174, YM 268, R 102380, NC 2100, NIP 223, NIP 221, MK 0767, ciglitazone, adaglitazone, CLX 0921, darglitazone, CP 92768, BM 152054) enhance insulin action, thus promoting glucose utilization in peripheral tissues; 5) glucagon-like-peptides and agonists (e.g. exendin) or stabilizers thereof (e.g. DPP4 inhibitors, such as sitagliptin) potentiate glucose-stimulated insulin secretion; and 6) insulin or analogues thereof (e.g. LANTUS®) stimulate tissue glucose utilization and inhibits hepatic glucose output. The above mentioned pharmacological approaches may be utilized individually or in combination therapy. However, each approach has its limitations and adverse effects. Over time, a large percentage of Type 2 diabetic subjects lose their response to these agents. 63% of Type 2 diabetes patients fail to reach global HbA_{1c} levels of <7% as advised by the American Diabetes Association, and are thus at high risk of developing complications. Moreover, almost invariably patients progress through the stages of declining pancreatic function. Insulin treatment is typically instituted after diet, exercise, and oral medications have failed to adequately control blood glucose. The drawbacks of insulin treatment are the need for drug injection, the potential for hypoglycemia, and weight gain. Consequently there is still an urgent need for novel anti-diabetic agents.

[0009] 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.

SUMMARY ~~OF THE INVENTION~~

[0010] The present disclosure is directed to polypeptide binding agents, e.g., antibodies or fragments thereof, that modulate and/or agonize the insulin-INSR signaling complex by

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 ~~aspect~~embodiment, the ~~invention~~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 embodiment, 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 embodiments, 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 exemplary embodiments, 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 embodiments, the binding rate parameter is the on rate or off rate. In specific exemplary embodiments, the antibody increases the on rate or decreases the off rate. Alternatively, in some embodiments 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 embodiment, an antibody that strengthens the binding affinity between insulin and INSR is a positive modulator.

[0013] In another ~~aspect~~embodiment, the antibody is an agonist.

[0014] In a related ~~aspect~~embodiment, an antibody that activates the INSR without dependence on insulin is an allosteric agonist. In certain embodiments, the ~~invention~~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 embodiment, 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 embodiments, 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 ~~aspect~~embodiment, the ~~invention~~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 embodiment, 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 embodiment, 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 embodiment, 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 exemplary embodiments, 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 embodiments, the binding rate parameter is the on rate or off rate. In specific exemplary embodiments, the antibody decreases the on rate or increases the off rate.

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

[0018] In still another embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, the antibody binds insulin receptor. In a related embodiment, the antibody binds the α subunit of INSR. In a further embodiment, the antibody binds the β subunit of INSR. In yet another embodiment, the antibody binds the α and β subunit of the receptor. In a related embodiment, the antibody binds an insulin/ insulin receptor complex. In another embodiment, 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 ~~aspect~~embodiment, the ~~invention~~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 embodiment, 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 embodiment, the antibody that specifically binds insulin receptor and/or a complex comprising insulin and insulin receptor with an equilibrium dissociation constant

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 embodiment, the antibody is a monoclonal antibody. In a related embodiment, the antibody is a human antibody.

[0028] In some specific embodiments, the ~~invention~~ 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 embodiments, the ~~invention~~ 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 ~~invention~~ 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 embodiments, the ~~invention~~disclosure excludes the humanized antibody 83-14 reported in Boado et al, Biotech and BioEng. 96(2): 381-391 or WO04/050016.

[0029] In exemplary embodiments, the ~~invention~~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),

[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 ~~aspect~~embodiment, the ~~invention~~disclosure provides variants or derivatives of the antibodies described herein. For example, in one embodiment the antibody is labeled with a detectable moiety as described herein. In a further embodiment, 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 embodiments, 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 embodiments, 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 embodiments, 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 ~~invention~~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 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.

[0043] It is further contemplated that the ~~invention~~ 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 ~~invention~~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 embodiments, the ~~invention~~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 embodiment, 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 embodiment, 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 embodiments, the antibody binds an insulin/ insulin receptor complex. In further embodiments, the antibody binds insulin receptor alone, in an uncomplexed form. In a related embodiment, the antibody does not detectably bind insulin receptor alone, e.g., in the absence of insulin. In certain embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the ~~invention~~ 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 ~~aspect~~embodiment, the ~~invention~~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 embodiments, 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 embodiments, 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 embodiment, the antibody activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

[0050] In some embodiments, 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 embodiment, 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 embodiments, the ~~invention~~ disclosure provides an antibody that competes with any of the antibodies described herein, e.g. by at least 70%, 75%, or 80%. In certain embodiments, 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 embodiment, 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 embodiment, 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 embodiment, 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 ~~a further~~one aspect, ~~the invention~~ there is provided ~~provides~~ an antibody that binds to (i) insulin receptor ~~and/~~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 about 3-fold, optionally up to 1000-fold. In certain ~~embodiments~~embodiments, the antibody weakens the affinity between said insulin and insulin receptor by about 3-fold to 500-fold. In some embodiments, 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 embodiments, 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 embodiment, the antibody increases the EC50 of insulin signaling activity by about 2-fold to 1000-fold, optionally in a pAKT assay. In certain embodiments, 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 embodiments, 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 embodiment, 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 embodiment, the ~~invention~~ 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 embodiment, the ~~invention~~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.

[0062] In a related embodiment, the ~~invention~~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 ~~aspect~~embodiment, the ~~invention~~disclosure provides polynucleotides encoding antibodies and polypeptides of the ~~invention~~disclosure, vectors comprising such polynucleotides, host cells comprising such polynucleotides or vectors, and methods of producing antibodies and polypeptides of the ~~invention~~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 embodiment, the ~~invention~~ 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 embodiments 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 embodiments, 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 embodiments, the ~~invention~~ 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 embodiments, 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 embodiments, 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 embodiments, C1 and C2 are selected from the group consisting of insulin and insulin receptor.

[0068] In another aspect, ~~the invention contemplates~~there is provided a method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent

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

[0069] ~~Also contemplated~~In another aspect, there is provided ~~is~~ a sterile composition comprising an antibody ~~of the invention~~ as defined herein and a sterile pharmaceutically acceptable diluent.

[0070] The ~~invention~~ disclosure further contemplates that the antibodies of the ~~invention~~disclosure modulate binding between the INSR and insulin or insulin analogs or insulin mimetics. The antibodies of the ~~invention~~ 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 embodiments, the antibodies are capable of increasing the rate or total amount of glucose uptake, or both.

[0071a] In one aspect, there is provided the use of an antibody as defined herein in the manufacture of a medicament for treating a disorder associated with insulin resistance.

[0071] In ~~a further aspect~~one embodiment, the ~~invention~~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 ~~invention~~disclosure in an amount effective to treat insulin resistance. In a related embodiment, the treatment enhances glucose uptake. In a further embodiment, 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 embodiment, 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 ~~aspects~~embodiments, 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 embodiments, treatment improves impaired glucose tolerance. In one embodiment glucose tolerance is measured by glucose tolerance test (GTT).

[0073] In other embodiments, the treatment slows, reduces, or normalizes weight gain of a subject. In one embodiment, 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 embodiments, the treatment slows, reduces, or normalizes weight loss of a subject. In one embodiment, 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 ~~aspect~~embodiment, it is contemplated that the antibodies or polypeptides described herein promote or induce weight loss in a subject. In one embodiment, the ~~invention~~ 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 embodiment, the modulating antibody is a positive modulator or partial agonist. In a related embodiment, the modulating antibody is a negative modulator.

[0075] It certain embodiments, 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 embodiment, 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, there is provided 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 ~~another aspect~~one embodiment, the ~~invention~~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 ~~invention~~disclosure in an amount effective to treat insulin overproduction and/or sensitivity. In one embodiment, the disorder associated with insulin sensitivity is selected from the group consisting of cancer, Kaposi's sarcoma, insulinoma, diabetic renal disease, hypoglycemia, nesidioblastosis (KATP-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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 ~~invention~~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 ~~invention~~ 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 ~~invention~~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 ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of diagnosing insulin resistance or insulin sensitivity using antibodies as described herein. In one embodiment, 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 embodiment, 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 ~~aspect~~embodiment, the ~~invention~~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 embodiment, or combination, described herein is a non-limiting, illustrative example of any of the ~~aspects~~ embodiments of the ~~invention~~disclosure 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", "further embodiment", "specific exemplary embodiments", and/or "another embodiment", each of these types of 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 ~~aspects~~embodiments of the ~~invention~~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 ~~invention~~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.

We claim:

1. An 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 strengthening the binding affinity between insulin and insulin receptor by about 5-fold to 200-fold.

2. An allosteric agonist antibody that binds to insulin receptor with an affinity 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, and (c) when present does not alter the K_D of insulin for INSR by more than 2-fold.

3. An agonist antibody that binds to insulin receptor with an affinity 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.

4. An 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 about 3-fold, optionally up to 1000-fold.

5. The antibody of claim 1 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}.

6. The antibody of claim 5 in which 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}.

7. The antibody of any one of claims 1 and 5 to 6 wherein the antibody binds insulin receptor.

8. The antibody of any one of claims 1 and 5 to 6 wherein the antibody binds an insulin/ insulin receptor complex.

9. The antibody of any one of claim 1, claims 5 to 6 and claim 8 wherein the antibody does not detectably bind insulin receptor alone.

10. The antibody of any of claims 1 and 5 to 9, wherein the antibody is capable of strengthening the binding affinity between insulin and insulin receptor by about 5-fold to 25-fold.

11. The antibody of claim 10, 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.

12. The antibody of any of claims 1 to 8 and 10 to 11 that activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

13. The antibody of any of claims 1 to 8 and 10 to 11 that activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

14. The antibody of any of claims 1, 3 or 5 to 13, wherein the antibody comprises a heavy chain variable region selected from the group consisting of 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 SEQ ID NOs: 141, 138, 137, 35, 135, 57, 144, 136, and 98.

15. The antibody of any of claims 1, 3 or 5 to 14, wherein 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, 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; 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 SEQ ID NO: 76, 80, 101, 128, 132, 291, 196, 239, 267, and 271.

16. The antibody of any of claims 1, 2, 3 and 5 to 15 that exhibits greater than or equal to 70% competition with any one, two, three or all antibodies selected from the group consisting of Ab079, Ab076, Ab083, Ab080, Ab062, and 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,

17. The antibody of any of claims 1,2, 3 and 5 to 15 that exhibits greater than or equal to 70% 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

18. The antibody of any of claims 1, 3, 5 to 6 and 8 to 9 that exhibits greater than or equal to 70% competition with any one, two, three or all antibodies selected from the group consisting of Ab064, Ab062, Ab085, and Ab078.

19. The antibody of claim 4 wherein the antibody is capable of weakening the binding affinity between said insulin and insulin receptor by about 3-fold to 500-fold.

20. The antibody of claim 4, 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.

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

22. The antibody of any of claims 4 or 19 to 21, wherein the antibody comprises a heavy chain variable region selected from the group consisting of SEQ ID NOs: 241, 279,

~~258, 155, and 228 and a light chain variable region selected from the group consisting of SEQ~~ ID NOs: 103, 139, 119, 8, and 89.

23. The antibody of any of claims 4 or 19 to 22, wherein 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, 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, Ab081and/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.

24. The antibody of any of claims 4 and 19 to 23 that exhibits greater than or equal to 70% 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 wherein the antibody binds human receptor or complex and not murine receptor or complex.

25. The antibody of claim 2 or 3, wherein the antibody comprises a heavy chain variable region selected from the group consisting of SEQ ID NOs: 195, 220, 303, 197, 208, 243, 245 and 251 and a light chain variable region selected from the group consisting of SEQ ID NOs: 77, 50, 90, 84, 34, 104, 106 and 112.

26. The antibody of any of claims 2 or 3, wherein 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 269and 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, 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; or

(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.

27. The antibody of any of claims 2, 3, 25 and 26 that exhibits greater than or equal to 70%, 75% or 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.

28. The antibody of any of claims 1 to 27 that comprises at least one heavy chain CDR HCDR1, HCDR2 and HCDR3 set out in SEQ ID NOS: 151-303.

29. The antibody of any of claims 1 to 28 that comprises a heavy chain variable region of SEQ ID NOS: 151-303.

30. The antibody of any of claims 1 to 29 that comprises at least one light chain CDR LCDR1, LCDR2, or LCDR3 set out in SEQ ID NOS: 1-150.

31. The antibody of any of claims 1 to 30 that comprises a light chain variable region of SEQ ID NOS: 1-150.

32. The antibody of any of claims 1 to 31, further comprising a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant region.

33. The antibody of claim 32, further comprising a human light chain constant region.

34. An antibody that specifically binds (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor or both (i) and (ii), comprising at least one of HCDR1, HCDR2 and HCDR3 of SEQ ID NOS: 151-303 and having an equilibrium dissociation constant K_D of 10^{-5}M or less.

35. The antibody of claim 34 that comprises a heavy chain variable region of SEQ ID NOS: 151-303.

36. The antibody of claim 34, further comprising at least one of LCDR1, LCDR2, or LCDR3 of SEQ ID NOS: 1-150.

37. The antibody of any one of claims 34 to 36, wherein the antibody comprises one, two, three, four, five or six CDRs.

38. The antibody of any one of claims 34 to 37, wherein the antibody comprises one, two or three heavy chain CDRs set out in SEQ ID NOS: 151-303.

39. The antibody of any one of claims 37 to 38, wherein the antibody comprises one, two or three light chain CDRs set out in SEQ ID NOS: 1-150.

40. The antibody of claim 34 that comprises a light chain variable region of SEQ ID NOS: 1-150.

41. The antibody of any one of claims 34 to 40, further comprising a human IgG1, IgG2, IgG3 or IgG4 constant region.

42. The antibody of any one of claims 34 to 41, wherein the antibody binds insulin receptor.

43. The antibody of any one of claims 34 to 41, wherein the antibody binds an insulin/ insulin receptor complex.

44. The antibody of claim 43, wherein the antibody does not detectably bind insulin receptor alone.

45. The antibody of any one of claims 1 to 3, 5 to 18, and 25 to 44, wherein the antibody reduces fasting blood glucose levels in a subject having elevated blood glucose toward normal glucose levels.

46. The antibody of any of claims 34 to 44 that activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

47. The antibody of any of claims 34 to 44 that activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

48. The antibody of any of the preceding claims, wherein said antibody is a monoclonal antibody.

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

50. The antibody of any one of claims 1 to 49, wherein the antibody is conjugated to a hydrophobic moiety.

51. A method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent to an antibody of any of claims 1 to 50.

52. A sterile composition comprising the antibody of any of claims 1 to 50 and a sterile pharmaceutically acceptable diluent.

53. A method of treating a disorder associated with insulin resistance, comprising administering an antibody of any of claims 1, 2, 3, 5 to 18 and 25 to 50 in an amount effective to treat insulin resistance.

54. The method of claim 53, wherein the disorder 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.

55. The method of claim 54, wherein the treatment enhances glucose uptake.

56. The method of claim 55, wherein 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.

57. The method of claim 56, wherein the treatment slows or reduces weight gain in the subject compared to an untreated subject.

58. The method of claim 53, wherein the treatment results in a decrease in HbA1c levels compared to an untreated subject.

59. The method of claim 53, wherein the treatment results in an improved glucose tolerance test, or reduced 2-hour glucose level during a glucose tolerance test.

60. The method of claim 53, wherein the treatment results in an improvement in a symptom associated with insulin resistance selected from the group consisting of dyslipidemia, plasma triglycerides, HOMA-IR, plasma unesterified cholesterol, plasma total cholesterol, plasma insulin, non-HDL/HDL cholesterol ratio, total/HDL cholesterol ratio, beta cell function and plasma leptin levels.

61. A method of treating a condition associated with hyperinsulinemia or excess insulin signaling, comprising administering an antibody of claims 4 and 19 to 24 in an amount effective to treat hypoglycemia or insulin sensitivity.

62. The method of claim 61, wherein the condition is selected from the group consisting of cancer, insulinoma, Kaposi's sarcoma, insulin overdose, hypoglycemia, nesidioblastosis (KATP-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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 or chronic), and hypoglycemia due to chronic kidney disease.

CLAIMS

We claim:

1. An 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 about 3-fold, optionally up to 1000-fold.

2. The antibody of claim 1that activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

3. The antibody of claim 1that activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

4. The antibody of any of claims 2 or 3, wherein the antibody comprises a heavy chain variable region selected from the group consisting of 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 SEQ ID NOs: 141, 138, 137, 35, 135, 57, 144, 136, and 98.

5. The antibody of any of claims 2 to 4, wherein 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, 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; 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 SEQ ID NO: 76, 80, 101, 128, 132, 291, 196, 239, 267, and 271.

6. The antibody of any of claims 2 to 5 that exhibits greater than or equal to 70% competition with any one, two, three or all antibodies selected from the group consisting of Ab079, Ab076, Ab083, Ab080, Ab062, and 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,

7. The antibody of any of claims 2 to 6 that exhibits greater than or equal to 70% 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

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

9. 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.

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

11. The antibody of any of claims 1, 8 to 10, wherein the antibody comprises a heavy chain variable region selected from the group consisting of SEQ ID NOs: 241, 279, 258, 155, and 228 and a light chain variable region selected from the group consisting of SEQ ID NOs: 103, 139, 119, 8, and 89.

12. The antibody of any of claims 1 or 8 to 11, wherein 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, 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, Ab081and/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.

13. The antibody of any of claims 1 and 8 to 12 that exhibits greater than or equal to 70% 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 wherein the antibody binds human receptor or complex and not murine receptor or complex.

14. The antibody of any of claims 1 to 13 that comprises at least one heavy chain CDR HCDR1, HCDR2 and HCDR3 set out in SEQ ID NOS: 151-303.

15. The antibody of any of claims 1 to 14 that comprises a heavy chain variable region of SEQ ID NOS: 151-303.

16. The antibody of any of claims 1 to 15 that comprises at least one light chain CDR LCDR1, LCDR2, or LCDR3 set out in SEQ ID NOS: 1-150.

17. The antibody of any of claims 1 to 16 that comprises a light chain variable region of SEQ ID NOS: 1-150.

18. The antibody of any of claims 1 to 17, further comprising a human IgG1, IgG2, IgG3, or IgG4 heavy chain constant region.

19. The antibody of claim 18, further comprising a human light chain constant region.

20. The antibody of any one of claims 2-7, and 14 to 19, wherein the antibody reduces fasting blood glucose levels in a subject having elevated blood glucose toward normal glucose levels.

21. The antibody of any of claim 20 that activates insulin receptor by at least 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

22. The antibody of any of claim 20 that activates insulin receptor by less than 10% of the maximal signal of insulin, optionally in a phosphorylated AKT assay.

23. The antibody of any of the preceding claims, wherein said antibody is a monoclonal antibody.

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

25. The antibody of any one of claims 1 to 24, wherein the antibody is conjugated to a hydrophobic moiety.

26. A method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent to an antibody of any of claims 1 to 25.

27. A sterile composition comprising the antibody of any of claims 1 to 25 and a sterile pharmaceutically acceptable diluent.

28. Use of an antibody of any of claims 2-7 and 14-25 in the manufacture of a medicament for treating a disorder associated with insulin resistance.

29. The use of claim 28, wherein the disorder 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.

30. The use of claim 29, wherein the treatment enhances glucose uptake.

31. The use of claim 30, wherein 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.

32. The use of claim 31, wherein the treatment slows or reduces weight gain in the subject compared to an untreated subject.

33. The use of claim 28, wherein the treatment results in a decrease in HbA1c levels compared to an untreated subject.

34. The use of claim 28, wherein the treatment results in an improved glucose tolerance test, or reduced 2-hour glucose level during a glucose tolerance test.

35. The use of claim 28, wherein the treatment results in an improvement in a symptom associated with insulin resistance selected from the group consisting of dyslipidemia, plasma triglycerides, HOMA-IR, plasma unesterified cholesterol, plasma total cholesterol, plasma insulin, non-HDL/HDL cholesterol ratio, total/HDL cholesterol ratio, beta cell function and plasma leptin levels.

36. Use an antibody of claims 1 and 8 to 13 in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling.

37. The use of claim 36, wherein the condition is selected from the group consisting of cancer, insulinoma, Kaposi's sarcoma, insulin overdose, 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), Congenital Hyperinsulinism, hypoglycemia due to renal failure (acute or chronic), and hypoglycemia due to chronic kidney disease.