007, Ab011, Ab001, Ab012, Ab010, Ab003, Ab008, Ab002, Ab005, Ab076, Ab077, Ab079, Ab080, Ab083, Ab059, Ab078, Ab085 or antibodies having the variable regions set out in SEQ ID NO: 76, 80, 101, 128, 132, 291, 196, 239, 267, and 271, optionally paired as set forth in Table 3.

[0052] In other examples, the disclosure provides an antibody that competes with any of the antibodies described herein, e.g. by at least 70%, 75%, or 80%. In certain examples, the antibody exhibits greater than or equal to 70% competition, e.g. at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab079, Ab076, Ab083, Ab080, Ab062, Ab020, Ab019, Ab088, and Ab089, and optionally exhibits greater than or equal to 30% competition with any one, two, three or all antibodies selected from the group consisting of Ab086, Ab064, Ab001, and Ab018. Optionally, the antibody does not compete with one or more of Ab062 and Ab086, and optionally may bind both human and murine insulin receptor or complex.

[0053] In a related example, the antibody exhibits greater than or equal to 70% competition, e.g., at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab040, Ab062, Ab030, Ab001, and Ab018, and optionally exhibits greater than or equal to 30% competition with any one, two, three or all antibodies selected from the group consisting of Ab037, Ab078, Ab083, Ab080, and

Ab085. In a related example, the antibody does not compete with any one, two, three or more of antibodies selected from the group consisting of Ab053, Ab064, 83-7, Ab019, Ab088, and Ab089. Optionally, the antibody binds both human and murine insulin receptor or complex. In another example, the antibody exhibits greater than or equal to 70% competition, e.g. at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab064, Ab062, Ab085, and Ab078. Optionally, the antibody exhibits no competition with any one, two, three or more of antibodies selected from the group consisting of Ab077, Ab001, Ab018, Ab030, Ab037, Ab079, Ab076, Ab083, Ab019, Ab088, Ab089, and Ab040. Optionally, the antibody binds both human and murine insulin receptor or complex.

[0054] In one aspect, the present disclosure refers to a monoclonal antibody that binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii), with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of weakening the binding affinity between insulin and insulin receptor by at least 3-fold, optionally up to 1000-fold, wherein the antibody binds (i) or (ii) in an allosteric manner, wherein the antibody comprises

(a) the heavy chain variable region of any of SEQ ID NO: 279, SEQ ID NO: 241, SEQ ID NO: 258, SEQ ID NO: 155, SEQ ID NO: 228, SEQ ID NO: 169, SEQ ID NO: 160, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 226, SEQ ID NO: 231, SEQ ID NO: 233, SEQ ID NO: 244, SEQ ID NO: 246, SEQ ID NO: 260, SEQ ID NO: 262, and the light chain variable region of any of SEQ ID NO: 139, SEQ ID NO: 103, SEQ ID NO: 119, SEQ ID NO: 8, SEQ ID NO: 89, SEQ ID NO: 18, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 121, and SEQ ID NO: 123, wherein the heavy chain and light chain are paired as set out in Table 3; or

(b) three heavy chain CDRs of any of SEQ ID NO: 279, SEQ ID NO: 241, SEQ ID NO: 258, SEQ ID NO: 155, SEQ ID NO: 228, SEQ ID NO: 169, SEQ ID NO: 160, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 226, SEQ ID NO: 231, SEQ ID NO: 233, SEQ ID NO: 244, SEQ ID NO: 246, SEQ ID NO: 260, SEQ ID NO: 262, and three light chain CDRs of any of SEQ ID NO: 139, SEQ ID NO: 103, SEQ ID NO: 119, SEQ ID NO: 8, SEQ ID NO: 89, SEQ ID NO: 18, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 121, and SEQ ID NO: 123, wherein the heavy chain and light chain are paired as set out in Table 3; or

(c) all six CDRs of any of SEQ ID NO: 279 and 139, SEQ ID NO: 241 and 103, SEQ ID NO: 258 and 119, SEQ ID NO: 155 and 8, SEQ ID NO: 228 and 89, SEQ ID NOs: 169 and 18, SEQ ID NOs: 160 and 1, SEQ ID NOs: 153 and 2, SEQ ID NOs: 154 and 4, SEQ ID NOs: 226 and 87, SEQ ID NOs: 231 and 92, SEQ ID NOs: 233 and 94, SEQ ID NOs: 244 and 105, SEQ ID NOs: 246 and 107, SEQ ID NOs: 260 and 121, and SEQ ID NOs: 262 and 123. In certain examples, the antibody weakens the affinity between said insulin and insulin receptor by about 3-fold to 500-fold. In some examples, the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

[0055] In some examples, for any of the antibodies described herein, the difference in binding affinity or binding rate parameter ranges from about 1.5-fold to about 1000-fold, or about 1.5-fold to about 500-fold, about1.5-fold to about 100-fold, or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, about 5-fold to about 500-fold, or about 5-fold to about 200-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to 500-fold, or up to 200-fold, or up to 150-fold, or up to 100-fold, or up to 90-fold, or up to 80-fold, or up to 70-fold, or up to 60-fold, or up to 50-fold, or up to 40-fold, up to 30-fold, up to 20-fold, or up to 10-fold, or up to 5-fold or up to 3-fold.

[0056] In a related example, the antibody increases the EC50 of insulin signaling activity by about 2-fold to 1000-fold, optionally in a pAKT assay. In certain examples, the antibody increases the EC50 by at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000-fold.

[0057] In certain examples, the antibody comprises a heavy chain variable region selected from the group consisting of the mature heavy chain variable region sequences set forth in SEQ ID NOs: 241, 279, 258, 155, and 228 and a light chain variable region selected from the group consisting of the mature light chain variable region sequences set forth in SEQ ID NOs: 103, 139, 119, 8, and 89, optinoally paired as set forth in Table 3.

[0058] In a further example, the antibody comprises (a) the heavy chain variable region of any of Ab087, Ab019, Ab088, Ab089, Ab020, Ab050, Ab052, Ab055, Ab057, Ab061, Ab063, Ab065, Ab070, Ab072, Ab074, Ab081 and the light chain variable region of any of Ab087, Ab019, Ab088, Ab089, Ab020, Ab050, Ab052, Ab055, Ab057, Ab061, Ab063, Ab065, Ab070, Ab072, Ab074, Ab081, preferably the mature portions thereof, or (b) one, two or three heavy chain CDRs of any of Ab087, Ab019, Ab088, Ab089, Ab020, Ab050, Ab052, Ab055, Ab057, Ab061, Ab063, Ab065, Ab070, Ab072, Ab074, Ab081 and/or one, two or three light chain CDRs of any of Ab087, Ab019, Ab088, Ab089, Ab020, Ab050, Ab052, Ab055, Ab057, Ab061, Ab063, Ab065, Ab070, Ab072, Ab074, Ab081, optionally including one or two mutations in any one, two or three of such heavy or light chain CDRs, e.g., a conservative or non-conservative substitution; or (c) all six CDRs of any of Ab087, Ab019, Ab088, Ab089, Ab020, Ab050, Ab052, Ab055, Ab057, Ab061, Ab063, Ab065, Ab070, Ab072, Ab074, Ab081.

[0059] In a further example, the disclosure provides an antibody that competes with the above antibodies, wherein the antibody exhibits greater than or equal to 70% competition, e.g., at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab079, Ab076, Ab083, Ab080, Ab062, and Ab020, Ab019, Ab088, Ab089. Optionally, the antibody does not exhibit competition with any one, two, three or more of the antibodies selected from the group consisting of Ab062, Ab086, Ab001, Ab018, Ab030, Ab037, Ab064; and optionally, the antibody is human reactive only, and does not bind murine insulin receptor or complex.

[0060] In one example, the disclosure provides an antibody that is an agonist, wherein the antibody comprises a heavy chain variable region selected from the group consisting of the mature heavy chain variable region sequences set forth in SEQ ID NOs: 195, 220, 303, 197, 208, 243, 245 and 251 and a light chain variable region selected from the group consisting of the mature light chain variable region sequences set forth in SEQ ID NOs: 77, 50, 90, 84, 34, 104, 106 and 112, optionally paired as set forth in Table 3.

[0061] In a related example, the antibody comprises (a) the heavy chain variable region of any of Ab021, Ab029, Ab022, Ab017, Ab023, Ab024, Ab025, Ab026, Ab031, Ab035, Ab027, Ab036, Ab037, Ab028, Ab038, Ab039, Ab040, Ab041, Ab042, Ab032, Ab043, Ab044, Ab045, Ab046, Ab047, Ab018, Ab033, Ab048, Ab014, Ab015, Ab049, Ab034, Ab051, Ab053, Ab054, Ab056, Ab058, Ab062, Ab064, Ab066, Ab067, Ab068, Ab086, Ab069, Ab071, Ab073, Ab075, Ab082, Ab084 set out in SEQ ID NOs: 252, 253, 263, 265 and 269 and the light chain variable region of any of Ab021, Ab029, Ab022, Ab017, Ab023, Ab024, Ab025, Ab026, Ab031, Ab035, Ab027, Ab036, Ab037, Ab028, Ab038, Ab039, Ab040, Ab041, Ab042, Ab032, Ab043, Ab044, Ab045, Ab046, Ab047, Ab018, Ab033, Ab048, Ab014, Ab015, Ab049, Ab034, Ab051, Ab053, Ab054, Ab056, Ab058, Ab062, Ab064, Ab066, Ab067, Ab068, Ab086, Ab069, Ab071, Ab073, Ab075, Ab082, Ab084 or set out in SEQ ID NOs: 7, 113, 114, 124, 126 and 130, optionally paired as set forth in Table 3 and preferably the mature portions thereof, or (b) one, two or three heavy chain CDRs of any of Ab021, Ab029, Ab022, Ab017, Ab023, Ab024, Ab025, Ab026, Ab031, Ab035, Ab027, Ab036, Ab037, Ab028, Ab038, Ab039, Ab040, Ab041, Ab042, Ab032, Ab043, Ab044, Ab045, Ab046, Ab047, Ab018, Ab033, Ab048, Ab014, Ab015, Ab049, Ab034, Ab051, Ab053, Ab054, Ab056, Ab058, Ab062, Ab064, Ab066, Ab067, Ab068, Ab086, Ab069, Ab071, Ab073, Ab075, Ab082, Ab084 or set out in SEQ ID NOs: 252, 253, 263, 265 and 269 and/or one, two or three light chain CDRs of any of Ab021, Ab029, Ab022, Ab017, Ab023, Ab024, Ab025, Ab026, Ab031, Ab035, Ab027, Ab036, Ab037, Ab028, Ab038, Ab039, Ab040, Ab041, Ab042, Ab032, Ab043, Ab044, Ab045, Ab046, Ab047, Ab018, Ab033, Ab048, Ab014, Ab015, Ab049, Ab034, Ab051, Ab053, Ab054, Ab056, Ab058, Ab062, Ab064, Ab066, Ab067, Ab068, Ab086, Ab069, Ab071, Ab073, Ab075, Ab082, Ab084 or set out in SEQ ID NOs: 7, 113, 114, 124, 126 and 130, optionally including one or two mutations in any one, two or three of such heavy or light chain CDRs, e.g., a conservative or non-conservative substitution, optionally paired as set forth in Table 3; (c) all six CDRs of any of Ab021, Ab029, Ab022, Ab017, Ab023, Ab024, Ab025, Ab026, Ab031, Ab035, Ab027, Ab036, Ab037, Ab028, Ab038, Ab039, Ab040, Ab041, Ab042, Ab032, Ab043, Ab044, Ab045, Ab046, Ab047, Ab018, Ab033, Ab048, Ab014, Ab015, Ab049, Ab034, Ab051, Ab053, Ab054, Ab056, Ab058, Ab062, Ab064, Ab066, Ab067, Ab068, Ab086, Ab069, Ab071, Ab073, Ab075, Ab082, Ab084 or set out in SEQ ID NOs: 7, 113, 114, 124, 126, 130, 252, 253, 263, 265 and 269, optionally paired as set forth in Table 3.

[0062] In a related example, the disclosure provides an antibody that competes with the above antibodies for binding to target, wherein the antibody exhibits greater than or equal to 70% competition, e.g., at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab030, Ab037, Ab053, Ab001, Ab018, Ab064, Ab040 and optionally exhibits greater than or equal to 30% competition with any one, two, three or all antibodies selected from the group consisting of Ab085 and Ab086. Optionally, the antibody exhibits no competition with any one, two, three or more of the antibodies selected from the group consisting of Ab079, Ab076 and Ab088; and optionally binds to both human and murine insulin receptor or complex.

[0063] In a another example, the disclosure provides polynucleotides encoding antibodies and polypeptides of the disclosure, vectors comprising such polynucleotides, host cells comprising such polynucleotides or vectors, and methods of producing antibodies and polypeptides of the disclosure comprising growing such host cells in culture medium under suitable conditions and optionally isolating the encoded antibody or polypeptide from the host cells or culture medium, optionally followed by further purification of the antibody or polypeptide, e.g., as described herein.

[0064] Antibodies having the properties described herein may be isolated using a screening method to determine binding to the INSR and modulation of the insulin/INSR complex.

[0065] In one example, the disclosure provides a positive modulating antibody that strengthens the binding of a first component (C1) to a second component (C2) of a signaling complex, said antibody characterized by the following equilibrium dissociation constant K_D binding properties: (i) said antibody binds with an equilibrium dissociation constant K_D of about 10^{-5}M or less, e.g., 10^{-6}M or less, or 10^{-7}M or less, or 10^{-8}M or less, to any one of C1, C2, or a complex comprising C1 and C2 (C1C2); and (ii) any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$ is at least about 50% (1.5-fold) lower than any of K_{AC2} or K_{AC1}. In some examples any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$ is about 1.5-fold to about 100-fold lower than any of K_{AC2} or K_{AC1}; or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to about 100-fold, or up to about 90-fold, or up to about 80-fold, or up to about 70-fold, or up to about 60-fold, or up to about 50-fold, or up to about 40-fold, or up to about 30-fold, or up to about 20-fold, or up to about 10-fold lower. In some examples, any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$ is at least about 1.5-fold

lower than both of K_{AC2} or K_{AC1}; or 1.5-fold to about 100-fold lower, or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to about 100-fold, or up to about 90-fold, or up to about 80-fold, or up to about 70-fold, or up to about 60-fold, or up to about 50-fold, or up to about 40-fold, or up to about 30-fold, or up to about 20-fold, or up to about 10-fold lower.

[0066] In some examples, the disclosure provides a negative modulating antibody that weakens the binding of a first component (C1) to a second component (C2) of a signaling complex, said antibody characterized by the following equilibrium dissociation constant K_D binding properties: (i) said antibody binds with an equilibrium dissociation constant K_D of about 10^{-5}M or less, e.g., 10^{-6}M or less, or 10^{-7}M or less, or 10^{-8}M or less, to any one of C1, C2, or a complex comprising C1 and C2 (C1C2), and (ii) any of K_{AC2} or K_{AC1} is at least about 50% (1.5-fold) lower than any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$. In some examples, any of K_{AC2} or K_{AC1} is at least about 1.5-fold to 100-fold lower than any of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$; or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to about 100-fold, or up to about 90-fold, or up to about 80-fold, or up to about 70-fold, or up to about 60-fold, or up to about 50-fold, or up to about 40-fold, or up to about 30-fold, or up to about 20-fold, or up to about 10-fold lower. In some examples, any of K_{AC2} or K_{AC1} is at least about 1.5-fold lower than all of $K_{[C1C2]A}$, $K_{[AC2]C1}$, or $K_{[AC1]C2}$; or 1.5-fold to about 100-fold lower, or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to about 100-fold, or up to about 90-fold, or up to about 80-fold, or up to about 70-fold, or up to about 60-fold, or up to about 50-fold, or up to about 40-fold, or up to about 30-fold lower, or up to about 20-fold, or up to about 10-fold.

[0067] In specific examples, C1 and C2 are selected from the group consisting of insulin and insulin receptor.

[0068] In another aspect, the present disclosure refers to a method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent

to an antibody as defined herein. Optionally small amounts of a preservative such as a bactericidal or bacteriostatic agent are also included in the composition.

[0069] In another aspect, the present disclosure refers to a sterile composition comprising an antibody as defined herein and a sterile pharmaceutically acceptable diluent.

[0070] The disclosure further contemplates that the antibodies of the disclosure modulate binding between the INSR and insulin or insulin analogs or insulin mimetics. The antibodies of the disclosure preferably also exhibit desirable biological properties, including but not limited to enhancing glucose uptake in vitro or in vivo in animal models, and preferably the glucose uptake induced by exogenous insulin. In some examples, the antibodies are capable of increasing the rate or total amount of glucose uptake, or both.

[0071] In one example, the disclosure contemplates a method of treating a disorder associated with insulin resistance, comprising administering to a subject in need thereof a positive modulating antibody or agonist antibody of the disclosure in an amount effective to treat insulin resistance. In a related example, the treatment enhances glucose uptake. In a further example, the enhanced glucose uptake is selected from the group consisting of an increase in the rate of glucose uptake, an increase in the total amount of glucose uptake, or both. It is further contemplated that the treatment reduces fasting blood glucose levels, in a subject having elevated levels of blood glucose, hyperglycemia or a disorder associated with insulin resistance, back toward the normal range of fasting blood glucose levels. In a related example, the fasting blood glucose is reduced by approximately 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more compared to an untreated subject.

[0072] In related examples, the treatment reduces elevated HbA1c levels, which are a marker of elevated glucose levels over the preceding several-month period, and are indicative of diabetes. In further examples, treatment improves impaired glucose tolerance. In one example glucose tolerance is measured by glucose tolerance test (GTT).

[0073] In other examples, the treatment slows, reduces, or normalizes weight gain of a subject. In one example, the treatment reduces or slows weight gain by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% compared to an untreated subject. In some examples, the treatment slows, reduces, or normalizes weight loss of a subject. In one example, the treatment reduces or slows weight loss by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% compared to an untreated subject.

[0074] In a related example, it is contemplated that the antibodies or polypeptides described herein promote or induce weight loss in a subject. In one example, the disclosure provides a method to promote or induce weight loss by administration of a modulating antibody, fragment thereof or polypeptide as described herein. In one example, the modulating antibody is a positive modulator or partial agonist. In a related example, the modulating antibody is a negative modulator.

[0075] It certain examples, the treatment further results in improvement of one, two, three or more symptoms of diabetes or insulin resistance selected from the group consisting of dyslipidemia, elevated plasma triglycerides, elevated HOMA-IR, elevated plasma unesterified cholesterol, plasma total cholesterol elevated plasma insulin (indicative of insulin resistance), low non-HDL/HDL cholesterol ratio (or low total cholesterol/HDL cholesterol ratio), and elevated plasma leptin levels (indicative of leptin resistance).

[0076] It is further provided that the effects of treatment are also measured using in vitro and in vivo analysis using factors as described in the Detailed Description.

[0077] In one example, the disorder associated with insulin resistance is selected from the group consisting of hyperglycemia, pre-diabetes, metabolic syndrome (also referred to as insulin resistance syndrome), Type 2 diabetes mellitus, polycystic ovary disease (PCOS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), steatosis, obesity, dyslipidemia, Rabson-Mendenhall syndrome, Donohue syndrome or Leprechaunism.

[0077a] In one aspect, the present disclosure refers to the use of an antibody as defined herein in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling.

[0078] In one example, the disclosure provides a method of treating a condition or disorder associated with hyperinsulinemia, abnormal production and/or sensitivity to insulin that manifests as excess insulin signaling, comprising administering to a subject in need thereof a negative modulating antibody or an antagonist antibody of the disclosure in an amount effective to treat insulin overproduction and/or sensitivity. In one example, the disorder associated with insulin sensitivity is selected from the group consisting of cancer, Kaposi's sarcoma, insulinoma, diabetic renal disease, hypoglycemia, nesidioblastosis (KATP-Hl Diffuse Disease, KATP-Hl Focal Disease, or "PHHI"), GDH-Hl (Hyperinsulinism/Hyperammonaemia Syndrome (HI/HA), leucine-sensitive hypoglycemia, or diazoxide-sensitive hypoglycemia), islet cell dysregulation syndrome, idiopathic hypoglycemia of infancy, Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), and Congenital Hyperinsulinism, insulin overdose, hypoglycemia due to renal failure (acute or chronic), and chronic kidney disease, e.g., type III, IV or V.

[0079] Use of any of the foregoing antibodies or polypeptides of the disclosure that modulate the insulin-INSR signaling interaction in preparation of a medicament for treatment of any of the disorders described herein is also contemplated. 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 contemplated.

[0080] Any of the foregoing antibodies or polypeptides of the disclosure may be concurrently administered with any anti-diabetic agents known in the art or described herein, as adjunct therapy. Compositions comprising any of the foregoing antibodies or polypeptides of the disclosure together with other anti-diabetic agents are also contemplated.

[0081] A number of anti-diabetic agents are known in the art, including but not limited to: 1) sulfonylureas (*e.g.*, glimepiride, glisentide, sulfonylurea, AY31637); 2) biguanides (*e.g.*, metformin); 3) alpha-glucosidase inhibitors (*e.g.*, acarbose, miglitol); 4) thiazol-idinediones (*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); 5) 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); and 6) insulin or analogues or mimetics thereof (e.g. LANTUS®).

[0082] In a related example, the disclosure provides a method of diagnosing insulin resistance or insulin sensitivity using antibodies as described herein. In one example, the method comprises measuring levels of insulin or insulin receptor in a sample from a subject using an insulin receptor antibody described herein, wherein an increased level of insulin or free insulin receptor, or a decreased level of membrane-bound insulin receptor indicates the subject has or is at risk for diabetes or insulin resistance, and optionally administering a diabetes therapeutic to said subject who has or is at risk of diabetes or insulin resistance. In another example, the method comprises measuring levels of insulin receptor in a sample from a subject using an insulin receptor antibody described herein, wherein an increased level of free insulin receptor or a decreased level of membrane-bound insulin receptor indicates the subject has or is at risk for cancer, and optionally administering a cancer therapeutic to said subject.

[0083] In another example, the disclosure provides methods for identifying antibodies that modulate the binding of insulin to the insulin receptor as described herein.

[0084] It is understood that each feature or example, or combination, described herein is a non-limiting, illustrative example of any of the examples of the disclosure and, as such, is meant to be combinable with any other feature or example, or combination, described herein. For example, where features are described with language such as “one example,” “some examples,” “further example,” “specific examples,” “another example,” “one embodiment”, “some embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of examples or embodiments is a non-limiting 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 examples or embodiments of the disclosure. Similarly, where a method describes identifying polypeptide binding agents, such as antibodies, characterized by certain features, polypeptide binding agents characterized by those features are also contemplated by the disclosure. 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.

BRIEF DESCRIPTION OF THE FIGURES

[0085] Figure 1 depicts representative results from an INSR receptor occupancy screen showing test antibodies binding to IM-9 cells expressing the INSR in the presence and absence of insulin.

[0086] Figure 2 shows representative results from a biotinylated ligand screen showing the effects of test antibodies on insulin binding to insulin receptor.

[0087] Figure 3 shows results from an assay measuring the ability of test antibodies to modulate insulin dependent pIRS-1 phosphrylation.

[0088] Figure 4 depicts results from a pIRS-1 activity assay showing binding of representative antibodies to INSR from different functional classes. A) Positive Modulators; B) Positive modulators with significant agonism; C) Non-modulators; D) Agonist Antibodies; E) Negative modulators.

CLAIMS

We claim:

1. A monoclonal antibody that binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii), with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of weakening the binding affinity between insulin and insulin receptor by at least 3-fold, optionally up to 1000-fold, wherein the antibody binds (i) or (ii) in an allosteric manner, wherein the antibody comprises

(a) the heavy chain variable region of any of SEQ ID NO: 279, SEQ ID NO: 241, SEQ ID NO: 258, SEQ ID NO: 155, SEQ ID NO: 228, SEQ ID NO: 169, SEQ ID NO: 160, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 226, SEQ ID NO: 231, SEQ ID NO: 233, SEQ ID NO: 244, SEQ ID NO: 246, SEQ ID NO: 260, SEQ ID NO: 262, and the light chain variable region of any of SEQ ID NO: 139, SEQ ID NO: 103, SEQ ID NO: 119, SEQ ID NO: 8, SEQ ID NO: 89, SEQ ID NO: 18, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 121, and SEQ ID NO: 123, wherein the heavy chain and light chain are paired as set out in Table 3; or

(b) three heavy chain CDRs of any of SEQ ID NO: 279, SEQ ID NO: 241, SEQ ID NO: 258, SEQ ID NO: 155, SEQ ID NO: 228, SEQ ID NO: 169, SEQ ID NO: 160, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 226, SEQ ID NO: 231, SEQ ID NO: 233, SEQ ID NO: 244, SEQ ID NO: 246, SEQ ID NO: 260, SEQ ID NO: 262, and three light chain CDRs of any of SEQ ID NO: 139, SEQ ID NO: 103, SEQ ID NO: 119, SEQ ID NO: 8, SEQ ID NO: 89, SEQ ID NO: 18, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 87, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 121, and SEQ ID NO: 123, wherein the heavy chain and light chain are paired as set out in Table 3; or

(c) all six CDRs of any of SEQ ID NO: 279 and 139, SEQ ID NO: 241 and 103, SEQ ID NO: 258 and 119, SEQ ID NO: 155 and 8, SEQ ID NO: 228 and 89, SEQ ID NOs: 169 and 18, SEQ ID NOs: 160 and 1, SEQ ID NOs: 153 and 2, SEQ ID NOs: 154 and 4, SEQ ID NOs: 226 and 87, SEQ ID NOs: 231 and 92, SEQ ID NOs: 233 and 94, SEQ ID NOs: 244 and 105, SEQ ID NOs: 246 and 107, SEQ ID NOs: 260 and 121, and SEQ ID NOs: 262 and 123.

2. The antibody of claim 1, wherein the antibody is capable of weakening the binding affinity between said insulin and insulin receptor by 3-fold and 500-fold.

3. The antibody of claim 1, wherein the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

4. The antibody of claim 1, wherein the antibody increases the EC50 of insulin signaling activity by 2-fold to 1000-fold, optionally in a pAKT assay.

5. The antibody of any of claims 1 to 4 that exhibits greater than or equal to 70% competition with any one, two, three or all antibodies selected from the group consisting of Ab061 (SEQ ID NO: 241, 103), Ab074 (SEQ ID NOs: 262, 123), Ab081 (SEQ ID NO: 279, 139), Ab020 (SEQ ID NOs: 155, 8), Ab019 (SEQ ID NOs: 160, 1), Ab087 (SEQ ID NOs: 169, 18), Ab088 (SEQ ID NOs: 2, 153), and Ab089 (SEQ ID NOs: 154, 4), optionally wherein the antibody binds human receptor or complex and not murine receptor or complex.

6. The antibody of claim 1 wherein the variable heavy chain is set out in SEQ ID NOs: 279, 258 or 241 and the variable light chain is set out in SEQ ID NOs: 139, 119 or 103, respectively.

7. The antibody of claim 1 comprising three heavy chain CDRs set out in SEQ ID NOs: 279, 258 or 241 and three light chain CDRs set out in SEQ ID NOs: 139, 119 or 103, respectively.

8. The antibody of claim 1 wherein the variable heavy chain is set out in SEQ ID NO: 279 and the variable light chain is set out in SEQ ID NO: 139.

9. The antibody of claim 1 comprising three heavy chain CDRs set out in SEQ ID NO: 279 and three light chain CDRs set out in SEQ ID NO: 139.

10. The antibody of any of claims 1 to 9, further comprising a human IgG1, IgG2, IgG3 or IgG4 heavy chain constant region.

11. The antibody of claim 10, further comprising a human light chain constant region.

12. The antibody of any of the preceding claims, wherein said antibody is a human antibody.

13. The antibody of any one of claims 1 to 12, wherein the antibody is conjugated to a hydrophobic moiety.

14. A method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent to an antibody of any of claims 1 to 13.

15. A sterile composition comprising the antibody of any of claims 1 to 13 and a sterile pharmaceutically acceptable diluent.

16. Use an antibody of claims 1 to 13 in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling.

17. The use of claim 16, wherein the condition is selected from the group consisting of cancer, insulinoma, Kaposi' s sarcoma, insulin overdose, hypoglycemia, nesidioblastosis (KATP-H1 Diffuse Disease, KATP-H1 Focal Disease, or " PHHI"), GDH-H1 (Hyperinsulinism/Hyperammonaemia Syndrome (HI/HA), leucine-sensitive hypoglycemia, or diazoxide-sensitive hypoglycemia), islet cell dysregulation syndrome, idiopathic hypoglycemia of infancy, Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), Congenital Hyperinsulinism, hypoglycemia due to renal failure (acute of chronic), and hypoglycemia due to chronic kidney disease.