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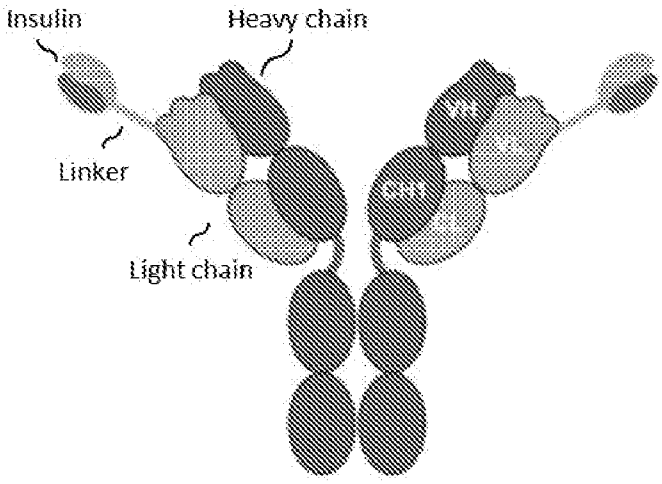
(54) **Title**: INSULIN IMMUNOGLOBULIN FUSION PROTEINS

FIG. 1A



(57) **Abstract**: Disclosed herein are immunoglobulin fusion proteins comprising an insulin therapeutic peptide and an immunoglobulin region that targets the insulin therapeutic peptide to the liver of an individual in need thereof. Further disclosed herein are compositions comprising the immunoglobulin fusion proteins and methods for using the immunoglobulin fusion proteins for the treatment or prevention of a disease or condition in a subject, for example, diabetes and diabetes related conditions.

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INSULIN IMMUNOGLOBULIN FUSION PROTEINS

PRIORITY

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/214,605 filed September 4, 2015, the entirety of which is incorporated herein.

BACKGROUND OF THE INVENTION

[0002] A pharmacologic limitation of current insulin therapies in type 1 diabetes (T1D) patients is that portal-systemic insulin concentration gradient, which ensures that the liver is exposed to higher concentrations of insulin than peripheral tissues, is absent in T1D patients. Subcutaneous injection of insulin results in peripheral hyperinsulinemia, which is associated with atherosclerosis, cancer, hypoglycemia, and other adverse metabolic effects. In contrast, intraportal insulin infusion or adequate hepatic insulinization in T1D patients requires lower doses of insulin and is associated with more rapid and significant lowering of plasma glucose and hemoglobin A1c levels, as well as normalization of circulating cortisol, growth hormone, glucagon, and three-carbon precursors such as lactate, pyruvate, and alanine.

SUMMARY OF THE INVENTION

[0003] Disclosed herein are insulin compositions and methods of using the same that address limitations of current insulin therapies with a liver-biased tissue distribution profile, thus focusing the glucose-lower effects of insulin on the liver. One such composition is an insulin fusion protein comprises an insulin molecule fused to an immunoglobulin having an antigen binding domain specific for an antigen of a liver cell. For example, the antigen binding domain is specific for asialoglycoprotein receptor (ASGPR), a molecule selectively expressed on hepatocytes. The anti-ASGPR portion of the fusion protein may be designed to lack or have a reduced rate of internalization to allow the insulin molecule to interact with the insulin receptor. In many cases, an insulin fusion protein has improved efficacy over the insulin molecule administered without a fused immunoglobulin region. Accordingly, the dosing requirements of the insulin fusion protein may be lower than those of current insulin therapies. Furthermore, in some cases, the insulin molecule of a fusion protein comprising an anti-ASGPR domain may be distributed to the liver by at least 2-fold over an insulin molecule of a fusion protein comprising an anti-ASGPR domain lacking binding specificity for ASGPR (control), or the insulin molecule alone.

[0004] In one aspect of the disclosure, provided herein are insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell. In some embodiments, the antigen is expressed by a hepatocyte. In some embodiments, the antigen is asialoglycoprotein receptor (ASGPR). In some embodiments, the antigen binding domain binds to a one or more amino acids of an epitope of ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140,

H142, and K173. In some embodiments, the one or more amino acids of the epitope comprise any combination of W134, E135, K138, V140, H142, and K173.

[0005] In some embodiments, the first immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a first CDR having an amino acid sequence that differs from SEQ ID NO: 45 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 46 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 55 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a third CDR having an amino acid sequence that differs from SEQ ID NO: 47 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some embodiments, the first immunoglobulin region comprises a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some embodiments, the first immunoglobulin region comprises an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the first immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the insulin immunoglobulin fusion protein further comprises a second immunoglobulin region. In some embodiments, the second immunoglobulin region comprises one or more portions of the antigen binding domain. In some embodiments, the second immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a first CDR having an amino acid sequence that differs from SEQ ID NO: 48 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 49 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a third CDR having an amino acid sequence that differs from SEQ ID NO: 50 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some embodiments, the second immunoglobulin region comprises a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some embodiments, the second immunoglobulin region comprises an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the second immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.

[0006] In some embodiments, the first immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a first CDR having an amino acid sequence that differs from SEQ ID NO: 48 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 49 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a third CDR having an amino acid sequence that differs from SEQ ID NO: 50 by no more than 2 amino acids. In some embodiments, the first immunoglobulin region comprises a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NO: 41 and SEQ: 44. In some embodiments, the first immunoglobulin region comprises a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NO: 41 and SEQ: 44. In some embodiments, the first immunoglobulin region comprises an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the first immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the insulin immunoglobulin fusion protein further comprises a second immunoglobulin region. In some embodiments, the second immunoglobulin region comprises one or more portions of the antigen binding domain. In some embodiments, the second immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a first CDR having an amino acid sequence that differs from SEQ ID NO: 45 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 46 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a second CDR having an amino acid sequence that differs from SEQ ID NO: 55 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a third CDR having an amino acid sequence that differs from SEQ ID NO: 47 by no more than 2 amino acids. In some embodiments, the second immunoglobulin region comprises a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some embodiments, the second immunoglobulin region comprises a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some embodiments, the second immunoglobulin region comprises an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the second immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.

[0007] In some embodiments, the insulin therapeutic peptide is connected to the amino-terminus of the first immunoglobulin region. In some embodiments, the first immunoglobulin region comprises SEQ ID NO: 155 ($QVQLX_1QX_2GAE$), wherein X_1 and X_2 are independently selected from a naturally or non-

naturally occurring amino acid. In some embodiments, X_1 is Q or V. In some embodiments, X_2 is P or S. In some embodiments, X_1 is V and X_2 is S. In some embodiments, the first immunoglobulin region comprises SEQ ID NO: 156 ($EX_1VLTQSPX_2T$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_1 is T or I. In some embodiments, X_2 is T or G. In some embodiments, X_1 is I and X_2 is G.

[0008] In some embodiments, the insulin therapeutic peptide is connected to the first immunoglobulin region by a linker peptide. In some embodiments, the linker peptide comprises between 3 and 50 amino acids, and the linker peptide comprises an amino acid sequence selected from: (a) an amino acid sequence having at least 50% glycine, serine, or glycine and serine amino acids; and (b) an amino acid sequence having at least 50% glycine, alanine, or glycine and alanine amino acids. In some embodiments, the linker peptide comprises an amino acid sequence at least 90% identical to any one of SEQ ID NOS: 141-147. In some embodiments, the linker comprises a protease cleavage site.

[0009] In some embodiments, the insulin therapeutic peptide comprises a single amino acid chain having the formula: B-C-A or A-C-B; wherein B comprises SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); A comprises SEQ ID NO 158: $GIVEQCCX_DSICSLYQLENYCN$; and C comprises a connecting peptide having between 3 and 50 amino acids; and wherein X_A, X_B, X_C and X_D are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_A is D or H. In some embodiments, X_B is D or P. In some embodiments, X_C is P or K. In some embodiments, X_D is H or T. In some embodiments, the connecting peptide comprises an amino acid sequence comprising at least 50% glycine amino acids. In some embodiments, the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_1 is P, G or S. In some embodiments, X_2 is R, S, G or K. In some embodiments, C comprises a protease cleavage site. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence selected from SEQ ID NOS: 111, 113, 116, 118, 119-140. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence at least 90% identical to any one of SEQ ID NOS: 111, 113, 116, 118, 119-140.

[0010] In some embodiments, the insulin therapeutic peptide comprises a single amino acid chain having the formula B-C-A or A-C-B; wherein B comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT); A comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC); and C comprises a connecting peptide having between 3 and 50 amino acids. In some embodiments, B comprises SEQ ID NO: 160. In some embodiments, A comprises SEQ ID NO: 161. In some embodiments, the connecting peptide comprises an amino acid sequence having at least 50% glycine amino acids. In some embodiments, the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_1 is P, G or S. In some embodiments, X_2 is R, S, G or K. In some embodiments, C comprises a protease cleavage site.

[0011] In some embodiments, insulin therapeutic peptide comprises an A peptide comprising SEQ ID NO: 158 (GIVEQCCX$_D$SICSLYQLENYCN), and X$_D$ is a naturally or non-naturally occurring amino acid. In some embodiments, X$_D$ is selected from H and T. In some embodiments, one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide. In some embodiments, the B peptide comprises SEQ ID NO: 157 (FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$T); and X$_A$, X$_B$, and X$_C$ are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X$_A$ is D or H. In some embodiments, X$_B$ is D or P. In some embodiments, X$_C$ is P or K. In some embodiments, the B peptide comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some embodiments, B comprises SEQ ID NO: 160.

[0012] In some embodiments, the insulin therapeutic peptide comprises an A peptide comprising an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC). In some embodiments, the A peptide comprises SEQ ID NO: 161. In some embodiments, one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide. In some embodiments, the B peptide comprises SEQ ID NO: 157 (FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$T); and X$_A$, X$_B$, and X$_C$ are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X$_A$ is D or H. In some embodiments, X$_B$ is D or P. In some embodiments, X$_C$ is P or K. In some embodiments, the B peptide comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some embodiments, B comprises SEQ ID NO: 160.

[0013] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence having no more than 2 amino acid differences from any of SEQ ID NOS: 109-140. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence having at least 75% sequence identity to any of SEQ ID NOS: 109-140. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence having at least 85% sequence homology to any of SEQ ID NOS: 109-140.

[0014] In some embodiments, the insulin immunoglobulin fusion protein comprises an amino acid sequence having no more than 5 amino acid differences from any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98. In some embodiments, the insulin immunoglobulin fusion protein comprises an amino acid sequence having at least 75% sequence identity to any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98. In some embodiments, the insulin immunoglobulin fusion protein comprises an amino acid sequence having at least 85% sequence homology to any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98.

[0015] Further provided herein is a method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the insulin immunoglobulin fusion protein. In some embodiments, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an insulin or insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver and/or a hepatocyte. In some embodiments, the additional therapeutic agent

comprises an insulin B peptide, insulin A peptide, insulin C peptide, or a combination thereof. In some embodiments, the additional therapeutic agent comprises an amino acid sequence differing from a sequence selected from SEQ ID NOS: 138-140, 157 and 158, by no more than 2 amino acids. In some embodiments, the additional therapeutic agent comprises an amino acid sequence selected from SEQ ID NOS: 138-140. In some embodiments, the additional therapeutic agent is administered in a composition with the insulin immunoglobulin fusion protein. In some embodiments, the additional therapeutic agent is administered in a composition separate from the insulin immunoglobulin fusion protein. In some embodiments, the insulin immunoglobulin fusion protein is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route. In some embodiments, the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route. In some embodiments, the disease or condition is diabetes. In some embodiments, the disease or condition is obesity.

[0016] Further provided herein is a genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of the insulin immunoglobulin fusion protein. Further provided herein is a first expression vector comprising the first genetic construct. Further provided herein is a mammalian expression host comprising the first expression vector.

[0017] In another aspect of the disclosure, provided herein are compositions comprising a molecule of Formula XVII:

I-L-G (Formula XVII)

wherein:

I has the formula B-A, A-B, B-C-A, or A-C-B; wherein B comprises an insulin B chain; A comprises an insulin A chain; if present, C comprises a connecter connecting B and A; and B-A, A-B, or both B-A and A-B are linked by a moiety or disulfide bond;

L comprises a linker; and

G comprises an immunoglobulin, immunoglobulin fragment, peptide or other ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte.

[0018] In some embodiments, I has the formula B-A or A-B, and B-A or A-B are linked by a disulfide bond. In some embodiments, I has the formula B-A or A-B, and B-A or A-B are chemically linked by a moiety. In some embodiments, I has the formula B-C-A or A-C-B, and the connecter is a connecting peptide comprising 2 to 50 amino acids. In some embodiments, the connecting peptide comprises an amino acid sequence having at least 50% glycine amino acids. In some embodiments, the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_1 is P, G or S. In some embodiments, X_2 is R, S, G or K. In some embodiments, C comprises a protease cleavage site. In some embodiments, I has the formula B-C-A or A-C-B, and the connecter is a linker that chemically conjugates B and A.

[0019] In some embodiments, the insulin B chain comprises a sequence of SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); and X_A, X_B, and X_C are independently selected

from a naturally or non-naturally occurring amino acid. In some embodiments, X_A is D or H. In some embodiments, X_B is D or P. In some embodiments, X_C is P or K. In some embodiments, the insulin B chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some embodiments, the insulin B chain comprises SEQ ID NO: 160. In some embodiments, the insulin B chain comprises a sequence at least about 75% identical to an insulin B chain in any one of SEQ ID NOS: 109-140. In some embodiments, the insulin B chain is selected from human insulin B chain, porcine insulin B chain and bovine insulin B chain. In some embodiments, the insulin A chain comprises a sequence of SEQ ID NO: 158 (GIVEQCCX_DSICSLYQLENYCN), and X_D is a naturally or non-naturally occurring amino acid. In some embodiments, X_D is selected from H and T.

[0020] In some embodiments, the insulin A chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC). In some embodiments, the insulin A chain comprises SEQ ID NO: 161. In some embodiments, the insulin A chain comprises a sequence at least about 75% identical to an insulin A chain in any one of SEQ ID NOS: 109-140. In some embodiments, the insulin A chain is selected from human insulin A chain, porcine insulin A chain and bovine insulin A chain.

[0021] In some embodiments, the linker comprises a linker peptide. In some embodiments, the linker peptide comprises between 3 and 100 amino acids. In some embodiments, the linker peptide comprises an amino acid sequence selected from: (a) an amino acid sequence having at least 50% glycine, serine, or glycine and serine amino acids; and (b) an amino acid sequence having at least 50% glycine, alanine, or glycine and alanine amino acids. In some embodiments, the linker peptide comprises an amino acid sequence at least 90% identical to any one of SEQ ID NOS: 141-147. In some embodiments, the linker comprises a protease cleavage site.

[0022] In some embodiments, the antigen is ASGPR. In some embodiments, G comprises an immunoglobulin or immunoglobulin fragment. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises: (a) a heavy chain variable region sequence comprising SEQ ID NO: 45; (b) a heavy chain variable region sequence comprising SEQ ID NO: 46; (c) a heavy chain variable region sequence comprising SEQ ID NO: 55; (d) a heavy chain variable region sequence comprising SEQ ID NO: 47; (e) a light chain variable region sequence comprising SEQ ID NO: 48; (f) a light chain variable region sequence comprising SEQ ID NO: 49; (g) a light chain variable region sequence comprising SEQ ID NO: 50; (h) a combination of (a), (b) and (d); (i) a combination of (a), (c) and (d); (j) a combination of (e), (f) and (g); (k) a combination of (h) and (j); or (l) a combination of (i) and (j). In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a heavy chain variable region sequence comprising SEQ ID NOS: 45, 46 and 47. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a heavy chain variable region sequence comprising SEQ ID NOS: 45, 55 and 47. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a heavy chain variable region sequence that differs from SEQ ID NO: 39 or SEQ ID NO: 43 by no more than 2 amino acids. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a

heavy chain variable region sequence at least about 75% identical to SEQ ID NO: 39 or SEQ ID NO: 43. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a heavy chain variable region sequence at least about 85% homologous to SEQ ID NO: 39 or SEQ ID NO: 43. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence that differs from a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43 by no more than 2 amino acids. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence at least about 75% identical to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.

[0023] In some embodiments, the immunoglobulin or immunoglobulin fragment comprising a CH1 domain. In some embodiments, the CH1 domain comprises a sequence at least about 85% homologous to SEQ ID NO: 40. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a human Fc region. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a light chain variable region sequence comprising SEQ ID NOS: 48-50. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a light chain variable region sequence that differs from SEQ ID NO: 41 or SEQ ID NO: 44 by no more than 2 amino acids. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a light chain variable region sequence at least about 75% identical to SEQ ID NO: 41 or SEQ ID NO: 44. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a light chain variable region sequence at least about 85% homologous to SEQ ID NO: 41 or SEQ ID NO: 44. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence that differs from a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44by no more than 2 amino acids. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence at least about 75% identical to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the immunoglobulin or immunoglobulin fragment comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the immunoglobulin or immunoglobulin fragment is humanized.

[0024] In some embodiments, G binds to one or more amino acids of an epitope of ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140, H142, and K173. In some embodiments, the one or more amino acids of the epitope comprises any combination of W134, E135, K138, V140, H142, and K173.

[0025] In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 2 amino acids. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some

embodiments, G is an immunoglobulin or immunoglobulin fragment comprising an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 2 amino acids. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a variable region having an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising a variable region having an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising an amino acid sequence at least about 75% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, G is an immunoglobulin or immunoglobulin fragment comprising an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.

[0026] Further provided herein is a method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the composition having Formula XVII. In some embodiments, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an insulin or insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver and/or a hepatocyte. In some embodiments, the additional therapeutic agent comprises an insulin B peptide, insulin A peptide, insulin C peptide, or a combination thereof. In some embodiments, the additional therapeutic agent comprises an amino acid sequence differing from a sequence selected from SEQ ID NOS: 138-140, 157 and 158, by no more than 2 amino acids. In some embodiments, the additional therapeutic agent comprises an amino acid sequence selected from SEQ ID NOS: 138-140. In some embodiments, the additional therapeutic agent is administered with the composition having Formula XVII. In some embodiments, the additional therapeutic agent is administered in a composition separate from the composition having Formula XVII. In some embodiments, the composition having Formula XVII is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route. In some embodiments, the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route. In some embodiments, the disease or condition is diabetes. In some embodiments, the disease or condition is obesity.

[0027] In another aspect of the disclosure, provided herein are immunoglobulins for specific binding to asialoglycoprotein receptor (ASGPR), the immunoglobulin comprising: (a) a heavy chain variable region sequence comprising SEQ ID NO: 45; (b) a heavy chain variable region sequence comprising SEQ ID NO: 46; (c) a heavy chain variable region sequence comprising SEQ ID NO: 55; (d) a heavy chain

variable region sequence comprising SEQ ID NO: 47; (e) a light chain variable region sequence comprising SEQ ID NO: 48; (f) a light chain variable region sequence comprising SEQ ID NO: 49; (g) a light chain variable region sequence comprising SEQ ID NO: 50; (h) a combination of (a), (b) and (d); (i) a combination of (a), (c) and (d); (j) a combination of (e), (f) and (g); (k) a combination of (h) and (j); or (l) a combination of (i) and (j). In some embodiments, the immunoglobulin comprises a heavy chain variable region sequence comprising SEQ ID NOS: 45, 46 and 47. In some embodiments, the immunoglobulin comprises a heavy chain variable region sequence comprising SEQ ID NOS: 45, 55 and 47. In some embodiments, the immunoglobulin comprises a heavy chain variable region sequence that differs from SEQ ID NO: 39 or SEQ ID NO: 43 by no more than 2 amino acids. In some embodiments, the immunoglobulin comprises a heavy chain variable region sequence at least about 75% identical to SEQ ID NO: 39 or SEQ ID NO: 43. In some embodiments, the immunoglobulin comprises a heavy chain variable region sequence at least about 85% homology to SEQ ID NO: 39 or SEQ ID NO: 43. In some embodiments, the immunoglobulin comprises a sequence that differs from a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43 by no more than 2 amino acids.

[0028] In some embodiments, the immunoglobulin comprises a sequence at least about 75% identical to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the immunoglobulin comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some embodiments, the immunoglobulin comprises comprising a CH1 domain. In some embodiments, the CH1 domain comprises a sequence at least about 85% homologous to SEQ ID NO: 40. In some embodiments, the immunoglobulin comprises a human Fc region. In some embodiments, the immunoglobulin comprises a light chain variable region sequence comprising any one of SEQ ID NOS: 48-50.

[0029] In some embodiments, the immunoglobulin comprises a light chain variable region sequence that differs from SEQ ID NO: 41 or SEQ ID NO: 44 by no more than 2 amino acids. In some embodiments, the immunoglobulin comprises a light chain variable region sequence at least about 75% identical to SEQ ID NO: 41 or SEQ ID NO: 44. In some embodiments, the immunoglobulin comprises a light chain variable region sequence at least about 85% homology to SEQ ID NO: 41 or SEQ ID NO: 44. In some embodiments, the immunoglobulin comprises a sequence that differs from a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44by no more than 2 amino acids. In some embodiments, the immunoglobulin comprises a sequence at least about 75% identical to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the immunoglobulin comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some embodiments, the immunoglobulin is humanized.

[0030] Further provided herein is an immunoglobulin that competes with the immunoglobulin described herein for binding to ASGPR.

[0031] Further provided herein is a method of targeting a molecule to a hepatocyte in a subject in need thereof, the method comprising administering to the subject a composition comprising the molecule and the immunoglobulin. In some embodiments, the molecule is fused or linked to the immunoglobulin. In

some embodiments, the molecule comprises a human insulin B chain, human insulin A chain, or a derivative or combination thereof. In some embodiments, the subject has diabetes.

[0032] In another aspect of the disclosure, provided herein are methods of treating a disease or condition associated with glucose metabolism in a subject in need thereof, the method comprising administering an effective amount of an insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide and an immunoglobulin region comprising an antigen binding domain, wherein the antigen binding domain targets a hepatocyte receptor. In some embodiments, the hepatocyte receptor is ASGPR. In some embodiments, the disease or condition is diabetes. In some embodiments, the disease or condition is obesity.

[0033] In some embodiments, the method further comprises administering to the subject an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an insulin or insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver and/or a hepatocyte. In some embodiments, the additional therapeutic agent comprises an insulin B peptide, insulin A peptide, insulin C peptide, or a combination thereof. In some embodiments, the additional therapeutic agent comprises an amino acid sequence differing from a sequence selected from SEQ ID NOS: 138-140, 157 and 158, by no more than 2 amino acids. In some embodiments, the additional therapeutic agent comprises an amino acid sequence selected from SEQ ID NOS: 138-140. In some embodiments, the additional therapeutic agent is administered in a composition with the insulin immunoglobulin fusion protein. In some embodiments, the additional therapeutic agent is administered in a composition separate from the insulin immunoglobulin fusion protein. In some embodiments, the insulin immunoglobulin fusion protein is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route. In some embodiments, the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion (*e.g.*, pump), transdermal, oral or nasal route.

[0034] In some embodiments, the insulin therapeutic peptide has the formula B-A, A-B, B-C-A, or A-C-B; wherein B comprises an insulin B chain; A comprises an insulin A chain; if present, C comprises a connecter connecting B and A; and B-A, A-B, or both B-A and A-B are linked by a moiety or disulfide bond. In some embodiments, B-A or A-B, and B-A or A-B are linked by a disulfide bond. In some embodiments, the connecter is a connecting peptide comprising 2 to 50 amino acids. In some embodiments, the connecting peptide comprises an amino acid sequence having at least 50% glycine amino acids. In some embodiments, the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_1 is P, G or S. In some embodiments, X_2 is R, S, G or K. In some embodiments, C comprises a protease cleavage site. In some embodiments, the insulin B chain comprises a sequence of SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid. In some embodiments, X_A is D or H. In some embodiments, X_B is D or P. In some embodiments, X_C is P or K.

[0035] In some embodiments, the insulin B chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some embodiments, the insulin B chain comprises a sequence at least about 75% identical to an insulin B chain in any one of SEQ ID NOS: 109-140. In some embodiments, insulin B chain is selected from human insulin B chain, porcine insulin B chain and bovine insulin B chain. In some embodiments, the insulin A chain comprises a sequence of SEQ ID NO: 158 (GIVEQCCX$_D$SICSLYQLENYCN), and X$_D$ is a naturally or non-naturally occurring amino acid. In some embodiments, X$_D$ is selected from H and T. In some embodiments, the insulin A chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC). In some embodiments, the insulin A chain comprises a sequence at least about 75% identical to an insulin A chain in any one of SEQ ID NOS: 109-140. In some embodiments, the insulin A chain is selected from human insulin A chain, porcine insulin A chain and bovine insulin A chain.

[0036] In some embodiments, the immunoglobulin region comprises: (a) a heavy chain variable region sequence comprising SEQ ID NO: 45; (b) a heavy chain variable region sequence comprising SEQ ID NO: 46; (c) a heavy chain variable region sequence comprising SEQ ID NO: 55; (d) a heavy chain variable region sequence comprising SEQ ID NO: 47; (e) a light chain variable region sequence comprising SEQ ID NO: 48; (f) a light chain variable region sequence comprising SEQ ID NO: 49; (g) a light chain variable region sequence comprising SEQ ID NO: 50; (h) a combination of (a), (b) and (d); (i) a combination of (a), (c) and (d); (j) a combination of (e), (f) and (g); (k) a combination of (h) and (j); or (l) a combination of (i) and (j). In some embodiments, the immunoglobulin region comprises a sequence at least about 75% identical to a sequence selected from SEQ ID NOS: 29, 30 and 33-44. In some embodiments, the immunoglobulin region comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 30 and 33-44. In some embodiments, the immunoglobulin region is humanized. In some embodiments, the antigen binding domain binds to one or more amino acids of an epitope of ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140, H142, and K173.

[0037] In another aspect of the disclosure, provided herein are insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide and a first immunoglobulin region comprising an amino acid sequence of an antigen binding domain; wherein the insulin immunoglobulin fusion proteins are targeted to the liver. The insulin immunoglobulin fusion protein may be targeted to the liver by the binding of the antigen binding domain to an antigen expressed by a hepatocyte. In some embodiments, the antigen comprises an amino acid sequence of asialoglycoprotein receptor (ASGPR). In some embodiments, the first immunoglobulin region comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to an amino acid sequence derived from an anti-ASGPR antibody. In some embodiments, the first immunoglobulin region comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to an amino acid sequence of any one of SEQ ID NOS: 29, 30, 33-56, 16, or a combination thereof. In some embodiments, the insulin immunoglobulin fusion

protein is configured to bind to the antigen via the amino acid sequence of the antigen binding domain. In some embodiments, the insulin immunoglobulin fusion protein binds to the antigen with an affinity that is at least about 50%, 60%, 70%, 80%, 90%, or 95% of an affinity of the antigen binding domain within a native immunoglobulin. A native immunoglobulin may include, without limitation, an antibody, or region thereof (*e.g.*, Fab), comprising the antigen binding domain configured to bind the antigen expressed by a hepatocyte, wherein the antibody does not comprise and/or is not connected to, a non-antibody moiety (*e.g.*, therapeutic peptide/protein, small molecule).

[0038] In some embodiments, the amino acid sequence of the antigen binding domain comprises an amino acid sequence of a variable region derived from a variable light chain, a variable heavy chain, or both a variable light chain and a variable heavy chain. In some embodiments, the insulin immunoglobulin fusion protein further comprises a second immunoglobulin region comprising a second amino acid sequence of the antigen binding domain. In some cases, the second amino acid sequence of the antigen binding domain comprises an amino acid sequence of a variable region derived from a variable light chain, a variable heavy chain, or both a variable light chain and a variable heavy chain. In some embodiments, the first immunoglobulin region is humanized. In some embodiments, the first immunoglobulin region is a mouse immunoglobulin region.

[0039] In some embodiments, an activity of the insulin therapeutic peptide in the insulin immunoglobulin fusion protein is comparable to an activity of reference insulin therapeutic peptide. A reference therapeutic peptide may include a native formulation of the insulin therapeutic peptide, wherein the native formulation comprises the insulin therapeutic peptide not linked to an immunoglobulin, or region thereof. In some embodiments, the activity of the insulin therapeutic peptide in the insulin immunoglobulin fusion protein is at least about 50%, 60%, 70%, 80%, 90%, or 95% of the activity of the reference insulin therapeutic peptide. In some embodiments, the insulin therapeutic peptide of the insulin immunoglobulin fusion protein has an EC_{50} that is at least about 10%, 20%, 50%, or 100% less than an EC_{50} of a reference insulin therapeutic peptide in a hepatocyte activity assay. In some cases, the reference insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of any one of SEQ ID NOS: 109-140, 157, 158, 160, 161, or a combination thereof. In some cases, the reference insulin therapeutic peptide comprises an amino acid sequence derived from human insulin, porcine insulin, bovine insulin, or a combination thereof. In some cases, the reference insulin therapeutic peptide comprises an amino acid sequence derived from human insulin B chain, human insulin A chain, or a combination thereof. In some embodiments, the reference insulin peptide comprises an insulin analog, or a portion thereof. Non-limiting examples of insulin analogs include glargine, glulisine, insulin detemir, and insulin degludec.

[0040] In some embodiments, the insulin therapeutic peptide, or an amino acid sequence thereof, is linked to the amino terminus or the carboxyl terminus of the first immunoglobulin region. In some cases, the insulin therapeutic peptide, or an amino acid sequence thereof, is linked to the amino terminus of the first immunoglobulin region. In some embodiments, the insulin therapeutic peptide, or an amino acid sequence thereof, is linked to the first immunoglobulin region by a linker. In some cases, the linker

comprises an amino acid sequence. In some cases, the linker comprises from about 3 to about 40 amino acids. In some cases, the linker comprises one or more glycine residues; wherein the one or more glycine residues make up at least about 30%, 40% or 50% of the linker amino acid sequence. In some embodiments, the linker comprises a protease cleavage site. In some cases, the protease cleavage site is located at the amino terminus, carboxyl terminus, or within the linker peptide amino acid sequence. In some cases, the protease cleavage site is recognized by a proprotein convertase.

[0041] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain, an amino acid sequence derived from insulin A chain, or a combination thereof. In some embodiments, the insulin B chain comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to human insulin B chain. In some embodiments, the insulin A chain comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to human insulin A chain. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain and an amino acid sequence derived from insulin A chain. In some embodiments, the amino acid sequence derived from insulin B chain is connected to the amino acid sequence derived from insulin A chain. In some instances, the connection is via a connecting peptide. In some instances, the connecting peptide comprises from about 3 to about 25 amino acids. In some instances, the connecting peptide comprises one or more glycine residues, and wherein the one or more glycine residues make up at least about 30%, 40%, or 50% of the connecting peptide amino acid sequence. In some cases, the connecting peptide comprises a protease cleavage site. In some cases, the protease cleavage site of the connecting peptide is located at the amino terminus, carboxyl terminus, or within the connecting peptide amino acid sequence. In some cases, the protease cleavage site of the connecting peptide is recognized by a proprotein convertase. In some embodiments, the insulin therapeutic peptide comprises from amino to carboxyl terminus: the amino acid sequence derived from insulin B chain, the connecting peptide, and the amino acid sequence derived from insulin A chain. In some embodiments, the insulin therapeutic peptide comprises from amino to carboxyl terminus: the amino acid sequence derived from insulin A chain, the connecting peptide, and the amino acid sequence derived from insulin B chain.

[0042] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[0043] In some embodiments, the immunoglobulin fusion protein comprises a first chain comprising a first amino acid sequence of the insulin therapeutic peptide; and a second chain comprising a second amino acid sequence of the insulin therapeutic peptide linked to the first immunoglobulin region. In some embodiments, the first amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain and the second amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin A chain. In some embodiments, the first amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin A chain and the second amino acid sequence of the insulin therapeutic peptide comprises an amino

acid sequence derived from insulin B chain. In some implementations, the first amino acid sequence of the insulin therapeutic peptide is connected to the second amino acid sequence of the insulin therapeutic peptide. In some cases, the connection is via one or more disulfide bonds.

[0044] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[0045] In another aspect of the disclosure, provided herein are insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide; and a first immunoglobulin region comprising an amino acid sequence of an antigen binding domain; wherein the insulin therapeutic peptide, or an amino acid sequence of a region thereof, is connected to the amino terminus or carboxyl terminus of the first immunoglobulin region; and wherein the insulin immunoglobulin fusion protein is configured to bind to the antigen via the amino acid sequence of the antigen binding domain. In some embodiments, the insulin immunoglobulin fusion protein binds to the antigen with an affinity that is at least about 50%, 60%, 70%, 80%, 90%, or 95% of an affinity of the antigen binding domain within a native immunoglobulin. In some embodiments, an activity of the insulin therapeutic peptide in the insulin immunoglobulin fusion protein is comparable to an activity of a reference insulin therapeutic peptide. In some embodiments, the activity of the insulin therapeutic peptide in the insulin immunoglobulin fusion protein is at least about 50%, 60%, 70%, 80%, 90%, or 95% of the activity of the reference insulin therapeutic peptide. In some cases, the reference insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of any one of SEQ ID NOS: 109-140, 157, 158, 160, 161, or a combination thereof.

[0046] In some embodiments, the antigen binding domain is configured to bind to an antigen expressed by a hepatocyte. In some embodiments, the antigen is asialoglycoprotein receptor (ASGPR). In some embodiments, the first immunoglobulin region comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to an amino acid sequence derived from an anti-ASGPR antibody. In some embodiments, the first immunoglobulin region comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to an amino acid sequence of any one of SEQ ID NOS: 29, 30, 33-56, 167, or a combination thereof.

[0047] In some embodiments, the amino acid sequence of the antigen binding domain comprises an amino acid sequence of a variable region derived from a variable light chain, a variable heavy chain, or both a variable light chain and a variable heavy chain. In some embodiments, the insulin immunoglobulin fusion protein further comprises a second immunoglobulin region comprising a second amino acid sequence of the antigen binding domain. In some cases, the second amino acid sequence of the antigen binding domain comprises an amino acid sequence of a variable region derived from a variable light chain, a variable heavy chain, or both a variable light chain and a variable heavy chain.

[0048] In some embodiments, the insulin therapeutic peptide, or an amino acid sequence thereof, is linked to the amino terminus of the first immunoglobulin region. In some embodiments, the insulin therapeutic peptide, or an amino acid sequence thereof, is linked to the first immunoglobulin region by a

linker. In some embodiments, the linker comprises an amino acid sequence. In some cases, the linker comprises from about 3 to about 40 amino acids. In some cases, the linker comprises one or more glycine residues; and wherein the one or more glycine residues make up at least about 30%, 40% or 50% of the linker amino acid sequence. In some cases, the linker comprises a protease cleavage site. In some cases, the protease cleavage site is located at the amino terminus, carboxyl terminus, or within the linker peptide amino acid sequence. In some cases, the protease cleavage site is recognized by a proprotein convertase.

[0049] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain, an amino acid sequence derived from insulin A chain, or a combination thereof. In some embodiments, the insulin B chain comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to human insulin B chain. In some embodiments, the insulin A chain comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95% or 100% identical to human insulin A chain. In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain and an amino acid sequence derived from insulin A chain. In some embodiments, the amino acid sequence derived from insulin B chain is connected to the amino acid sequence derived from insulin A chain. In some embodiments, the connection is via a connecting peptide. In some cases, the connecting peptide comprises from about 3 to about 25 amino acids. In some cases, the connecting peptide comprises one or more glycine residues, and wherein the one or more glycine residues make up at least about 30%, 40%, or 50% of the connecting peptide amino acid sequence. In some cases, the connecting peptide comprises a protease cleavage site. In some cases, the protease cleavage site of the connecting peptide is located at the amino terminus, carboxyl terminus, or within the connecting peptide amino acid sequence. In some instances, the protease cleavage site of the connecting peptide is recognized by a proprotein convertase.

[0050] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[0051] In some embodiments, the insulin therapeutic peptide comprises from amino to carboxyl terminus: the amino acid sequence derived from insulin B chain, the connecting peptide, and the amino acid sequence derived from insulin A chain. In some embodiments, the insulin therapeutic peptide comprises from amino to carboxyl terminus: the amino acid sequence derived from insulin A chain, the connecting peptide, and the amino acid sequence derived from insulin B chain.

[0052] In some embodiments, the immunoglobulin fusion protein comprises: a first chain comprising a first amino acid sequence of the insulin therapeutic peptide; and a second chain comprising a second amino acid sequence of the insulin therapeutic peptide linked to the first immunoglobulin region. In some embodiments, the first amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin B chain and the second amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin A chain. In some embodiments, the first amino acid sequence of the insulin therapeutic peptide comprises an amino acid sequence derived from insulin A chain and the second amino acid sequence of the insulin therapeutic peptide comprises an amino

acid sequence derived from insulin B chain. In some cases, the first amino acid sequence of the insulin therapeutic peptide is connected to the second amino acid sequence of the insulin therapeutic peptide. In some cases, the connection is via one or more disulfide bonds.

[0053] In some embodiments, the insulin therapeutic peptide comprises an amino acid sequence that is about or at least about 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[0054] In another aspect of the disclosure, provided are pharmaceutical compositions comprising any of the insulin immunoglobulin fusion proteins described herein. Further provided herein, in various embodiments, are methods of treating a disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an insulin immunoglobulin fusion protein described herein. In some cases, the disease is diabetes. In some cases, the disease is obesity.

[0055] In another aspect of the disclosure, provided is a first genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of any one of the insulin immunoglobulin fusion proteins described herein. In various embodiments, provided herein is a first expression vector comprising the first genetic construct. In various embodiments, provided herein is a mammalian expression host comprising the first expression vector. In some cases, the mammalian expression host further comprises one or more additional expression vectors. In some instances, one of the one of more additional expression vectors comprises a second genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of an additional immunoglobulin domain. In some instances, one of the one or more additional expression vectors comprises a third genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of a protease. In some embodiments, the first expression vector further comprises a genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of an additional immunoglobulin domain. In some embodiments, the first expression vector further comprises a genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of a protease.

[0056] Further provided herein, in various embodiments, is a method of producing an immunoglobulin fusion protein comprising transfecting the first expression vector transiently in a mammalian cell culture; growing the cell culture in an expression medium at a controlled temperature and percentage CO_2; and harvesting the secreted immunoglobulin fusion protein. In some instances, the method further comprises co-transfecting one or more additional expression vectors. In some cases, one of the one of more additional expression vectors comprises a second genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of an additional immunoglobulin domain. In some cases, one of the one or more additional expression vectors comprises a third genetic construct comprising a nucleic acid sequence encoding an amino acid sequence of a protease. In some embodiments, the method further comprises purifying the harvested immunoglobulin fusion protein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] The foregoing summary, as well as the following detailed description of the disclosure, will be better understood when read in conjunction with the appended figures. It should be understood, however,

that the disclosure is not limited to the precise examples shown. It is emphasized that, according to common practice, the various features of the drawings are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures.

[0058] **FIG. 1A** depicts a schematic of an insulin immunoglobulin fusion protein comprising: an immunoglobulin heavy chain having a variable domain (VH) and constant region (CH1), and an insulin therapeutic peptide connected to the amino terminus of an immunoglobulin light chain having a variable domain (VL) and a constant region (CH1).

[0059] **FIG. 1B** depicts a schematic of an insulin immunoglobulin fusion protein comprising: an immunoglobulin light chain, and an insulin therapeutic peptide connected to the amino terminus of an immunoglobulin heavy chain.

[0060] **FIG. 2** shows SDS-PAGE gels of purified insulin fusion proteins reduced (+) or not reduced (-) with DTT. Panel A shows a purified insulin fusion protein Ins1-L1-Ab1L IgG comprising Ab1H (SEQ ID NO: 29) and Ins1-L1-Ab1L (SEQ ID NO: 79). Panel B shows a purified insulin fusion protein Ins1-L1-Ab1H IgG comprising Ab1L (SEQ ID NO: 30) and Ins1-L1-Ab1H (SEQ ID NO: 78).

[0061] **FIG. 3** is a graph showing the binding of insulin immunoglobulin fusion proteins as shown in FIG. 2 (Ins1-L1-Ab1L IgG; Ins1-L1-Ab1H IgG) to human ASGPR in an in vitro assay.

[0062] **FIG. 4** is a graph showing the binding of insulin immunoglobulin fusion proteins as shown in FIG. 2 (Ins1-L1-Ab1L IgG; Ins1-L1-Ab1H IgG) to rat ASGPR.

[0063] **FIG. 5** is a graph showing the activity of insulin immunoglobulin proteins (Ins1-L1-Ab1L IgG; Ins1-L1-Ab1H IgG) on HepG2 cells.

[0064] **FIG. 6** is flow cytometry histogram showing the binding of insulin immunoglobulin fusion proteins as shown in FIG. 2 (Ins1-L1-Ab1L IgG (panel A); Ins1-L1-Ab1H IgG (panel B)) to HepG2 cells.

[0065] **FIG. 7** is graph corresponding to the histograms of FIG. 6.

[0066] **FIG. 8** shows an SDS-PAGE gel of purified Ins1-L1-Ab2L IgG (SEQ ID NOS: 80, 31) fusion protein.

[0067] **FIG. 9** shows an SDS-PAGE gel of purified Ins2-L2-Ab3L (SEQ ID NO: 81) and Ab3H (SEQ ID NO: 167) fusion protein; with and without proteolytic cleavage by the enzyme PC2.

[0068] **FIG. 10** shows an SDS-PAGE gel of purified Ins3-L2-Ab3L IgG fusion protein.

[0069] **FIG. 11** is a graph showing the activity of insulin immunoglobulin proteins (Ins1-L1-Ab2L IgG; Ins3-L2-Ab1L IgG; Ins3-L2-Ab1L IgG with PC2 cleavage; Ins2-L2-Ab1L IgG; Ins2-L2-Ab1L IgG with PC2 cleavage) on HepG2 cells.

[0070] **FIG. 12** shows an SDS-PAGE gel of purified Ins1-L3-Ab4L IgG fusion protein.

[0071] **FIG. 13** shows an SDS-PAGE gel of purified Ins1-L3-Ab5L IgG fusion protein.

[0072] **FIG. 14** shows an SDS-PAGE gel of purified Ins1-L3-Ab4L(Fab) fusion protein.

[0073] **FIG. 15** is a graph showing the activity of insulin immunoglobulin proteins (Ins1-L3-Ab4L IgG; Ins1-L3-Ab4L (Fab)) on HepG2 cells.

[0074] **FIGS. 16**, panels A-C are graphs showing the binding of insulin immunoglobulin fusion proteins (Ins1-L3-Ab4L and Ab4H; Ins1-L3-Ab4L and Ab4H(Fab)) to extracellular domains of human, rat or cynomolgus monkey ASGPR.

[0075] **FIG. 17** shows an SDS-PAGE gel of purified Ins4-L3-Ab4L IgG fusion protein and Ins4-L3-Ab2L IgG fusion protein.

[0076] **FIG. 18** is a graph showing the activity of insulin immunoglobulin proteins (Ins4-L3-Ab4L and Ab4H; Ins4-L3-Ab2L and Ab42) on HepG2 cells.

[0077] **FIG. 19** shows an SDS-PAGE gel of purified Ins4-L6-Ab4L IgG fusion protein; Ins4-L6-Ab4L(Fab) fusion protein; and Ins5-L7-Ab4L IgG fusion protein.

[0078] **FIG. 20** is a graph showing the activity of insulin immunoglobulin protein Ins4-L6-Ab4L IgG on HepG2 cells.

[0079] **FIG. 21** is a graph showing the activity of insulin immunoglobulin proteins (Ins4-L6-Ab4L(Fab) and Ins5-L7-Ab4L IgG) on HepG2 cells.

[0080] **FIG. 22** is a graph showing the activity of insulin immunoglobulin proteins (Ins1-L3-Ab4L IgG; Ins1-L4-Ab4L IgG; Ins1-L5-Ab4L IgG) on HepG2 cells.

[0081] **FIG. 23** shows an SDS-PAGE gel of purified Ins1-L3-Ab4 Fab fusion protein.

[0082] **FIG. 24** shows an SDS-PAGE gel of purified Ins1-L3-Ab5 Fab fusion protein.

[0083] **FIG. 25** shows an SDS-PAGE gel of purified Ins7-L3-Ab4 Fab fusion protein.

[0084] **FIG. 26** shows an SDS-PAGE gel of purified Ins7-L3-Ab5 Fab fusion protein.

[0085] **FIG. 27** shows a graph showing size exclusion purification of Ins1-L3-Ab4 Fab fusion protein.

[0086] **FIG. 28** shows a graph showing size exclusion purification of Ins1-L3-Ab5 Fab fusion protein.

[0087] **FIG. 29** shows a graph showing size exclusion purification of Ins7-L3-A5 Fab fusion protein.

[0088] **FIG. 30** shows a graph of mass-spectrum characterization of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab fusion proteins.

[0089] **FIG. 31**, panels A-C are graphs of thermal stability of A4Fab, Ins1-L3-Ab4 Fab, and Ins1-L3-Ab4 Fab gel filtration major peak collection.

[0090] **FIG. 32** is a graph showing the activity of insulin binding on HepG2 cells of WT insulin, Ins1-L3-Ab4 Fab, and Ins1-L3-Ab5 Fab.

[0091] **FIG. 33** is a graph showing the activity of insulin binding on HepG2 cells of WT Insulin, Ins1-L3-Ab4 Fab, and Ins7-L3-Ab4 Fab.

[0092] **FIG. 34** is a graph showing the activity of insulin binding on A673 cells of WT Insulin, Ins1-L3-Ab4 Fab, and Ins1-L3-Ab5 Fab.

[0093] **FIG. 35** is a graph showing the activity of insulin binding on SGBS cells of WT Insulin, Ins1-L3-Ab4 Fab, and Ins1-L3-Ab5 Fab.

[0094] **FIG. 36** is a graph of binding Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, Ab4, and Ab5 on HepG2 cells as measured by flow cytometry.

[0095] **FIG. 37** is a graph of the binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab to extracellular domains of human ASGPR.

[0096] **FIG. 38** is a graph of the binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab to extracellular domains of rat ASGPR.

[0097] **FIG. 39** is a graph of the binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab to extracellular domains of cynomolgus monkey ASGPR.

[0098] **FIG. 40** is a graph of the pharmacology kinetics of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab at a 1 mg/kg intravenous dose.

[0099] **FIG. 41** is a graph of the blood glucose concentration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab over time at a 0.1 mg/kg or 1 mg/kg intravenous dose compared to Vehicle, Levimir (6U/kg, subcutaneous), and Naïve control.

[00100] **FIG. 42** is a graph of the pharmacology kinetics of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab at a 20 mg/kg intravenous dose.

[00101] **FIG. 43** is a graph of the blood glucose concentration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab over time at a 20 mg/kg intravenous dose compared to Vehicle, Levimir (6U/kg, subcutaneous), and Naïve control.

[00102] **FIG. 44** is a graph of the pharmacology kinetics of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab at a 10 mg/kg subcutaneous dose.

[00103] **FIG. 45** is a graph of the blood glucose concentration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab over time at a 10 mg/kg subcutaneous dose compared to Vehicle, Levimir (6U/kg, subcutaneous), and Naïve control.

[00104] **FIG. 46**, panels A-C are graphs of the bio-distribution of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in normal rats as measured in the liver, muscle, or fat tissue.

[00105] **FIG. 47** shows an alignment of human, cynomolgus monkey, rat and mouse ASGPR.

DETAILED DESCRIPTION OF THE INVENTION

[00106] In one aspect of the disclosure, provided herein are insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide connected to an immunoglobulin or portion thereof. The insulin immunoglobulin fusion proteins may be useful for the treatment of various diseases and conditions associated with insulin and glucose metabolism, such as diabetes. In various embodiments, the immunoglobulin portion of the fusion protein comprises or is part of an antigen binding domain that targets the fusion protein to the liver by binding to an antigen expressed or displayed by a hepatocyte. An exemplary antigen is asialoglycoprotein receptor (ASGPR).

[00107] According to one feature of the subject matter described herein, an insulin immunoglobulin fusion protein comprises a first immunoglobulin region and an insulin therapeutic peptide; wherein the insulin therapeutic peptide, or an amino acid sequence of a region thereof, is connected to the amino terminus of the immunoglobulin region. In another feature of the subject matter described herein, an insulin immunoglobulin fusion protein comprises a first immunoglobulin region; and an insulin therapeutic peptide; wherein the insulin therapeutic peptide, or an amino acid sequence of a region thereof, is connected to the carboxyl terminus of the immunoglobulin region. The insulin therapeutic

peptide, or an amino acid sequence thereof, may be connected to the immunoglobulin region with a linker. The first immunoglobulin region may comprise a single immunoglobulin domain or portion thereof, for example, a light chain domain, heavy chain domain, or a combination thereof. In some embodiments, the insulin therapeutic peptide comprises a first amino acid sequence connected to a second amino acid sequence. In some cases, the connection is through a chemical bond. In some cases, the connection is through a disulfide bond. In some cases, the connection is through a connecting peptide. In some embodiments, the immunoglobulin fusion protein further comprises one or more protease cleavage sites. In some cases, wherein the insulin immunoglobulin fusion protein comprises a linker, the linker comprises a protease cleavage site. In some cases, wherein the insulin immunoglobulin fusion protein comprises a connecting peptide, the connecting peptide comprises a protease cleavage site.

[00108] The insulin therapeutic peptides of the insulin immunoglobulin fusion proteins described herein may include an amino acid sequence from insulin B chain, insulin A chain, or a combination thereof. In some embodiments, the insulin is B chain, insulin A chain, or both chains comprise amino acid sequences derived from human insulin. In some embodiments, the insulin is B chain, insulin A chain, or both chains comprise amino acid sequences derived from non-human insulin. As a non-limiting example, porcine insulin. In some embodiments, the insulin is B chain, insulin A chain, or both chains comprise amino acid sequences derived from an insulin analog.

[00109] In some embodiments, an insulin therapeutic peptide of an insulin immunoglobulin fusion protein comprises a single chain amino acid sequence. The single chain amino acid sequence may comprise an amino acid sequence from insulin B chain, insulin A chain, or a combination thereof. In some cases, the single chain amino acid sequence of an insulin therapeutic peptide comprises an amino acid sequence from insulin B chain connected to an amino acid sequence from insulin A chain by a connecting peptide.

[00110] In some embodiments, an insulin therapeutic peptide of an insulin immunoglobulin fusion protein comprises a first chain comprising a first amino acid sequence of the therapeutic peptide and a second chain comprising a second amino acid sequence of the therapeutic peptide. In some cases, the first amino acid sequence of the insulin therapeutic protein is connected to the first immunoglobulin region. In some cases, the second amino acid sequence of the therapeutic protein is connected to the first immunoglobulin region. In some embodiments, the first chain and the second chain are connected. As a non-limiting example, the first chain and the second chain are connected by one or more disulfide bonds. The first chain amino acid sequence may comprise an amino acid sequence from insulin B chain, insulin A chain, or a combination thereof. In some cases, the first chain amino acid sequence of an insulin therapeutic peptide comprises an amino acid sequence from insulin B chain and the second chain amino acid sequence comprises an amino acid sequence from insulin A chain. In some cases, the first chain amino acid sequence of an insulin therapeutic peptide comprises an amino acid sequence from insulin A chain and the second chain amino acid sequence comprises an amino acid sequence from insulin B chain.

[00111] Exemplary embodiments of insulin immunoglobulin fusion proteins are depicted in Formulas I-XVI, wherein T is an insulin therapeutic peptide or a portion of a therapeutic peptide, L is a linker, and

A is an immunoglobulin region. The therapeutic peptide, linker, connecting peptide, or any combination thereof, may comprise a protease cleavage site. The amino acids that are not connected by peptide bonds, e.g., are separate chains, are separated by a semicolon. In some embodiments, one or more of the separate chains are linked by a non-covalent bond. As a non-limiting example, one or more separate chains are linked by one or more disulfide bonds.

Formula	Immunoglobulin fusion protein
I	T^1-A^1
II	T^1-A^1; A^2
III	T^1-A^1; T^2
IV	T^1-A^1; T^2; A^2
V	T^1-L-A^1
VI	T^1-L-A^1; A^2
VII	T^1-L-A^1; T^2
VIII	T^1-L-A^1; T^2; A^2
IX	A^1-T^1
X	A^1-T^1; A^2
XI	A^1-T^1; T^2
XII	A^1-T^1; T^2; A^2
XIII	A^1-L-T^1
XIV	A^1-L-T^1; A^2
XV	A^1-L-T^1; T^2
XVI	A^1-L-T^1; T^2; A^2

[00112] The insulin therapeutic peptide, T^n (n=1 or 2), represents a therapeutic peptide comprising one or more amino acid sequences derived from an insulin peptide. The insulin therapeutic peptide, T^n, may further comprise one or more connecting peptides. In some embodiments, T^n comprises a first amino acid sequence derived from an insulin peptide, a connecting peptide, and a second amino acid sequence derived from an insulin peptide. For example, the first amino acid sequence is derived from an insulin B chain amino acid sequence and the second amino acid sequence is derived from an insulin A chain amino acid sequence, or vice versa. In some embodiments, T^n comprises a first amino acid sequence derived from an insulin peptide and a connecting peptide. In some embodiments, T^n comprises an amino acid derived from an insulin B chain amino acid sequence. In some embodiments, T^n comprises an amino acid derived from an insulin A chain amino acid sequence. In some cases, T^1 comprises an amino acid sequence derived from an insulin B chain amino acid sequence and T^2 comprises an amino acid sequence derived from an insulin A chain amino acid sequence, wherein either T^1, T^2 or both T^1 and T^2 further comprise one or more connecting peptides. In some cases, T^1 comprises an amino acid sequence derived from an insulin A chain amino acid sequence and T^2 comprises an amino acid sequence derived from an

insulin B chain amino acid sequence, wherein either T^1, T^2 or both T^1 and T^2 further comprise one or more connecting peptides. In some embodiments, the connecting peptide comprises a protease cleavage site.

[00113] The immunoglobulin region, A^n (n=1 or 2), represents a first immunoglobulin region, A^1 and a second immunoglobulin region, A^2. In some embodiments, A^1 comprises an amino acid sequence of an immunoglobulin light chain. In some embodiments, A^2 comprises an amino acid sequence of an immunoglobulin light chain. In some embodiments, A^1 comprises an amino acid sequence of an immunoglobulin heavy chain. In some embodiments, A^2 comprises an amino acid sequence of an immunoglobulin heavy chain. In some embodiments, for insulin fusion proteins comprising A^1 and A^2, the two immunoglobulin regions are connected. In some cases, the two regions are connected by one or more disulfide bonds. An amino acid sequence of A^1 may comprise an amino acid sequence derived from an anti-ASGPR antibody. An amino acid sequence of A^2 may comprise an amino acid sequence derived from an anti-ASGPR antibody.

[00114] In another aspect of the disclosure, provided herein are pharmaceutical compositions comprising an immunoglobulin fusion protein disclosed herein. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

[00115] Further disclosed herein, in various aspects, are methods of treating a disease or condition in a subject in need thereof. Generally, the method comprises administering to the subject an insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide. In some cases, the disease is diabetes and/or a complication thereof. In some embodiments, an insulin immunoglobulin fusion protein having the formula of I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, or any modification, portions, or additions thereof is administered to the subject.

[00116] Further disclosed herein, in various aspects, are methods of improving the delivery of an insulin therapeutic peptide. The methods may involve generation of an insulin immunoglobulin fusion protein from a genetic construct. In some embodiments, the insulin immunoglobulin fusion protein is recombinantly produced from a genetic construct encoding the insulin immunoglobulin fusion protein. In some embodiments, the construct is expressed in vitro using standard mammalian cell culture techniques. In some embodiments, one construct encoding an insulin therapeutic peptide connected to the amino or carbosyl terminus of a first immunoglobulin region is co-expressed with a second construct comprising a second immunoglobulin region, to produce a recombinant insulin immunoglobulin fusion protein. In some embodiments, a construct encoding a protease is co-expressed with an immunoglobulin fusion protein. The method may further comprise generating immunoglobulin genetic fusion constructs comprising a linker, connecting peptide, proteolytic cleavage site, or a combination thereof.

[00117] Before the present methods and compositions are described, it is to be understood that this disclosure is not limited to a particular method or composition described, and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. Examples are put forth so as to provide those of ordinary skill in the art with a disclosure and description of how to make and use the immunoglobulin fusion proteins provided herein, and are not intended to limit the scope of what the inventors regard as their invention nor

are they intended to represent that the provided experiments encompass all of the experiments performed. Efforts have been made to ensure accuracy with respect to numbers used but some experimental errors and deviations should be accounted for.

[00118] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[00119] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

[00120] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible. Any recited combination of amino acid sequences can have the order recited, or any other order which is logically possible. As a non-limiting example, an immunoglobulin fusion protein comprising an insulin therapeutic peptide, T, and an immunoglobulin region, A, includes, for example and without limitation: T-A, A-T, T-A-T, and A-T-A.

[00121] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, e.g. polypeptides, known to those skilled in the art, and so forth.

[00122] The terms "homologous," "homology," or "percent homology" when used herein to describe to an amino acid sequence or a nucleic acid sequence, relative to a reference sequence, can be determined using the formula described by Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87: 2264-2268, 1990, modified as in Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such a formula is incorporated into the basic local alignment search tool (BLAST) programs of Altschul et al. (J. Mol. Biol. 215: 403-410, 1990). Percent homology of sequences can be determined using the most recent version of BLAST, as of the filing date of this application.

Insulin Immunoglobulin Fusion Proteins

[00123] Various insulin immunoglobulin fusion proteins disclosed herein comprise a first immunoglobulin region and an insulin therapeutic peptide, wherein the insulin therapeutic peptide, or an amino acid sequence thereof, is connected to an amino or carboxyl terminus of the first immunoglobulin region. In various instances, the insulin immunoglobulin fusion proteins further comprise a second immunoglobulin region. The immunoglobulin region (first and/or second) may be any portion, in part or whole, of an immunoglobulin.

[00124] The immunoglobulin region may comprise an entire immunoglobulin molecule or any polypeptide comprising a fragment of an immunoglobulin including, but not limited to, heavy chain, light chain, variable domain, constant domain, complementarity determining region (CDR), framework region, fragment antigen binding (Fab) region, Fab', F(ab')2, F(ab')3, Fab', fragment crystallizable (Fc) region, single chain variable fragment (scFV), di-scFv, single domain immunoglobulin, trifunctional immunoglobulin, chemically linked F(ab')2, and any portion or combination thereof. In some embodiments, an immunoglobulin heavy chain may comprise an entire heavy chain or a portion of a heavy chain. For example, a variable domain or region thereof derived from a heavy chain may be referred to as a heavy chain or a region of a heavy chain. In some embodiments, an immunoglobulin light chain may comprise an entire light chain or a portion of a light chain. For example, a variable domain or region thereof derived from a light chain may be referred to as a light chain or a region of a light chain. The immunoglobulin region may be bispecific or trispecific. A single domain immunoglobulin includes, but is not limited to, a single monomeric variable immunoglobulin domain. The single domain immunoglobulin may be a shark variable new antigen receptor immunoglobulin fragment (VNAR). The immunoglobulin may be derived from any type known to one of skill in the art including, but not limited to, IgA, IgD, IgE, IgG, IgM, IgY, IgW. The immunoglobulin region may be a glycoprotein. The immunoglobulin region may comprise one or more functional units, including but not limited to, 1, 2, 3, 4, and 5 units. The immunoglobulin region may comprise one or more units connected by one or more disulfide bonds. The immunoglobulin region may comprise one or more units connected by a peptide linker, for example, a scFv immunoglobulin. The immunoglobulin may be a recombinant immunoglobulin including immunoglobulins with amino acid mutations, substitutions, and/or deletions. The immunoglobulin may be a recombinant immunoglobulin comprising chemical modifications. The immunoglobulin may comprise a whole or part of an immunoglobulin-drug conjugate. The immunoglobulin may comprise a small molecule. The immunoglobulin may comprise a whole or part of an immunoglobulin-drug conjugate comprising a small molecule. The immunoglobulin may be from a mammalian source. The immunoglobulin may be a chimeric immunoglobulin. The immunoglobulin region may be derived in whole or in part from an engineered immunoglobulin or recombinant immunoglobulin. The immunoglobulin may be from a humanized, human engineered or fully human immunoglobulin. The mammalian immunoglobulin may be a bovine immunoglobulin. The mammalian immunoglobulin may be a human immunoglobulin. The mammalian immunoglobulin may be a murine immunoglobulin. The mammalian immunoglobulin may be a non-human primate immunoglobulin. The

immunoglobulin may be an avian immunoglobulin. The immunoglobulin may be a shark immunoglobulin.

[00125] Fusion proteins described herein may be modified by any means known in the art and can thus deviate from the embodiments described. As a non-limiting example, reference to immunoglobulin region is not limited to an antibody and includes any molecule which may bind to an antigen.

[00126] In one aspect of the disclosure, provided are insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell. An exemplary schematic showing a light chain fusion and a heavy chain fusion is shown in FIGS. 1A and 1B, respectively. The antigen targeted by the antigen binding domain may be expressed by a hepatocyte. As a non-limiting example, the antigen is asialoglycoprotein receptor (ASGPR). The antigen binding domain may bind to an epitope of an ASGPR having a sequence selected from SEQ ID NOS: 162-165. The antigen binding domain may be specific for human ASGPR over mouse ASGPR. Non-limiting examples of epitopes are shown in the sequence alignment of FIG. 47. For instance, the antigen binding domain may bind to a one or more amino acids of an epitope of human ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140, H142, and K173. In some cases, the one or more amino acids of the epitope comprises any combination of W134, E135, K138, V140, H142, and K173.

[00127] The immunoglobulin fusion protein may comprise an amino acid sequence that is based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOs 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to any one of SEQ ID NOS: 78-98. In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to an amino acid sequence of any one of SEQ ID NOS: 78-98. In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence that is at least about 50%, 55%,

60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to an amino acid sequence of any one of SEQ ID NOS: 78-98.

[00128] The immunoglobulin fusion protein may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence comprising 125, 150, 175, 200, 225, 250 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence comprising 50 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence comprising 100 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The immunoglobulin fusion protein may comprise an amino acid sequence comprising 200 or more amino acids based on or derived from any one of SEQ ID NOS: 78-98. The amino acids may be consecutive. Alternatively, or additionally, the amino acids are nonconsecutive. In some embodiments, the immunoglobulin fusion protein comprises amino acids derived from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of SEQ ID NOS: 78-98.

[00129] The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is based on or derived from any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to an amino acid sequence of any one of SEQ ID NOS: 57-77. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to an amino acid sequence of any one of SEQ ID NOS: 57-77.

[00130] The immunoglobulin fusion protein may be encoded by a nucleic acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence comprising 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 450, 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence comprising 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 57-77. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence comprising 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 57-77. The nucleotides may be consecutive. Alternatively, or additionally, the nucleotides are nonconsecutive. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence derived from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of SEQ ID NOS: 57-77.

[00131] Further disclosed herein are nucleotide constructs comprising a nucleic acid sequence that is based on or derived from any one of SEQ ID NOS: 57-77. The nucleotide construct may be a plasmid for expression in a host cell. For example, a mammalian or bacterial expression plasmid. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is 100% identical to any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to an amino acid sequence of any one of SEQ ID NOS: 57-77. In some embodiments, the construct comprises a nucleic acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to an amino acid sequence of any one of SEQ ID NOS: 57-77.

Insulin immunoglobulin light chain fusions

[00132] In one feature of the disclosure, provided herein is an immunoglobulin fusion protein comprising an insulin therapeutic peptide comprising one or more regions connected to the amino or carboxyl terminus of a region of an immunoglobulin light chain, wherein the immunoglobulin fusion is referred to herein as an immunoglobulin light chain fusion. In some embodiments, the immunoglobulin fusion protein further comprises one or more regions of an immunoglobulin heavy chain. In some cases,

the immunoglobulin light chain fusion is connected to the one or more regions of an immunoglobulin heavy chain by disulfide bonds or a linker. In some embodiments, the insulin therapeutic peptide comprises one or more regions of a therapeutic peptide. In some embodiments, the insulin therapeutic peptide comprises two regions of a therapeutic peptide connected by a connecting peptide. In some embodiments, the therapeutic peptide comprises a protease cleavage site. In some embodiments, the connecting peptide comprises a protease cleavage site.

[00133] In some embodiments, the immunoglobulin light chain fusion comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody. In some embodiments, the heavy chain comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody.

[00134] In one aspect of the disclosure, provided are light chain insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell. The antigen targeted by the antigen binding domain may be expressed by a hepatocyte. As a non-limiting example, the antigen is asialoglycoprotein receptor (ASGPR). The first immunoglobulin region may comprise a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a first CDR having an amino acid sequence that differs from SEQ ID NO: 48 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a second CDR having an amino acid sequence that differs from SEQ ID NO: 49 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a third CDR having an amino acid sequence that differs from SEQ ID NO: 50 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NO: 41 and SEQ: 44. The first immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NO: 41 and SEQ: 44. The first immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. The first immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. The insulin immunoglobulin fusion protein may further comprise a second immunoglobulin region. The second immunoglobulin region may comprise one or more portions of the antigen binding domain. The second immunoglobulin region may comprise a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a first CDR having an amino acid sequence that differs from SEQ ID NO: 45 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a second CDR having an amino acid sequence that differs from SEQ ID NO: 46 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may

comprise a second CDR having an amino acid sequence that differs from SEQ ID NO: 55 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a third CDR having an amino acid sequence that differs from SEQ ID NO: 47 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. The second immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. The second immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. The second immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.

[00135] The immunoglobulin light chain fusion may comprise an amino acid sequence that is based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence that is 100% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an

amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin heavy chain may comprise an amino acid sequence that is 100% identical to any one of SEQ ID NOS: 79-92, 94-98.

[00136] The insulin immunoglobulin light chain fusion may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence comprising 125, 150, 175, 200 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence comprising 50 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence comprising 100 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The immunoglobulin light chain fusion may comprise an amino acid sequence comprising 200 or more amino acids based on or derived from any one of SEQ ID NOS: 79-92, 94-98. The amino acids may be consecutive. Alternatively, or additionally, the amino acids are nonconsecutive. In some embodiments, the immunoglobulin light chain fusion comprises amino acids derived from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of SEQ ID NOS: 79-92, 94-98.

[00137] The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is based on or derived from any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence that is 100% identical to any one of SEQ ID NOS: 58-71, 73-77.

[00138] The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence comprising 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 450, 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence comprising 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 58-71, 73-77. The immunoglobulin light chain fusion may be encoded by a nucleic acid sequence comprising 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 58-71, 73-77. The nucleotides may be consecutive. Alternatively, or additionally, the nucleotides are nonconsecutive. In some embodiments, the immunoglobulin light chain fusion is encoded by a nucleic acid sequence derived from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of SEQ ID NOS: 58-71, 73-77.

Insulin immunoglobulin heavy chain fusions

[00139] In one feature of the disclosure, provided herein is an immunoglobulin fusion protein comprising an insulin therapeutic peptide comprising one or more regions connected to the amino or carboxyl terminus of a region of an immunoglobulin heavy chain, wherein the immunoglobulin fusion is referred to herein as an immunoglobulin heavy chain fusion. In some embodiments, the immunoglobulin fusion protein further comprises one or more regions of an immunoglobulin light chain. In some cases, the immunoglobulin heavy chain fusion is connected to the one or more regions of an immunoglobulin light chain by disulfide bonds or a linker. In some embodiments, the insulin therapeutic peptide comprises one or more regions of a therapeutic peptide. In some embodiments, the insulin therapeutic peptide comprises two regions of a therapeutic peptide connected by a connecting peptide. In some embodiments, the therapeutic peptide comprises a protease cleavage site. In some embodiments, the connecting peptide comprises a protease cleavage site.

[00140] In some embodiments, the immunoglobulin heavy chain fusion comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody. In some embodiments, the light chain comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody.

[00141] In one aspect of the disclosure, provided are heavy chain insulin immunoglobulin fusion proteins comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell. The antigen targeted by the antigen binding domain may be expressed by a hepatocyte. As a non-limiting example, the antigen is asialoglycoprotein receptor (ASGPR). The first immunoglobulin region may comprise a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a first CDR having an amino acid sequence that differs from SEQ ID NO: 45 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a second CDR having an amino acid sequence that differs from SEQ ID NO: 46 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a second CDR having an amino acid

sequence that differs from SEQ ID NO: 55 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a third CDR having an amino acid sequence that differs from SEQ ID NO: 47 by no more than 5, 4, 3, 2 or 1 amino acids. The first immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. The first immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. The first immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. The first immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. The insulin immunoglobulin fusion protein may further comprise a second immunoglobulin region. The second immunoglobulin region may comprise one or more portions of the antigen binding domain. The second immunoglobulin region may comprise a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a first CDR having an amino acid sequence that differs from SEQ ID NO: 48 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a second CDR having an amino acid sequence that differs from SEQ ID NO: 49 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a third CDR having an amino acid sequence that differs from SEQ ID NO: 50 by no more than 5, 4, 3, 2 or 1 amino acids. The second immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 41 and 44. The second immunoglobulin region may comprise a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 41 and 44. The second immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. The second immunoglobulin region may comprise an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.

[00142] The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 50% homologous to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 70% homologous to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 80% homologous to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 50% identical to SEQ ID

NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 70% identical to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is at least about 80% identical to SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 50% homologous to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 70% homologous to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 80% homologous to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 50% identical to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 70% identical to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is at least about 80% identical to SEQ ID NO: 78 or 93. The immunoglobulin light chain may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 78 or 93.

[00143] The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 450, 500 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 50 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 100 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The immunoglobulin heavy chain fusion may comprise an amino acid sequence comprising 200 or more amino acids based on or derived from SEQ ID NO: 78 or 93. The amino acids may be consecutive. Alternatively, or additionally, the amino acids are nonconsecutive.

[00144] The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is based on or derived from SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 50% homologous to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 70%

homologous to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 80% homologous to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 50% identical to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 70% identical to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is at least about 80% identical to SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 57 or 72.

[00145] The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more nucleotides based on or derived from SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence comprising 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 450, 500 or more nucleotides based on or derived from SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence comprising 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more nucleotides based on or derived from any SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence comprising 100 or more nucleotides based on or derived from SEQ ID NO: 57 or 72. The immunoglobulin heavy chain fusion may be encoded by a nucleic acid sequence comprising 500 or more nucleotides based on or derived from SEQ ID NO: 57 or 72. The nucleotides may be consecutive. Alternatively, or additionally, the nucleotides are nonconsecutive.

Insulin immunoglobulin fusion proteins

[00146] In one feature of the disclosure, provided herein are immunoglobulin fusion proteins comprising (a) an insulin immunoglobulin light chain fusion, and (b) a second immunoglobulin region derived from an immunoglobulin heavy chain. In some cases, the immunoglobulin light chain fusion is connected to the second immunoglobulin region by one or more disulfide bonds and/or a linker. The insulin immunoglobulin light chain fusion comprises an insulin therapeutic peptide comprising one or more regions connected to the amino or carboxyl terminus of a region of an immunoglobulin light chain. In some embodiments, the insulin therapeutic peptide comprises one or more regions of a therapeutic peptide. In some embodiments, the insulin therapeutic peptide comprises two regions of a therapeutic peptide connected by a connecting peptide. In some embodiments, the therapeutic peptide comprises a protease cleavage site. In some embodiments, the connecting peptide comprises a protease cleavage site. In some embodiments, the therapeutic peptide comprises a first chain and a second chain, wherein the first chain comprises a first amino acid sequence of an insulin therapeutic peptide and the second chain comprises a second amino acid sequence of an insulin therapeutic peptide. In some embodiments, the immunoglobulin light chain fusion comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody. In some embodiments, the heavy chain comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody.

[00147] In some embodiments, the insulin immunoglobulin fusion proteins are configured to treat a metabolic disease such as obesity and/or diabetes, and/or a complication or condition thereof.

[00148] In another feature of the disclosure, provided herein are immunoglobulin fusion proteins comprising (a) an insulin immunoglobulin heavy chain fusion, and (b) a second immunoglobulin region derived from an immunoglobulin light chain. In some cases, the immunoglobulin heavy chain fusion is connected to the second immunoglobulin region by one or more disulfide bonds and/or a linker. The insulin immunoglobulin heavy chain fusion comprises an insulin therapeutic peptide comprising one or more regions connected to the amino or carboxyl terminus of a region of an immunoglobulin heavy chain. In some embodiments, the insulin therapeutic peptide comprises one or more regions of a therapeutic peptide. In some embodiments, the insulin therapeutic peptide comprises two regions of a therapeutic peptide connected by a connecting peptide. In some embodiments, the therapeutic peptide comprises a protease cleavage site. In some embodiments, the connecting peptide comprises a protease cleavage site. In some embodiments, the therapeutic peptide comprises a first chain and a second chain, wherein the first chain comprises a first amino acid sequence of an insulin therapeutic peptide and the second chain comprises a second amino acid sequence of an insulin therapeutic peptide. In some embodiments, the immunoglobulin heavy chain fusion comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody. In some embodiments, the light chain comprises an amino acid sequence comprising or derived from an amino acid sequence of an anti-ASGPR antibody.

[00149] In another feature of the disclosure, provided herein are immunoglobulin fusion proteins comprising (a) an insulin immunoglobulin light chain fusion, and (b) an insulin immunoglobulin heavy chain fusion.

[00150] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 78 and an amino acid sequence based on or derived from SEQ ID NO: 30. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 78 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 30. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 78 and an amino acid sequence that is 100% identical to SEQ ID NO: 30. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 57 and a nucleic acid sequence based on or derived from SEQ ID NO: 2. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 57 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 2. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 57 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 2.

[00151] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 79 and an amino acid sequence based on or derived from SEQ ID NO: 29. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about

60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 79 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 29. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 79 and an amino acid sequence that is 100% identical to SEQ ID NO: 29. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 58 and a nucleic acid sequence based on or derived from SEQ ID NO: 1. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 58 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 1. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 58 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 1.

[00152] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 80 and an amino acid sequence based on or derived from SEQ ID NO: 31. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 80 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 31. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 80 and an amino acid sequence that is 100% identical to SEQ ID NO: 31. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 59 and a nucleic acid sequence based on or derived from SEQ ID NO: 3. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 59 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 3. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 59 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 3.

[00153] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 81 and an amino acid sequence based on or derived from SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 81 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 81 and an amino acid sequence that is 100% identical to SEQ ID NO: 167. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 60 and a nucleic acid sequence based on or derived from SEQ ID NO: 166. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 60 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 166. The immunoglobulin fusion protein

may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 60 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 166.

[00154] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 82 and an amino acid sequence based on or derived from SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 82 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 82 and an amino acid sequence that is 100% identical to SEQ ID NO: 167. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 61 and a nucleic acid sequence based on or derived from SEQ ID NO: 166. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 61 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 166. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 61 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 166.

[00155] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 83 and an amino acid sequence based on or derived from SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 83 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 167. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 83 and an amino acid sequence that is 100% identical to SEQ ID NO: 167. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 62 and a nucleic acid sequence based on or derived from SEQ ID NO: 166. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 62 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 166. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 62 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 166.

[00156] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 84 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 84 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 84 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or

derived from SEQ ID NO: 63 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 63 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 63 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00157] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 85 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 85 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 85 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 64 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 64 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 64 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00158] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 86 and an amino acid sequence based on or derived from SEQ ID NO: 31. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 86 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 31. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 86 and an amino acid sequence that is 100% identical to SEQ ID NO: 31. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 65 and a nucleic acid sequence based on or derived from SEQ ID NO: 3. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 65 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 3. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 65 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 3.

[00159] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 87 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 87 and an amino acid sequence

that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 87 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 66 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 66 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 66 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00160] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 88 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 88 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 88 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 67 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 67 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 67 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00161] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 89 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 89 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 89 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 68 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 68 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 68 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00162] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 90 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 90 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 90 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 69 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 69 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 69 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00163] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 91 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 91 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 91 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 70 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 70 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 70 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00164] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 92 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 92 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 92 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 71 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%,

70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 71 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 71 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00165] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 95 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 95 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 95 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 74 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 74 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 74 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00166] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 96 and an amino acid sequence based on or derived from SEQ ID NO: 37 or 38. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 96 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 37 or 38. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 96 and an amino acid sequence that is 100% identical to SEQ ID NO: 37 or 38. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 75 and a nucleic acid sequence based on or derived from SEQ ID NO: 9 or 10. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 75 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 9 or 10. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 75 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 9 or 10.

[00167] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 97 and an amino acid sequence based on or derived from SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 97 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 34 or 36. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID

NO: 97 and an amino acid sequence that is 100% identical to SEQ ID NO: 34 or 36. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 76 and a nucleic acid sequence based on or derived from SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 76 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 6 or 8. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 76 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 6 or 8.

[00168] In some embodiments, the immunoglobulin fusion protein comprises an amino acid sequence based on or derived from SEQ ID NO: 98 and an amino acid sequence based on or derived from SEQ ID NO: 37 or 38. The immunoglobulin fusion protein may comprise an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 98 and an amino acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 37 or 38. The immunoglobulin fusion protein may comprise an amino acid sequence that is 100% identical to SEQ ID NO: 98 and an amino acid sequence that is 100% identical to SEQ ID NO: 37 or 38. In some embodiments, the immunoglobulin fusion protein is encoded by a nucleic acid sequence based on or derived from SEQ ID NO: 77 and a nucleic acid sequence based on or derived from SEQ ID NO: 9 or 10. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 77 and a nucleic acid sequence that is at least about 60%, 70%, 75%, 80%, 90%, 95%, or 97% identical to SEQ ID NO: 9 or 10. The immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO: 77 and a nucleic acid sequence that is 100% identical to SEQ ID NO: 9 or 10.

Immunoglobulin Region

[00169] The immunoglobulin fusion proteins disclosed herein comprise one or more immunoglobulin regions. For liver-targeted fusions, the immunoglobulin region comprises one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell. In some cases, the antigen is expressed by a hepatocyte. In some cases, the antigen is asialoglycoprotein receptor (ASGPR). The antigen binding domain may bind to one or more amino acids of an epitope of ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140, H142, and K173. The one or more amino acids of the epitope may comprise any combination of W134, E135, K138, V140, H142, and K173.

[00170] The immunoglobulin region of an insulin fusion protein may comprise: (a) a heavy chain variable region sequence comprising SEQ ID NO: 45; (b) a heavy chain variable region sequence comprising SEQ ID NO: 46; (c) a heavy chain variable region sequence comprising SEQ ID NO: 55; (d) a heavy chain variable region sequence comprising SEQ ID NO: 47; (e) a light chain variable region sequence comprising SEQ ID NO: 48; (f) a light chain variable region sequence comprising SEQ ID NO: 49; (g) a light chain variable region sequence comprising SEQ ID NO: 50; (h) a combination of (a), (b) and (d); (i) a combination of (a), (c) and (d); (j) a combination of (e), (f) and (g); (k) a combination of (h)

and (j); or (l) a combination of (i) and (j). Immunoglobulins specific for ASGPR which are useful in the insulin immunoglobulin fusion proteins described herein include those described in any of: US 2015/0299324, US 2013/0078216, WO 2011/086143, US 2016/0060354, and US 2016/0015821. Also envisioned for use in an insulin immunoglobulin fusion protein are anti-ASGPR immunoglobulins commercially available and immunoglobulins that compete with any anti-ASGPR described herein.

[00171] In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 45-47 and 55 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 45 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 46 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 55 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 47 by no more than 5, 4, 3, 2 or 1 amino acids.

[00172] In some cases, the immunoglobulin region comprises a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some cases, the immunoglobulin region comprises a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NO: 39 and SEQ: 43. In some cases, the immunoglobulin region comprises an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43. In some cases, the immunoglobulin region comprises an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.

[00173] In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from one or more of SEQ ID NOS: 48-50 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 48 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 49 by no more than 5, 4, 3, 2 or 1 amino acids. In some cases, the immunoglobulin region comprises a CDR having an amino acid sequence that differs from SEQ ID NO: 50 by no more than 5, 4, 3, 2 or 1 amino acids.

[00174] In some cases, the immunoglobulin region comprises a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some cases, the immunoglobulin region comprises a variable region having an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 41 and 44. In some cases, the immunoglobulin region comprises an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% identical to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44. In some cases, the immunoglobulin region

comprises an amino acid sequence at least about 75%, 80%, 85%, 90%, or 95% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.

[00175] The immunoglobulin region may comprise at least a portion of a variable domain. The immunoglobulin region may comprise one or more variable domains or portions thereof. The immunoglobulin region may comprise 2, 3, 4, 5 or more variable domains or portions thereof. The immunoglobulin region may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200 or more amino acids based on or derived from an amino acid sequence of one or more variable domains. The amino acids may be consecutive. The amino acids may be non-consecutive.

[00176] The immunoglobulin region may comprise at least a portion of a constant domain. The immunoglobulin region may comprise one or more constant domains or portions thereof. The immunoglobulin region may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more constant domains or portions thereof. The immunoglobulin region may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 225, 250, 275, 300, 350, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400 or more amino acids based on or derived from an amino acid sequence of one or more constant domains. The amino acids may be consecutive. The amino acids may be non-consecutive.

[00177] The immunoglobulin region may comprise at least a portion of a complementarity-determining region (CDR). The immunoglobulin region may comprise one or more complementarity-determining regions (CDRs) or portions thereof. The immunoglobulin region may comprise 2, 3, 4, 5 or more complementarity-determining regions (CDRs) or portions thereof. The immunoglobulin region may comprise 6, 7, 8 or more complementarity-determining regions (CDRs) or portions thereof. The immunoglobulin region may comprise four or more complementarity-determining regions (CDRs) or portions thereof. The immunoglobulin region may comprise 9, 10, 11 or more complementarity-determining regions (CDRs) or portions thereof. The one or more CDRs may be CDR1, CDR2, CDR3 or a combination thereof. The one or more CDRs may be CDR1. The one or more CDRs may be CDR2. The one or more CDRs may be CDR3. The CDR may be a heavy chain CDR. The one or more CDRs may be a light chain CDR.

[00178] The immunoglobulin region may comprise an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids based on or derived from an amino acid sequence of a CDR. The immunoglobulin region may comprise an amino acid sequence comprising 3 or more amino acids based on or derived from an amino acid sequence of a CDR. The immunoglobulin region may comprise an amino acid sequence comprising 5 or more amino acids based on or derived from an amino acid sequence of a CDR. The immunoglobulin region may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from an amino acid sequence of a CDR. The amino acids may be consecutive. The amino acids may be non-consecutive.

[00179] The immunoglobulin region may be based on or derived from at least a portion of an anti-T cell receptor immunoglobulin. The immunoglobulin region may be based on or derived from at least a portion of an anti-B cell receptor immunoglobulin.

[00180] The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds to at least a portion of a receptor on a cell. The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds to at least a portion of a co-receptor on a cell. The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds to at least a portion of an antigen or cell surface marker on a cell. The cell may be a hematopoietic cell. The hematopoietic cell may be a myeloid cell. The myeloid cell may be an erythrocyte, thrombocyte, neutrophil, monocyte, macrophage, eosinophil, basophil, or mast cell. The hematopoietic cell may be a lymphoid cell. The lymphoid cell may be a B-cell, T-cell, or NK-cell. The hematopoietic cell may be a leukocyte. The hematopoietic cell may be a lymphocyte.

[00181] The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds to at least a portion of a receptor on a hepatocyte cell. The receptor may be ASPGR.

[00182] The immunoglobulin region may be based on or derived from an anti-ASGPR immunoglobulin. The immunoglobulin region may comprise at least a portion of an anti-ASGPR immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-ASGPR immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-ASGPR immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-ASGPR immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-ASGPR immunoglobulin.

[00183] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-ASGPR immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-ASGPR immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-ASGPR immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-ASGPR immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-ASGPR immunoglobulin sequence.

[00184] The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds to at least a portion of a receptor on a lymphocyte, B-cell, macrophage, monocytes, neutrophils and/or NK cells. The receptor may be an Fc receptor. The Fc receptor may be an Fc-gamma receptor, Fc-alpha receptor and/or Fc-epsilon receptor. Fc-gamma receptors include, but are not limited to, FcγRI (CD64), FcγRIIA (CD32), FcγRIIB (CD32), FcγRIIIA (CD16a) and FcγRIIIB (CD16b). Fc-alpha receptors include, but are not limited to, FcαRI. Fc-epsilon

receptors include, but are not limited to, FcεRI and FcεRII. The receptor may be CD89 (Fc fragment of IgA receptor or FCAR).

[00185] The immunoglobulin region may be based on or derived from an immunoglobulin or immunoglobulin fragment that binds at least a portion of a co-receptor on a T-cell. The co-receptor may be a CD3, CD4, and/or CD8. The immunoglobulin region may be based on or derived from an immunoglobulin fragment that binds to a CD3 co-receptor. The CD3 co-receptor may comprise CD3-gamma, CD3-delta and/or CD3-epsilon. CD8 may comprise CD8-alpha and/or CD8-beta chains.

[00186] In some embodiments, the immunoglobulin region is not specific for a mammalian target. In some embodiments, the immunoglobulin is an anti-viral immunoglobulin. In some embodiments, the immunoglobulin is an anti-bacterial immunoglobulin. In some embodiments, the immunoglobulin is an anti-parasitic immunoglobulin. In some embodiments, the immunoglobulin is an anti-fungal immunoglobulin. In some embodiments, the immunoglobulin region is derived from an immunoglobulin vaccine.

[00187] In some embodiments, the immunoglobulin region is based on or derived from immunoglobulins including, but not limited to, actoxumab, bezlotoxumab, CR6261, edobacomab, efungumab, exbivirumab, felvizumab, foravirumab, ibalizumab (TMB-355, TNX-355), libivirumab, motavizumab, nebacumab, pagibaximab, palivizumab, panobacumab, rafivirumab, raxibacumab, regavirumab, sevirumab (MSL-109), suvizumab, tefibazumab, tuvirumab, and urtoxazumab.

[00188] In some embodiments, the immunoglobulin region is based on or derived from immunoglobulins targeting Clostridium difficile, Orthomyxoviruses (Influenzavirus A, Influenzavirus B, Influenzavirus C, Isavirus, Thogotovirus), Escherichia coli, Candida, Rabies, Human Immunodeficiency Virus, Hepatitis, Staphylococcus, Respiratory Syncytial Virus, Pseudomonas aeruginosa, Bacillus anthracis, Cytomegalovirus, or Staphylococcus aureus.

[00189] The immunoglobulin region may be based on or derived from an anti-viral immunoglobulin. The anti-viral immunoglobulin may be directed against an epitope of a viral protein. The anti-bacterial immunoglobulin may target one or more viruses including, but not limited to, Adenoviruses, Herpesviruses, Poxviruses, Parvoviruses, Reoviruses, Picornaviruses, Togaviruses, Orthomyxoviruses, Rhabdoviruses, Retroviruses and Hepadnaviruses. The viral protein may be from a respiratory syncytial virus. The viral protein may be an F protein of the respiratory syncytiral virus. The epitope may be in the A antigenic site of the F protein. The anti-viral immunoglobulin may be based on or derived from palivizumab. The immunoglobulin may be based on or derived from an anti-viral vaccine. The anti-viral immunoglobulin may be based on or derived from exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab.

[00190] The immunoglobulin region may be based on or derived from an anti-viral immunoglobulin G. The immunoglobulin region may comprise at least a portion of an anti-viral immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-viral immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more

homologous to at least a portion of an anti-viral immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-viral immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-viral immunoglobulin G. In some embodiments the immunoglobulin region comprises an amino acid sequence based on or derived from an anti-viral immunoglobulin M.

[00191] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-viral immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-viral immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-viral immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-viral immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-viral immunoglobulin G sequence.

[00192] The immunoglobulin region may be based on or derived from a palivizumab immunoglobulin. The immunoglobulin region may comprise at least a portion of a palivizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of a palivizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of a palivizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of a palivizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of a palivizumab immunoglobulin.

[00193] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of a palivizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of a palivizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of a palivizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of a palivizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of a palivizumab immunoglobulin sequence.

[00194] The immunoglobulin region may be based on or derived from an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin. The immunoglobulin region may comprise at least a portion of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin. The immunoglobulin region may

comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin.

[00195] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an exbivirumab, foravirumab, libivirumab, rafivirumab, regavirumab, sevirumab, tuvirumab, felvizumab, motavizumab, palivizumab, and/or suvizumab immunoglobulin sequence.

[00196] The immunoglobulin region may be based on or derived from an anti-bacterial immunoglobulin. The anti-bacterial immunoglobulin may be directed against an epitope of a bacterial protein. The anti-bacterial immunoglobulin may target bacteria including, but not limited to, *Acetobacter aurantius, Agrobacterium radiobacter, Anaplasma phagocytophilum, Azorhizobium caulinodans, Bacillus anthracis, Bacillus brevis, Bacillus cereus, Bacillus subtilis, Bacteroides fragilis, Bacteroides gingivalis, Bacteroides melaninogenicus, Bartonella quintana, Bordetella bronchiseptica, Bordetella pertussis, Borrelia burgdorferi, Brucella abortus, Brucella melitensis, Brucella suis, Burkholderia mallei, Burkholderia pseudomallei, Burkholderia cepacia, Calymmatobacterium granulomatis, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Campylobacter pylori, Chlamydia trachomatis,*

Chlamydophila pneumoniae, Chlamydophila psittaci, Clostridium botulinum, Clostridium difficile, Corynebacterium diphtheriae, Corynebacterium fusiforme, Coxiella burnetii, Enterobacter cloacae, Enterococcus faecalis, Enterococcus faecium, Enterococcus galllinarum, Enterococcus maloratus, Escherichia coli, Francisella tularensis, Fusobacterium nucleatum, Gardnerella vaginalis, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus pertussis, Haemophilus vaginalis, Helicobacter pylori, Klebsiella pneumoniae, Lactobacillus acidophilus, Lactococcus lactis, Legionella pneumophila, Listeria monocytogenes, Methanobacterium extroquens, Microbacterium multiforme, Micrococcus luteus, Moraxella catarrhalis, Mycobacterium phlei, Mycobacterium smegmatis, Mycobacterium tuberculosis, Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma pneumonie, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Pasteurella tularensis, Peptostreptococcus, Porphyromonas gingivalis, Prevotella melaninogenica, Pseudomonas aeruginosa, Rhizobium radiobacter, Rickettsia rickettsii, Rothia dentocariosa, Salmonella enteritidis, Salmonella typhi, Salmonella typhimurium, Shigella dysenteriae, Staphylococcus aureus, Staphylococcus epidermidis, Stenotrophomonas maltophilia, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Treponema denticola, Vibrio cholerae, Vibrio comma, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica and *Yersinia pseudotuberculosis*. The immunoglobulin may be based on or derived from a bacterial vaccine. The anti-viral immunoglobulin may be based on or derived from nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab.

[00197] The immunoglobulin region may be based on or derived from an anti-bacterial immunoglobulin G. The immunoglobulin region may comprise at least a portion of an anti-bacterial immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-bacterial immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-bacterial immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-bacterial immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-bacterial immunoglobulin G. In some embodiments the immunoglobulin region comprises an amino acid sequence based on or derived from an anti-viral immunoglobulin M.

[00198] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-bacterial immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-bacterial immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-bacterial immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-bacterial immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-bacterial immunoglobulin G sequence.

[00199] The immunoglobulin region may be based on or derived from a Nebacumab, Panobacumab, Raxibacumab, Edobacomab, Pagibaximab, and/or Tefibazumab immunoglobulin. The immunoglobulin region may comprise at least a portion of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin.

[00200] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of a nebacumab, panobacumab, raxibacumab, edobacomab, pagibaximab, and/or tefibazumab immunoglobulin sequence.

[00201] The immunoglobulin region may be based on or derived from an anti-parasitic immunoglobulin. The anti-parasitic immunoglobulin may be directed against an epitope of a parasite protein. The anti-parasitic immunoglobulin may target parasites or parasite proteins including, but not limited to parasites Acanthamoeba, Balamuthia mandrillaris, Babesia (B. divergens, B. bigemina, B. equi, B. microfti, B. duncani), Balantidium coli, Blastocystis, Cryptosporidium, Dientamoeba fragilis, Entamoeba histolytica, Giardia lamblia, Isospora belli, Leishmania, Naegleria fowleri, Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale curtisi, Plasmodium ovale wallikeri, Plasmodium malariae, Plasmodium knowlesi, Rhinosporidium seeberi, Sarcocystis bovihominis,Sarcocystis suihominis, Toxoplasma gondii, Trichomonas vaginalis, Trypanosoma brucei, Trypanosoma cruzi, Cestoda, Taenia multiceps, Diphyllobothrium latum, Echinococcus granulosus, Echinococcus multilocularis, Echinococcus vogeli, Echinococcus oligarthrus, Hymenolepis nana, Hymenolepis

diminuta, Taenia saginata, Taenia solium, Bertiella mucronata, Bertiella studeri, Spirometra erinaceieuropaei, Clonorchis sinensis; Clonorchis viverrini, Dicrocoelium dendriticum, Fasciola hepatica, Fasciola gigantica, Fasciolopsis buski, Gnathostoma spinigerum, Gnathostoma hispidum, Metagonimus yokogawai, Opisthorchis viverrini, Opisthorchis felineus, Clonorchis sinensis, Paragonimus westermani; Paragonimus africanus; Paragonimus caliensis; Paragonimus kellicotti; Paragonimus skrjabini; Paragonimus uterobilateralis, Schistosoma sp., Schistosoma mansoni, Schistosoma haematobium, Schistosoma japonicum, Schistosoma mekongi, Echinostoma echinatum, Trichobilharzia regenti, Schistosomatidae, Ancylostoma duodenale, Necator americanus, Angiostrongylus costaricensis, Anisakis, Ascaris sp. Ascaris lumbricoides, Baylisascaris procyonis, Brugia malayi, Brugia timori, Dioctophyme renale, Dracunculus medinensis, Enterobius vermicularis, Enterobius gregorii, Halicephalobus gingivalis, Loa filaria, Mansonella streptocerca, Onchocerca volvulus, Strongyloides stercoralis, Thelazia californiensis, Thelazia callipaeda, Toxocara canis, Toxocara cati, Trichinella spiralis, Trichinella britovi, Trichinella nelsoni, Trichinella nativa, Trichuris trichiura, Trichuris vulpis, Wuchereria bancrofti, Archiacanthocephala, Moniliformis moniliformis, Linguatula serrata, Oestroidea, Calliphoridae, Sarcophagidae, Tunga penetrans, Dermatobia hominis, Ixodidae, Argasidae, Cimex lectularius, Pediculus humanus, Pediculus humanus corporis, Pthirus pubis, Demodex folliculorum/brevis/canis, Sarcoptes scabiei, Cochliomyia hominivorax, and Pulex irritans.

[00202] The immunoglobulin region may be based on or derived from an anti-parasitic immunoglobulin G. The immunoglobulin region may comprise at least a portion of an anti-parasitic immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-parasitic immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-parasitic immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-parasitic immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-parasitic immunoglobulin G. In some embodiments the immunoglobulin region comprises an amino acid sequence based on or derived from an anti-parasitic immunoglobulin M.

[00203] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-parasitic immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-parasitic immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-parasitic immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-parasitic immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-parasitic immunoglobulin G sequence.

[00204] The immunoglobulin region may be based on or derived from an anti-fungal immunoglobulin. The anti-bacterial immunoglobulin may be directed against an epitope of a fungal protein. The anti-fungal immunoglobulin may target fungi or fungal proteins including, but not limited to *Cryptococcus neoformans, Cryptococcus gattii, Candida albicans, Candida tropicalis, Candida stellatoidea, Candida glabrata, Candida krusei, Candida parapsilosis, Candida guilliermondii, Candida viswanathii, Candida lusitaniae, Rhodotorula mucilaginosa, Schizosaccharomyces pombe, Saccharomyces cerevisiae, Brettanomyces bruxellensis, Candida stellata, Schizosaccharomyces pombe, Torulaspora delbrueckii, Zygosaccharomyces bailii, Yarrowia lipolytica, Saccharomyces exiguus* and *Pichia pastoris.* The anti-fungal immunoglobulin may be based on or derived from efungumab.

[00205] The immunoglobulin region may be based on or derived from an anti-fungal immunoglobulin G. The immunoglobulin region may comprise at least a portion of an anti-fungal immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-fungal immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-fungal immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-fungal immunoglobulin G. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-fungal immunoglobulin G. In some embodiments the immunoglobulin region comprises an amino acid sequence based on or derived from an anti-fungal immunoglobulin M.

[00206] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-fungal immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-fungal immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-fungal immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-fungal immunoglobulin G sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-fungal immunoglobulin G sequence.

[00207] The immunoglobulin region may be based on or derived from an efungumab immunoglobulin. The immunoglobulin region may comprise at least a portion of an efungumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an efungumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an efungumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an efungumab immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an efungumab immunoglobulin.

[00208] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an efungumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an efungumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an efungumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an efungumab immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an efungumab immunoglobulin sequence.

[00209] The immunoglobulin region may be based on or derived from a trastuzumab immunoglobulin G immunoglobulin. The immunoglobulin region may comprise at least a portion of a trastuzumab immunoglobulin G immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of a trastuzumab immunoglobulin G immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of a trastuzumab immunoglobulin G immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of a trastuzumab immunoglobulin G immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of a trastuzumab immunoglobulin G immunoglobulin.

[00210] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of a trastuzumab immunoglobulin G immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of a trastuzumab immunoglobulin G immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of a trastuzumab immunoglobulin G immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of a trastuzumab immunoglobulin G immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of a trastuzumab immunoglobulin G immunoglobulin sequence.

[00211] The immunoglobulin region may be based on or derived from an anti-Her2 immunoglobulin. The immunoglobulin region may comprise at least a portion of an anti-Her2 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-Her2 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-Her2 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-

Her2 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-Her2 immunoglobulin.

[00212] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-Her2 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-Her2 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-Her2 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-Her2 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-Her2 immunoglobulin sequence.

[00213] The immunoglobulin region may be based on or derived from an anti-CD47 immunoglobulin. The immunoglobulin region may comprise at least a portion of an anti-CD47 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to at least a portion of an anti-CD47 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, or 97% or more homologous to at least a portion of an anti-CD47 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to at least a portion of an anti-CD47 immunoglobulin. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to at least a portion of an anti-CD47 immunoglobulin.

[00214] The immunoglobulin region may comprise an amino acid sequence that comprises 10, 20, 30, 40, 50, 60, 70, 80, 90 or more amino acids of an anti-CD47 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100, 200, 300, 400, 500, 600, 700, 800, 900 or more amino acids of an anti-CD47 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 50 or more amino acids of an anti-CD47 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 100 or more amino acids of an anti-CD47 immunoglobulin sequence. The immunoglobulin region may comprise an amino acid sequence that comprises 200 or more amino acids of an anti-CD47 immunoglobulin sequence.

[00215] The immunoglobulin region may be based on or derived from an anti-cancer immunoglobulin. Examples of anti-cancer immunoglobulin include, but are not limited to, abciximab, adalimumab, alemtuzumab, basiliximab, belimumab, bevacizumab, brentuximab, canakinumab, certolizumab, cetuximab, daclizumab, denosumab, eculizumab, efalizumab, gemtuzumab, golimumab, ibritumomab, infliximab, ipilimumab, muromonab-cd3, natalizumab, ofatumumab, omalizumab, palivizumab, panitumumab, ranibizumab, rituximab, tocilizumab, tositumomab, trastuzumab.

[00216] The immunoglobulin region may comprise at least a portion of a human immunoglobulin. The immunoglobulin region may comprise at least a portion of a humanized immunoglobulin. The immunoglobulin region may comprise at least a portion of a chimeric immunoglobulin. The

immunoglobulin region may be based on or derived from a human immunoglobulin. The immunoglobulin region may be based on or derived from a humanized immunoglobulin. The immunoglobulin region may be based on or derived from a chimeric immunoglobulin. The immunoglobulin region may be based on or derived from a monoclonal immunoglobulin. The immunoglobulin region may be based on or derived from a polyclonal immunoglobulin. The immunoglobulin region may comprise at least a portion of an immunoglobulin from a mammal, avian, reptile, amphibian, or a combination thereof. The mammal may be a human. The mammal may be a non-human primate. The mammal may be a dog, cat, sheep, goat, cow, rabbit, or mouse.

[00217] The immunoglobulin region may comprise a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragment sequences. The immunoglobulin region may comprise a sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or more homologous to a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments. The immunoglobulin region may comprise a sequence that is at least about 70% homologous to a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments. The immunoglobulin region may comprise a sequence that is at least about 80% homologous to a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments. The immunoglobulin region may comprise a sequence that is at least about 90% homologous to a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments. The immunoglobulin region may comprise a sequence that is at least about 95% homologous to a sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments. The sequence may be a peptide sequence. The sequence may be a nucleic acid sequence.

[00218] The immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 17, 15, 12, 10, 8, 6, 5, 4 or fewer amino acids. The immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 4 or fewer amino acids. The immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 3 or fewer amino acids. The immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 2 or fewer amino acids. The immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 1 or fewer amino acids. The amino acids may be consecutive, nonconsecutive, or a combination thereof. For example, the immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 3 consecutive amino acids.

Alternatively, or additionally, the immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 2 non-consecutive amino acids. In another example, the immunoglobulin region may comprise a peptide sequence that differs from a peptide sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 5 amino acids, wherein 2 of the amino acids are consecutive and 2 of the amino acids are non-consecutive.

[00219] The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more antibodies and/or immunoglobulin fragments by less than or equal to about 500, 400, 300, 200, 100, 90, 80, 70, 60, 50, 40, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 15 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 12 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 9 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 6 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 4 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 3 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 2 or fewer nucleotides or base pairs. The immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than or equal to about 1 or fewer nucleotides or base pairs. The nucleotides or base pairs may be consecutive, nonconsecutive, or a combination thereof. For example, the immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 3 consecutive nucleotides or base pairs. Alternatively, or additionally, the immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 2 non-consecutive nucleotides or base pairs. In another example, the immunoglobulin region may comprise a nucleic acid sequence that differs from a nucleic

acid sequence based on or derived from one or more immunoglobulin and/or immunoglobulin fragments by less than about 5 nucleotides or base pairs, wherein 2 of the nucleotides or base pairs are consecutive and 2 of the nucleotides or base pairs are non-consecutive.

[00220] The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by one or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by two or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by three or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by four or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by five or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by six or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 15, 17, 20, 25 or more amino acid substitutions. The peptide sequence of the immunoglobulin region may differ from the peptide sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by about 20-30, 30-40, 40-50, 50-60, 60-70, 80-90, 90-100, 100-150, 150-200, 200-300 or more amino acid substitutions.

[00221] The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by one or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by two or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by three or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by four or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by five or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by six or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or

immunoglobulin fragment that it is based on and/or derived from by nine or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by twelve or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by fifteen or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by eighteen or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by 20, 22, 24, 25, 27, 30 or more nucleotide and/or base pair substitutions. The nucleic acid sequence of the immunoglobulin region may differ from the nucleic acid sequence of the immunoglobulin or immunoglobulin fragment that it is based on and/or derived from by about 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-200, 200-300, 300-400 or more nucleotide and/or base pair substitutions.

[00222] The immunoglobulin region may comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more amino acids. The immunoglobulin region may comprise at least about 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700 or more amino acids. The immunoglobulin region may comprise at least about 100 amino acids. The immunoglobulin region may comprise at least about 200 amino acids. The immunoglobulin region may comprise at least about 400 amino acids. The immunoglobulin region may comprise at least about 500 amino acids. The immunoglobulin region may comprise at least about 600 amino acids.

[00223] The immunoglobulin region may comprise less than about 2000, 1900, 1800, 1700, 1600, 1500, 1400, 1300, 1200 or 1100 amino acids. The immunoglobulin region may comprise less than about 1000, 950, 900, 850, 800, 750, or 700 amino acids. The immunoglobulin region may comprise less than about 1500 amino acids. The immunoglobulin region may comprise less than about 1000 amino acids. The immunoglobulin region may comprise less than about 800 amino acids. The immunoglobulin region may comprise less than about 700 amino acids.

[00224] The immunoglobulin fusion protein may further comprise an immunoglobulin region comprising 30 or fewer consecutive amino acids of a complementarity determining region 3 (CDR3). The immunoglobulin region may comprise 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 15 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 14 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 13 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 12 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 11 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 10 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 9 or fewer consecutive amino acids of a CDR3.

The immunoglobulin region may comprise 8 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 7 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 6 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 5 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 4 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 3 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 2 or fewer consecutive amino acids of a CDR3. The immunoglobulin region may comprise 1 or fewer consecutive amino acids of a CDR3. In some instances, the immunoglobulin region does not contain a CDR3.

[00225] The immunoglobulin region may comprise an amino acid sequence that is based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOs 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOs 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence that is 100% identical to any one of SEQ ID NOS: 29-56, 155, 156, 167. In some embodiments, the immunoglobulin region comprises an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to an amino acid sequence of any one of SEQ ID NOS: 29-56, 155, 156, 167. In some embodiments, the immunoglobulin region comprises an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to an amino acid sequence of any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region includes a Fab region that is based on or derived from a sequence from any one of SEQ ID NOS: 29-56, 155, 156, 167. In some embodiments, the immunoglobulin region comprises an amino acid Fab sequence derived from a sequence that is at least about 70%, 80%, 80%, 90%, 95% or 100% to any one of SEQ ID NOS: 29-56, 155, 156, 167.

[00226] The immunoglobulin region may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence comprising 125, 150, 175, 200 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167.

The immunoglobulin region may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence comprising 50 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence comprising 100 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The immunoglobulin region may comprise an amino acid sequence comprising 200 or more amino acids based on or derived from any one of SEQ ID NOS: 29-56, 155, 156, 167. The amino acids may be consecutive. Alternatively, or additionally, the amino acids are nonconsecutive. In some embodiments, the immunoglobulin region comprises amino acids derived from 1, 2, 3, or 4 of SEQ ID NOS: 29-56, 155, 156, 167.

[00227] The immunoglobulin region may be encoded by a nucleic acid sequence that is based on or derived from any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 70% identical to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence that is 100% identical to any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region includes a Fab region that is based on or derived from a sequence from any one of SEQ ID NOS: 1-28, 166. In some embodiments, the immunoglobulin region comprises an amino acid Fab sequence derived from a sequence that is at least about 70%, 80%, 80%, 90%, 95% or 100% to any one of SEQ ID NOS: 1-28, 166.

[00228] The immunoglobulin region may be encoded by a nucleic acid sequence comprising 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence comprising 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 450, 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence comprising 100 or more nucleotides based on or derived from any one of SEQ ID NOS: 1-28, 166. The immunoglobulin region may be encoded by a nucleic acid sequence comprising 500 or more nucleotides based on or derived from any one of SEQ ID NOS: 1-28, 166. The nucleotides may

be consecutive. In some embodiments, the immunoglobulin region is encoded by a nucleic acid sequence derived from 1, 2, 3, or 4 of SEQ ID NOS: 1-28, 166.

Therapeutic peptide

[00229] In one aspect of the disclosure, provided herein are immunoglobulin fusion proteins comprising an insulin therapeutic peptide and an immunoglobulin region. The immunoglobulin fusion proteins may comprise two or more therapeutic peptides. The immunoglobulin fusion proteins disclosed herein may comprise 3, 4, 5, or more therapeutic peptides. The therapeutic peptide may be attached to an immunoglobulin region via a linker. In some embodiments, one or more additional therapeutic peptides are attached to the first or a second immunoglobulin region. The one or more therapeutic peptides may be attached to one or more immunoglobulin regions. The two or more therapeutic peptides may be attached to two or more immunoglobulin regions. The two or more therapeutic peptides may be attached to one or more immunoglobulin chains. The two or more therapeutic peptides may be attached to two or more immunoglobulin chains. The two or more therapeutic peptides may be attached to one or more units within the one or more immunoglobulin regions. The two or therapeutic peptides may be attached to two or more units within the one or more immunoglobulin regions. In some embodiments, the therapeutic peptide is connected to the immunoglobulin region without the aid of a linker.

[00230] In one embodiment, the linker comprises from about 0 to about 50 amino acids. In one embodiment, the linker comprises from about 1 to about 50 amino acids. In one embodiment, the linker comprises from about 1 to about 20 amino acids, or about 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acids. In one embodiment, the amino acids of the linker do not form a regular secondary structure. In one embodiment, the linker comprises an amino acid sequence that is about or at least about 50%, 60%, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence of any one of SEQ ID NOS: 63-69. In one embodiment, the linker comprises 1, 2, 3, 4 or more glycine residues.

[00231] The immunoglobulin fusion proteins disclosed herein may comprise one or more therapeutic agents. The therapeutic agent may be a peptide. The therapeutic agent may be a small molecule. The immunoglobulin fusion proteins disclosed herein may comprise two or more therapeutic agents. The immunoglobulin fusion proteins disclosed herein may comprise 3, 4, 5, 6 or more therapeutic agents. The two or more therapeutic agents may be the same. The two or more therapeutic agents may be different.

[00232] The therapeutic peptide may comprise any secondary structure, for example alpha helix or beta strand or comprise no regular secondary structure. The therapeutic peptide may comprise amino acids with one or more modifications including, but not limited to, myristoylation, palmitoylation, isoprenylation, glypiation, lipoylation, acylation, acetylation, aklylation, methylation, glycosylation, malonylation, hydroxylation, iodination, nucleotide addition, oxidation, phosphorylation, adenylylation, propionylation, succinylation, sulfation, selenoylation, biotinylation, pegylation, deimination, deamidation, eliminylation, and carbamylation. The therapeutic peptide may comprise one or more amino acids conjugated to one or more small molecules, for example a drug. In some embodiments, the therapeutic peptide comprises one or more non-natural amino acids. In some embodiments, the

therapeutic peptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or more non-natural amino acids. In some embodiments, the therapeutic peptide comprises one or more amino acids substitutions. In some embodiments, the therapeutic peptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or more amino acid substitutions.

[00233] The therapeutic peptide may be inserted into the immunoglobulin region. Insertion of the therapeutic peptide into the immunoglobulin region may comprise removal or deletion of a portion of the immunoglobulin from which the immunoglobulin region is based on or derived from. The therapeutic peptide may replace at least a portion of a heavy chain. The therapeutic peptide may replace at least a portion of a light chain. The therapeutic peptide may replace at least a portion of a variable domain. The therapeutic peptide may replace at least a portion of a constant domain. The therapeutic peptide may replace at least a portion of a complementarity determining region (CDR). The therapeutic peptide may replace at least a portion of a CDR1. The therapeutic peptide may replace at least a portion of a CDR2. The therapeutic peptide may replace at least a portion of a CDR3. The therapeutic peptide may replace at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more of the immunoglobulin or a portion thereof. For example, the therapeutic peptide may replace at least about 50% of a variable domain. The therapeutic peptide may replace at least about 70% of a variable domain. The therapeutic peptide may replace at least about 80% of a variable domain. The therapeutic peptide may replace at least about 90% of a variable domain. The therapeutic peptide may replace at least about 95% of a variable domain. For example, the therapeutic peptide may replace at least about 50% of an amino terminus of an immunoglobulin region. The therapeutic peptide may replace at least about 70% of an amino terminus of an immunoglobulin region. The therapeutic peptide may replace at least about 80% of an amino terminus of an immunoglobulin region. The therapeutic peptide may replace at least about 90% of an amino terminus of an immunoglobulin region. The therapeutic peptide may replace at least about 95% of an amino terminus of an immunoglobulin region. The therapeutic peptide may replace at least about 50% of a CDR. The therapeutic peptide may replace at least about 70% of a CDR. The therapeutic peptide may replace at least about 80% of a CDR. The therapeutic peptide may replace at least about 90% of a CDR. The therapeutic peptide may replace at least about 95% of a CDR.

[00234] In some embodiments, one or more regions of the insulin therapeutic peptide is configured to treat diabetes and/or diabetes related conditions. In some embodiments, 2, 3, 4, 5 or more regions of the therapeutic peptide are configured to treat diabetes and/or diabetes related conditions. Diabetes may include, type I diabetes, type 2 diabetes, gestational diabetes, and prediabetes. In some embodiments, one or more regions of the therapeutic peptide is configured to treat obesity and/or obesity related conditions. In some embodiments, 2, 3, 4, 5 or more regions of the therapeutic peptide are configured to treat obesity and/or obesity related conditions. Conditions may include complications and diseases. Examples of diabetes related conditions include, but are not limited to, diabetic retinopathy, diabetic nephropathy, diabetic heart disease, diabetic foot disorders, diabetic neuropathy, macrovascular disease, diabetic cardiomyopathy, infection and diabetic ketoacidosis. Diabetic neuropathy may include, but is not limited

to symmetric polyneuropathy, autonomic neuropathy, radiculopathy, cranial neuropathy, and mononeuropathy. Obesity related conditions include, but are not limited to, heart disease, stroke, high blood pressure, diabetes, osteoarthritis, gout, sleep apnea, asthma, gallbladder disease, gallstones, abnormal blood fats (e.g., abnormal levels of LDL and HDL cholesterol), obesity hypoventilation syndrome, reproductive problems, hepatic steatosis, and mental health conditions.

[00235] Insulin immunoglobulin fusion proteins described herein comprise an insulin therapeutic peptide. In some cases, the insulin therapeutic peptide comprises a single amino acid chain having the formula: B-C-A or A-C-B; wherein B comprises SEQ ID NO: 157 (FVNQHLCGSX_ALVEALYLVCGERGFFYT$X_B$$X_C$T); A comprises SEQ ID NO 158: GIVEQCCX_DSICSLYQLENYCN; and C comprises a connecting peptide having between 3 and 50 amino acids; and wherein X_A, X_B, X_C and X_D are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_A is D or H. In some cases, X_A is D. In some cases, X_A is H. In some cases, X_B is D or P. In some cases, X_B is D. In some cases, X_B is P. In some cases, X_C is P or K. In some cases, X_C is P. In some cases, X_C is K. In some cases, X_D is H or T. In some cases, X_D is H. In some cases, X_D is T. The connecting peptide may comprise an amino acid sequence comprising at least 50% glycine amino acids. The connecting peptide may comprise SEQ ID NO: 159 (GGGX_1X_2), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_1 is P, G or S. In some cases, X_1 is P. In some cases, X_1 is G. In some cases, X_1 is S. In some cases, X_2 is R, S, G or K. In some cases, X_2 is R. In some cases, X_2 is S. In some cases, X_2 is G. In some cases, X_2 is K. C may comprise a protease cleavage site. As a non-limiting example, RKKR. The insulin therapeutic peptide may comprise an amino acid sequence selected from SEQ ID NOS: 111, 113, 116, 118, 119-140. The insulin therapeutic peptide may comprise an amino acid sequence at least 90% identical to any one of SEQ ID NOS: 111, 113, 116, 118, 119-140.

[00236] The insulin therapeutic peptide may comprise a single amino acid chain having the formula B-C-A or A-C-B; wherein B comprises an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT); A comprises an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC); and C comprises a connecting peptide having between 3 and 50 amino acids. In some cases, B comprises SEQ ID NO: 160. In some cases, A comprises SEQ ID NO: 161. In some cases, the connecting peptide comprises an amino acid sequence having at least 50% glycine amino acids. In some cases, the connecting peptide comprises SEQ ID NO: 159 (GGGX_1X_2), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_1 is P, G or S. In some cases, X_1 is P. In some cases, X_1 is G. In some cases, X_1 is S. In some cases, X_2 is R, S, G or K. In some cases, X_2 is R. In some cases, X_2 is S. In some cases, X_2 is G. In some cases, X_2 is K. C may comprise a protease cleavage site. As a non-limiting example, RKKR.

[00237] The insulin therapeutic peptide may comprise an A peptide comprising SEQ ID NO: 158 (GIVEQCCX_DSICSLYQLENYCN), wherein X_D is a naturally or non-naturally occurring amino acid. In some cases, X_D is selected from H and T. In some cases, X_D is H. In some cases, X_D is T. In some cases,

one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide. In some cases, the B peptide comprises SEQ ID NO: 157 (FVNQHLCGSX_ALVEALYLVCGERGFFYT$X_B$$X_C$T); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_A is D or H. In some cases, X_A is D. In some cases, X_A is H. In some cases, X_B is D or P. In some cases, X_B is D. In some cases, X_B is P. In some cases, X_C is P or K. In some cases, X_C is P. In some cases, X_C is K. In some cases, the B peptide comprises an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some cases, B comprises SEQ ID NO: 160. In some cases, the insulin therapeutic peptide comprises an A peptide comprising an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC). In some cases, the A peptide comprises SEQ ID NO: 161. In some cases, one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide.

[00238] The insulin therapeutic peptide may comprise an A peptide comprising an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC). In some cases, the A peptide comprises SEQ ID NO: 161. In some cases, one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide. In some cases, the B peptide comprises SEQ ID NO: 157 (FVNQHLCGSX_ALVEALYLVCGERGFFYT$X_B$$X_C$T); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_A is D or H. In some cases, X_A is D. In some cases, X_A is H. In some cases, X_B is D or P. In some cases, X_B is D. In some cases, X_B is P. In some cases, X_C is P or K. In some cases, X_C is P. In some cases, X_C is K. In some cases, the B peptide comprises an amino acid sequence having no more than 5, 4, 3, 2 or 1 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT). In some cases the insulin immunoglobulin fusion protein of claim 93, wherein B comprises SEQ ID NO: 160.

[00239] In some embodiments, amino acids of the therapeutic peptide, in whole or in part, are based on or derived from any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 50% homologous to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 70% homologous to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 80% homologous to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 50% identical to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 70% identical to any one of SEQ ID

NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is at least about 80% identical to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence that is 100% identical to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. In some embodiments, the therapeutic peptide comprises an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% homologous to an amino acid sequence of any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. In some embodiments, the therapeutic peptide comprises an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% identical to an amino acid sequence of any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. In some embodiments, the therapeutic peptide comprises an amino acid sequence that is 100% identical to an amino acid sequence of any one of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[00240] The therapeutic peptide may comprise an amino acid sequence comprising 10, 20, 30, 40, 50, 60 or more amino acids based on or derived from any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence comprising 10 or more amino acids based on or derived from any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The therapeutic peptide may comprise an amino acid sequence comprising 50 or more amino acids based on or derived from any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The amino acids may be consecutive. Alternatively, or additionally, the amino acids are nonconsecutive. For example, one or more amino acid sequences are connected by a connecting peptide and/or a disulfide bond. In some embodiments, the therapeutic peptide comprises amino acids derived from 1, 2, 3, or 4 of SEQ ID NOS: 109-140, 157, 158, 160, 161.

[00241] The therapeutic peptide may comprise a protease cleavage site. The protease cleavage site may be inserted within the therapeutic peptide. In some embodiments, the therapeutic peptide comprises a first therapeutic peptide region and a second therapeutic peptide region. In some embodiments, the therapeutic peptide comprises a protease cleavage site disposed between the first therapeutic peptide region and the second therapeutic peptide region. In some embodiments, the first therapeutic peptide region and the second therapeutic peptide region are derived from the same protein or set of amino acid sequences. In some embodiments, the first therapeutic peptide region and the second therapeutic peptide regions are derived from different proteins or sets of amino acid sequences. The one or more protease cleavage sites may be attached to the N-terminus, C-terminus or both the N- and C-termini of a region of a therapeutic peptide.

[00242] The therapeutic peptide may comprise one or more connecting peptides. The therapeutic peptide may comprise two or more connecting peptides. The therapeutic peptide may comprise 3, 4, 5, 6, 7 or more connecting peptides. The connecting peptides may be different. The connecting peptides may be the same. The one or more connecting peptides may be attached to the N-terminus, C-terminus or both the N- and C-termini of a region of a therapeutic peptide. The connecting peptide may be inserted within the therapeutic peptide. In some embodiments, the therapeutic peptide comprises a first therapeutic peptide region and a second therapeutic peptide region. In some embodiments, the therapeutic peptide comprises a connecting peptide disposed between the first therapeutic peptide region and the second

therapeutic peptide region. In some embodiments, the first therapeutic peptide region and the second therapeutic peptide region are derived from the same protein or set of amino acid sequences. In some embodiments, the first therapeutic peptide region and the second therapeutic peptide regions are derived from different proteins or sets of amino acid sequences. In some embodiments, the connecting peptide is derived from and/or comprises an amino acid sequence of any of SEQ ID NOS: 148-154. In some embodiments, the connecting peptide comprises amino acids having repeating sequences. In some embodiments, the connecting peptide has 2, 3, 4, 5, 6, 7, 8, 9, 10 or more repeating sequences. In some embodiments, the connecting peptide is low immunogenic. In some embodiments, the connecting peptide is biodegradable. In some cases, the connecting peptide comprises at least 3, 4, 5 or more glycine residues. In some cases, the at least 3, 4, 5 or more glycine residues are repeated in the connecting peptide sequence. In some embodiments, the connecting peptide comprises GGGS.

[00243] In some embodiments, an insulin therapeutic peptide comprises a connecting peptide comprising an amino acid sequence comprising at least 50% glycine amino acids. In some cases, the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid. In some cases, X_1 is P, G or S. In some cases, X_1 is P. In some cases, X_1 is G. In some cases, X_1 is S. In some cases, X_2 is R, S, G or K. In some cases, X_2 is R. In some cases, X_2 is S. In some cases, X_2 is G. In some cases, X_2 is K. In some cases, the connecting peptide comprises a protease cleavage site. As a non-limiting example, a RKKR cleavage site.

Proteolytic Cleavage Site

[00244] The immunoglobulin fusion proteins disclosed herein may further comprise one or more proteolytic cleavage sites. The immunoglobulin fusion proteins disclosed herein may further comprise 2 or more proteolytic cleavage sites. The immunoglobulin fusion proteins disclosed herein may further comprise 3 or more proteolytic cleavage sites. The immunoglobulin fusion proteins disclosed herein may further comprise 4, 5, 6, 7 or more proteolytic cleavage sites. The therapeutic peptides disclosed herein may further comprise one or more proteolytic cleavage sites.

[00245] The one or more proteolytic cleavage sites may be attached to the N-terminus, C-terminus or both N- and C-termini of a therapeutic peptide. The one or more proteolytic cleavage sites may attached to the N-terminus, C-terminus or both N- and C-termini of the extender peptide. The one or more proteolytic cleavage sites may attached to the N-terminus, C-terminus or both N- and C-termini of a linker. The one or more proteolytic cleavage sites may attached to the N-terminus, C-terminus or both N- and C-termini of a connecting peptide. The one or more proteolytic cleavage sites may attached to the N-terminus, C-terminus or both N- and C-termini of a linker. The one or more proteolytic cleavage sites may be attached to a therapeutic peptide, connecting peptide, linker, immunoglobulin region, or a combination thereof.

[00246] In some embodiments, the proteolytic cleavage site is located within the amino acid sequence of the therapeutic peptide, connecting peptide, linker, immunoglobulin region, or a combination thereof. The therapeutic peptide may comprise one or more proteolytic cleavage sites within its amino acid sequence.

[00247] Two or more proteolytic cleavage sites may surround a therapeutic peptide, connecting peptide, linker, immunoglobulin region, or combination thereof. Digestion of the proteolytic cleavage site may result in release of a peptide fragment located between the two or more proteolytic cleavage sites. For example, the proteolytic cleavage sites may flank a therapeutic peptide-linker peptide. Digestion of the proteolytic cleavage sites may result in release of the therapeutic peptide-linker.

[00248] The proteolytic cleavage site may be recognized by one or more proteases. The one or more proteases may be a serine protease, threonine protease, cysteine protease, aspartate protease, glutamic protease, metalloprotease, exopeptidases, endopeptidases, or a combination thereof. The proteases may be selected from the group comprising Factor VII or Factor Xa. Additional examples of proteases include, but are not limited to, aminopeptidases, carboxypeptidases, trypsin, chymotrypsin, pepsin, papain, and elastase. The protease may be a proprotein convertase (PC). In some cases, the protease is PC2. In some embodiments, the protease recognizes the amino acid sequence KR. In some embodiments, the protease recognizes the amino acid sequence RKKR.

[00249] In some embodiments, a genetic construct encoding an immunoglobulin fusion protein comprises a nucleic acid sequence encoding a protease cleavage site. In some cases, the protease cleavage site is cleaved after expression *in vivo*, wherein an endogenous protease and/or a protease co-expressed with the fusion protein cleaves the fusion protein at the cleavage site. In some cases, the protease cleavage site is RKKR and a protease co-expressed with the fusion protein cleaves at the carboxyl terminus of the site. In some cases, the protease cleavage site is RKKR and an endogenous protease cleaves at the amino terminus of the site.

Vectors, Host Cells and Recombinant Methods

[00250] Immunoglobulin fusion proteins, as disclosed herein, may be expressed and purified by known recombinant and protein purification methods. In some instances, the activity of the immunoglobulin fusion protein is affected by expression and/or purification methods. For example, the activity of an immunoglobulin fusion protein configured for use as a therapeutic, is enhanced or attenuated based on the identity of the expression vector, identity of the recombinant host, identity of the cell line, expression reaction conditions, purification methods, protein processing, or any combination thereof. Expression reaction conditions include, but are not limited to, temperature, % CO_2, media, expression time, cofactors, and chaperones. Purification methods include, but are not limited to, purification temperatures, chromatography resins, protease inhibitors, and buffer compositions.

[00251] Immunoglobulin fusion proteins, as disclosed herein, may be expressed by recombinant methods. Generally, a nucleic acid encoding an immunoglobulin fusion protein may be isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the immunoglobulin fusion protein may be prepared by PCR amplification and sequenced using conventional procedures (*e.g.,* by using oligonucleotide probes that are capable of binding specifically to nucleotides encoding Immunoglobulin fusion proteins). In an exemplary embodiment, nucleic acid encoding an immunoglobulin fusion protein is PCR amplified, restriction enzyme digested and gel purified. The digested nucleic acid may be inserted into a replicable vector. The replicable vector

containing the digested immunoglobulin fusion protein insertion may be transformed or transduced into a host cell for further cloning (amplification of the DNA) or for expression. Host cells may be prokaryotic or eukaryotic cells.

[00252] Polynucleic acid sequences encoding polypeptide components (e.g., immunoglobulin region, extender peptide, therapeutic peptide) of the immunoglobulin fusion proteins may be obtained by PCR amplification. Polynucleic acid sequences may be isolated and sequenced from cells containing nucleic acids encoding the polypeptide components. Alternatively, or additionally, polynucleotides may be synthesized using nucleotide synthesizer or PCR techniques. Once obtained, sequences encoding the polypeptide components may be inserted into a recombinant vector capable of replicating and expressing heterologous polynucleotides in prokaryotic and/or eukaryotic hosts.

[00253] In addition, phage vectors containing replicon and control sequences that are compatible with the host microorganism may be used as transforming vectors in connection with these hosts. For example, bacteriophage such as λGEM™-11 may be utilized in making a recombinant vector which may be used to transform susceptible host cells such as *E. coli* LE392.

[00254] Immunoglobulin fusion proteins may be expressed intracellularly (e.g., cytoplasm) or extracellularly (e.g., secretion). For extracellular expression, the vector may comprise a secretion signal which enables translocation of the immunoglobulin fusion proteins to the outside of the cell.

[00255] Suitable host cells for cloning or expression of immunoglobulin fusion proteins-encoding vectors include prokaryotic or eukaryotic cells. The host cell may be a eukaryotic. Examples of eukaryotic cells include, but are not limited to, Human Embryonic Kidney (HEK) cell, Chinese Hamster Ovary (CHO) cell, fungi, yeasts, invertebrate cells (e.g., plant cells and insect cells), lymphoid cell (*e.g.*, YO, NSO, Sp20 cell). Other examples of suitable mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); baby hamster kidney cells (BHK); mouse sertoli cells; monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TR1 cells; MRC 5 cells; and FS4 cells. The host cell may be a prokaryotic cell (e.g., *E. coli*).

[00256] Host cells may be transformed with vectors containing nucleotides encoding an immunoglobulin fusion proteins. Transformed host cells may be cultured in media. The media may be supplemented with one or more agents for inducing promoters, selecting transformants, or amplifying or expressing the genes encoding the desired sequences. Methods for transforming host cells are known in the art and may include electroporation, calcium chloride, or polyethylene glycol/DMSO.

[00257] Alternatively, host cells may be transfected or transduced with vectors containing nucleotides encoding an immunoglobulin fusion proteins. Transfected or transduced host cells may be cultured in media. The media may be supplemented with one or more agents for inducing promoters, selecting transfected or transduced cells, or expressing genes encoding the desired sequences.

[00258] The expressed immunoglobulin fusion proteins may be secreted into and recovered from the periplasm of the host cells or transported into the culture media. Protein recovery from the periplasm may

involve disrupting the host cell. Disruption of the host cell may comprise osmotic shock, sonication or lysis. Centrifugation or filtration may be used to remove cell debris or whole cells. The immunoglobulin fusion proteins may be further purified, for example, by affinity resin chromatography.

[00259] Alternatively, immunoglobulin fusion proteins that are secreted into the culture media may be isolated therein. Cells may be removed from the culture and the culture supernatant being filtered and concentrated for further purification of the proteins produced. The expressed polypeptides may be further isolated and identified using commonly known methods such as polyacrylamide gel electrophoresis (PAGE) and Western blot assay.

[00260] Immunoglobulin fusion proteins production may be conducted in large quantity by a fermentation process. Various large-scale fed-batch fermentation procedures are available for production of recombinant proteins. Large-scale fermentations have at least 1000 liters of capacity, preferably about 1,000 to 100,000 liters of capacity. These fermentors use agitator impellers to distribute oxygen and nutrients, especially glucose (a preferred carbon/energy source). Small scale fermentation refers generally to fermentation in a fermentor that is no more than approximately 100 liters in volumetric capacity, and can range from about 1 liter to about 100 liters.

[00261] In a fermentation process, induction of protein expression is typically initiated after the cells have been grown under suitable conditions to a desired density, *e.g.*, an OD550 of about 180-220, at which stage the cells are in the early stationary phase. A variety of inducers may be used, according to the vector construct employed, as is known in the art and described herein. Cells may be grown for shorter periods prior to induction. Cells are usually induced for about 12-50 hours, although longer or shorter induction time may be used.

[00262] To improve the production yield and quality of the immunoglobulin fusion proteins disclosed herein, various fermentation conditions may be modified. For example, to improve the proper assembly and folding of the secreted immunoglobulin fusion proteins polypeptides, additional vectors overexpressing chaperone proteins, such as Dsb proteins (DsbA, DsbB, DsbC, DsbD and or DsbG) or FkpA (a peptidylprolyl cis,trans-isomerase with chaperone activity) may be used to co-transform the host prokaryotic cells. The chaperone proteins have been demonstrated to facilitate the proper folding and solubility of heterologous proteins produced in bacterial host cells.

[00263] To minimize proteolysis of expressed heterologous proteins (especially those that are proteolytically sensitive), certain host strains deficient for proteolytic enzymes may be used for the present disclosure. For example, host cell strains may be modified to effect genetic mutation(s) in the genes encoding known bacterial proteases such as Protease III, OmpT, DegP, Tsp, Protease I, Protease Mi, Protease V, Protease VI and combinations thereof. Some *E. coli* protease-deficient strains are available.

[00264] Standard protein purification methods known in the art may be employed. The following procedures are exemplary of suitable purification procedures: fractionation on immunoaffinity or ion-exchange columns, ethanol precipitation, reverse phase HPLC, chromatography on silica or on a cation-exchange resin such as DEAE, chromatofocusing, SDS-PAGE, ammonium sulfate precipitation,

hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography and gel filtration using, for example, Sephadex G-75.

[00265] Immunoglobulin fusion proteins may be concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon® ultrafiltration unit.

[00266] Protease inhibitors or protease inhibitor cocktails may be included in any of the foregoing steps to inhibit proteolysis of the immunoglobulin fusion proteins.

[00267] In some cases, an immunoglobulin fusion protein may not be biologically active upon isolation. Various methods for "refolding" or converting a polypeptide to its tertiary structure and generating disulfide linkages, may be used to restore biological activity. Such methods include exposing the solubilized polypeptide to a pH usually above 7 and in the presence of a particular concentration of a chaotrope. The selection of chaotrope is very similar to the choices used for inclusion body solubilization, but usually the chaotrope is used at a lower concentration and is not necessarily the same as chaotropes used for the solubilization. In most cases the refolding/oxidation solution will also contain a reducing agent or the reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential allowing for disulfide shuffling to occur in the formation of the protein's cysteine bridge(s). Some of the commonly used redox couples include cysteine/cystamine, glutathione (GSH)/dithiobis GSH, cupric chloride, dithiothreitol(DTT)/dithiane DTT, and 2-mercaptoethanol(bME)/di-thio-b(ME). In many instances, a cosolvent may be used to increase the efficiency of the refolding, and common reagents used for this purpose include glycerol, polyethylene glycol of various molecular weights, arginine and the like.

Compositions and Combinations

[00268] Disclosed herein are compositions comprising an immunoglobulin fusion protein and/or component of an immunoglobulin fusion protein. In some cases, a composition comprises an immunoglobulin fusion protein and an additional therapeutic agent. Compositions may comprise 1, 2, 3, 4, 5 or more immunoglobulin fusion proteins and/or additional therapeutic agents. Immunoglobulin fusion proteins of the composition may comprise different immunoglobulin regions, linkers, therapeutic peptides or a combination thereof. Further disclosed herein are combinations of an immunoglobulin fusion protein and an additional therapeutic agent, wherein the additional therapeutic agent is formulated separately from the insulin immunoglobulin fusion protein. In such cases, the immunoglobulin fusion protein may be administered together or separately from the additional therapeutic agent. In a non-limiting example, the additional therapeutic agent is insulin, for instance, an insulin having at least about 80%, 85%, 90%, 95% or 100% identity to an insulin selected from any one of SEQ ID NOS: 109-140, 157, 158, 160 and 161. The additional insulin may not be part of a molecule that targets the insulin to the liver.

[00269] The compositions, immunoglobulin fusion proteins, and additional therapeutic agents may comprise one or more pharmaceutically acceptable salts, excipients or vehicles. Pharmaceutically acceptable salts, excipients, or vehicles for use in the present pharmaceutical compositions include carriers, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents,

emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials, and surfactants.

[00270] Neutral buffered saline or saline mixed with serum albumin are exemplary appropriate carriers. Pharmaceutical compositions may include antioxidants such as ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, pluronics, or polyethylene glycol (PEG). Also by way of example, suitable tonicity enhancing agents include alkali metal halides (preferably sodium or potassium chloride), mannitol, sorbitol, and the like. Suitable preservatives include benzalkonium chloride, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid and the like. Hydrogen peroxide also may be used as preservative. Suitable cosolvents include glycerin, propylene glycol, and PEG. Suitable complexing agents include caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxy-propyl-beta-cyclodextrin. Suitable surfactants or wetting agents include sorbitan esters, polysorbates such as polysorbate 80, tromethamine, lecithin, cholesterol, tyloxapal, and the like. The buffers may be conventional buffers such as acetate, borate, citrate, phosphate, bicarbonate, or Tris-HCl. Acetate buffer may be about pH 4-5.5, and Tris buffer may be about pH 7-8.5. Additional pharmaceutical agents are set forth in Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990.

[00271] Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringers' dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, anti-microbials, anti-oxidants, chelating agents, inert gases and the like. See generally, Remington's Pharmaceutical Science, 16th Ed., Mack Eds., 1980.

[00272] The compositions, immunoglobulin fusion proteins, and additional therapeutic agents may be in liquid form or in a lyophilized or freeze-dried form and may include one or more lyoprotectants, excipients, surfactants, high molecular weight structural additives and/or bulking agents (see, for example, U.S. Patent Nos. 6,685,940, 6,566,329, and 6,372,716). In one embodiment, a lyoprotectant is included, which is a non-reducing sugar such as sucrose, lactose or trehalose. The amount of lyoprotectant generally included is such that, upon reconstitution, the resulting formulation will be isotonic, although hypertonic or slightly hypotonic formulations also may be suitable. In addition, the amount of lyoprotectant should be sufficient to prevent an unacceptable amount of degradation and/or aggregation of the protein upon lyophilization. Exemplary lyoprotectant concentrations for sugars (*e.g.,* sucrose, lactose, trehalose) in the pre-lyophilized formulation are from about 10 mM to about 400 mM. In another embodiment, a surfactant

is included, such as for example, nonionic surfactants and ionic surfactants such as polysorbates (*e.g.,* polysorbate 20, polysorbate 80); poloxamers (*e.g.,* poloxamer 188); poly(ethylene glycol) phenyl ethers (*e.g.*, Triton); sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl-or stearyl-sarcosine; linoleyl, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (*e.g.,* lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl ofeyl-taurate; the MONAQUAT™ series (Mona Industries, Inc., Paterson, N.J.), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (*e.g.,* Pluronics, PF68 etc). Exemplary amounts of surfactant that may be present in the pre-lyophilized formulation are from about 0.001-0.5%. High molecular weight structural additives (*e.g.,* fillers, binders) may include for example, acacia, albumin, alginic acid, calcium phosphate (dibasic), cellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, dextran, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. Exemplary concentrations of high molecular weight structural additives are from 0.1% to 10% by weight. In other embodiments, a bulking agent (*e.g.,* mannitol, glycine) may be included.

[00273] Compositions, immunoglobulin fusion proteins, and additional therapeutic agents described herein may be formulated for controlled or sustained delivery in a manner that provides local concentration of the product (*e.g.,* bolus, depot effect) and/or increased stability or half-life in a particular local environment. The compositions, immunoglobulin fusion proteins, and additional therapeutic agents may be formulated with particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, *etc.*, as well as agents such as a biodegradable matrix, injectable microspheres, microcapsular particles, microcapsules, bioerodible particles beads, liposomes, and implantable delivery devices that provide for the controlled or sustained release of the active agent which then may be delivered as a depot injection. Techniques for formulating such sustained-or controlled-delivery means are known and a variety of polymers have been developed and used for the controlled release and delivery of drugs. Such polymers are typically biodegradable and biocompatible. Polymer hydrogels, including those formed by complexation of enantiomeric polymer or polypeptide segments, and hydrogels with temperature or pH sensitive properties, may be desirable for providing drug depot effect because of the mild and aqueous conditions involved in trapping bioactive protein agents. See, for example, the description of controlled release porous polymeric microparticles for the delivery of pharmaceutical compositions in WO 93/15722.

[00274] Suitable materials for this purpose include polylactides (see, *e.g.,* U.S. Patent No. 3,773,919), polymers of poly-(a-hydroxycarboxylic acids), such as poly-D-(-)-3-hydroxybutyric acid (EP 133,988A),

copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, Biopolymers, 22: 547-556 (1983)), poly(2-hydroxyethyl-methacrylate) (Langer *et al.*, J. Biomed. Mater. Res., 15: 167-277 (1981), and Langer, Chem. Tech., 12: 98-105 (1982)), ethylene vinyl acetate, or poly-D(-)-3-hydroxybutyric acid. Other biodegradable polymers include poly(lactones), poly(acetals), poly(orthoesters), and poly(orthocarbonates). Sustained-release compositions also may include liposomes, which may be prepared by any of several methods known in the art (see, *e.g.,* Eppstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688-92 (1985)). The carrier itself, or its degradation products, should be nontoxic in the target tissue and should not further aggravate the condition. This may be determined by routine screening in animal models of the target disorder or, if such models are unavailable, in normal animals.

[00275] Compositions, immunoglobulin fusion proteins, and additional therapeutic agents may be microencapsulated.

[00276] Compositions, immunoglobulin fusion proteins, and additional therapeutic agents may be suitable for parenteral administration. Exemplary compositions, immunoglobulin fusion proteins, and additional therapeutic agents are suitable for injection or infusion into an animal by any route available to the skilled worker, such as intraarticular, subcutaneous, intravenous, intramuscular, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intralesional, intravascular, intrathecal, intravitreal, infusion, or local), topical, oral, or nasal routes. A parenteral formulation typically will be a sterile, pyrogen-free, isotonic aqueous solution, optionally containing pharmaceutically acceptable preservatives.

[00277] Formulations suitable for intramuscular, subcutaneous, peritumoral, or intravenous injection can include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity is maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection also contain optional additives such as preserving, wetting, emulsifying, and dispensing agents.

[00278] For intravenous injections, a fusion protein or additional agent can be optionally formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

[00279] Parenteral injections optionally involve bolus injection or continuous infusion. Formulations for injection are optionally presented in unit dosage form, e.g., in ampoules or in multi dose containers, with an added preservative. The pharmaceutical compositions, immunoglobulin fusion proteins, and additional therapeutic agents described herein can be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral

administration include aqueous solutions of an active agent in water soluble form. Additionally, suspensions are optionally prepared as appropriate oily injection suspensions.

[00280] Alternatively or additionally, compositions, immunoglobulin fusion proteins, and additional therapeutic agents may be administered locally via implantation into the affected area of a membrane, sponge, or other appropriate material on to which an immunoglobulin fusion protein disclosed herein has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of an immunoglobulin fusion protein, nucleic acid, or vector disclosed herein may be directly through the device via bolus, or via continuous administration, or via catheter using continuous infusion.

[00281] Compositions comprising an immunoglobulin fusion protein and/or additional therapeutic agent disclosed herein may be formulated for inhalation, such as for example, as a dry powder. Inhalation solutions also may be formulated in a liquefied propellant for aerosol delivery. In yet another formulation, solutions may be nebulized. Additional pharmaceutical composition for pulmonary administration include, those described, for example, in WO 94/20069, which discloses pulmonary delivery of chemically modified proteins. For pulmonary delivery, the particle size should be suitable for delivery to the distal lung. For example, the particle size may be from 1 μm to 5 μm; however, larger particles may be used, for example, if each particle is fairly porous.

[00282] Immunoglobulin fusion proteins or additional therapeutic agents such as insulin may be delivered using an insulin pump, whereby a device periodically dispenses small amounts of therapeutic agent(s) according to a preprogrammed profile set to insulin needs. The pump may dispense a bolus amount of the therapeutic agent(s), for example, during or after a meal. The pump may also dispense the therapeutic agent(s) according to response to measured glucose levels. Exemplary pumps include those marketed by Medtronic (the MiniMed), Animas Corporation, Disetronic, and Dana.

[00283] Immunoglobulin fusion proteins or additional therapeutic agents such as insulin may be delivered using a transdermal patch. In some cases, the therapeutic agent(s) are formulated as lipophilic emulsions or buffered aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches are constructed for continuous, pulsatile, or on demand delivery of therapeutic agents. In some cases, transdermal delivery is accomplished by means of iontophoretic patches and the like. In some cases, transdermal patches provide controlled delivery. The rate of absorption can be slowed by using rate-controlling membranes or by trapping a therapeutic agent within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier includes absorbable pharmaceutically acceptable solvents to assist passage through the skin. In some cases, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing active agents and optional carriers, a rate controlling barrier to deliver the agents to the skin of the subject at a controlled and predetermined rate over a prolonged period of time, and adhesives to secure the device to the skin.

[00284] Certain formulations comprising an immunoglobulin fusion protein and/or additional therapeutic agent disclosed herein may be administered orally. Formulations administered in this fashion

may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents may be included to facilitate absorption of a selective binding agent. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders also may be employed.

[00285] Another preparation may involve an effective quantity of an immunoglobulin fusion protein and/or additional therapeutic agent in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[00286] Suitable and/or preferred pharmaceutical formulations may be determined in view of the present disclosure and general knowledge of formulation technology, depending upon the intended route of administration, delivery format, and desired dosage. Regardless of the manner of administration, an effective dose may be calculated according to patient body weight, body surface area, or organ size.

[00287] Further refinement of the calculations for determining the appropriate dosage for treatment involving each of the formulations described herein are routinely made in the art and is within the ambit of tasks routinely performed in the art. Appropriate dosages may be ascertained through use of appropriate dose-response data.

[00288] "Pharmaceutically acceptable" may refer to approved or approvable by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans.

[00289] "Pharmaceutically acceptable salt" may refer to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound.

[00290] "Pharmaceutically acceptable excipient, carrier or adjuvant" may refer to an excipient, carrier or adjuvant that may be administered to a subject, together with at least one immunoglobulin of the present disclosure, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[00291] "Pharmaceutically acceptable vehicle" may refer to a diluent, adjuvant, excipient, or carrier with which at least one immunoglobulin of the present disclosure is administered.

Therapeutic Use

[00292] Further disclosed herein are insulin immunoglobulin fusion proteins for and methods of treating, alleviating, inhibiting and/or preventing one or more diseases, disorders and/or conditions. The method may comprise administering to a subject in need thereof a composition comprising one or more insulin immunoglobulin fusion proteins disclosed herein. The insulin immunoglobulin fusion proteins may be used for regulating or ameliorating metabolic defects associated with glucose and insulin metabolism disorders, such as diabetes. In some cases, the subject is in need of reducing at

least one of the following indices of metabolism: insulin secretion, insulin resistance, glucose intolerance, hyperinsulinemia, hyperglycemia, and body fat stores. The subject may be human or animal, including but not limited to primates, cows, pigs, sheep, goats, rabbits, horses, chickens, cats, dogs, mice, and the like.

[00293] In some embodiments, the subject is administered an immunoglobulin fusion protein comprising an amino acid sequence comprising an antigen binding domain specific for an antigen presented on or expressed by a hepatocyte, thus targeting the immunoglobulin fusion protein to the liver. The insulin immunoglobulin fusion protein may comprise an insulin therapeutic peptide comprising an amino acid sequence having about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more amino acid sequence identity to any one of SEQ ID NOS: 109-140, 157, 158, 160, 161. The insulin immunoglobulin fusion protein may comprise an immunoglobulin region comprising an amino acid sequence having about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more amino acid sequence identity to any one of SEQ ID NOS: 29, 30, 33-56, 167. The insulin immunoglobulin fusion protein sequence may comprise about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more amino acid sequence identity to any one of SEQ ID NOS: 78-98. SEQ ID NOS:The insulin immunoglobulin fusion protein may be encoded by a nucleic acid sequence that is at least about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more identical to any one of SEQ ID NOS: 57-77SEQ ID NOS:

[00294] In some embodiments, an insulin immunoglobulin fusion protein described herein is administered and/or formulated in combination with an additional therapeutic agent. The two therapeutic agents may be administered at the same time or at different times and/or schedules. For example, a fusion protein may be administered once daily, weekly, monthly, quarterly, etc., and the additional therapeutic agent may be independently administered daily, weekly, monthly, quarterly, etc. The two therapeutic agents may be administered by different means or the same means. As a non-limiting example, each therapeutic agent is independently or jointing administered orally, transdermally, intravenously, nasally, subcutaneously, or any method as described elsewhere herein.

Pharmacological Properties

[00295] Further disclosed herein are methods of improving one or more pharmacological properties of a therapeutic peptide. The method may comprise producing an immunoglobulin fusion protein disclosed herein. Examples of pharmacological properties may include, but are not limited to, half-life, stability, solubility, immunogenicity, toxicity, bioavailability, absorption, liberation, distribution, metabolization, and excretion. Liberation may refer to the process of releasing of a therapeutic peptide from the pharmaceutical formulation. Absorption may refer to the process of a substance entering the blood circulation. Distribution may refer to the dispersion or dissemination of substances throughout the fluids and tissues of the body. Metabolization (or biotransformation, or inactivation) may refer to the recognition by an organism that a foreign substance is present and the irreversible transformation of parent compounds into daughter metabolites. Excretion may refer to the removal of the substances from the body.

[00296] The half-life of a therapeutic peptide may greater than the half-life of the non-fused therapeutic peptide. The half-life of the therapeutic peptide may be greater than 4 hours, greater than 6 hours, greater than 12 hours, greater than 24 hours, greater than 36 hours, greater than 2 days, greater than 3 days, greater than 4 days, greater than 5 days, greater than 6 days, greater than 7 days, greater than 8 days, greater than 9 days, greater than 10 days, greater than 11 days, greater than 12 days, greater than 13 days, or greater than 14 days when administered to a subject. The half-life of the therapeutic peptide may be greater than 4 hours when administered to a subject. The half-life of the therapeutic peptide may be greater than 6 hours when administered to a subject.

[00297] The half-life of the therapeutic peptide may increase by at least about 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 or more hours. The half-life of the therapeutic peptide may increase by at least about 2 hours. The half-life of the therapeutic peptide may increase by at least about 4 hours. The half-life of the therapeutic peptide may increase by at least about 6 hours. The half-life of the therapeutic peptide may increase by at least about 8 hours.

[00298] The half-life of a therapeutic peptide may be at least about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10-fold greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50-fold greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 2-fold greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 5-fold greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 10-fold greater than the half-life of the non-conjugated therapeutic peptide.

[00299] The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 97% greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 10% greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 20% greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 30% greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 40% greater than the half-life of the non-conjugated therapeutic peptide. The half-life of a therapeutic peptide an immunoglobulin described herein may be at least about 50% greater than the half-life of the non-conjugated therapeutic peptide.

Kits

[00300] Further disclosed herein are kits which comprise one or more immunoglobulin fusion proteins or components thereof. The immunoglobulin fusion proteins may be packaged in a manner which facilitates their use to practice methods of the present disclosure. For example, a kit comprises an immunoglobulin fusion protein described herein packaged in a container with a label affixed to the

container or a package insert that describes use of the immunoglobulin fusion protein in practicing the method. Suitable containers include, for example, bottles, vials, syringes, *etc.* The containers may be formed from a variety of materials such as glass or plastic. The container may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The kit may comprise a container with an immunoglobulin fusion protein contained therein. The kit may comprise a container with (a) an immunoglobulin fusion protein as described herein and an additional therapeutic agent. The additional therapeutic agent may be an insulin molecule lacking a liver targeting moiety. The kit may further comprise a package insert indicating that the first and second compositions may be used to treat a particular condition. Alternatively, or additionally, the kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer (e.g., bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution). It may further comprise other materials desirable from a commercial and user standpoint, including, but not limited to, other buffers, diluents, filters, needles, and syringes. The immunoglobulin fusion protein may be packaged in a unit dosage form. The kit may further comprise a device suitable for administering the immunoglobulin fusion protein according to a specific route of administration or for practicing a screening assay. The kit may contain a label that describes use of the immunoglobulin fusion protein composition.

[00301] The composition comprising the immunoglobulin fusion protein may be formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to mammals, such as humans, bovines, felines, canines, and murines. Typically, compositions for intravenous administration comprise solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and/or a local anaesthetics such as lignocaine to ease pain at the site of the injection. Generally, the ingredients may be supplied either separately or mixed together in unit dosage form. For example, the immunoglobulin fusion protein may be supplied as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of the immunoglobulin fusion protein. Where the composition is to be administered by infusion, it may be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline may be provided so that the ingredients may be mixed prior to administration.

[00302] The amount of the composition described herein which will be effective in the treatment, inhibition and/or prevention of a disease or disorder associated with aberrant expression and/or activity of a therapeutic peptide may be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation may also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro, animal model test systems or clinical trials.

EXAMPLES

[0303] The activity data provided in the following examples are generally obtained using the immunoglobulin fusion proteins defined in the example and exemplified by the provided SEQ ID. It is to be understood that the activities of any immunoglobulin fusion protein disclosed herein may be enhanced or attenuated depending on conditions not relating to immunoglobulin fusion protein sequence, for example, expression and purification conditions.

[0304] ***Example 1: Construction of Ins-L1-Ab1L and Ins-L1-Ab1H fusion proteins for expression in mammalian cells***

[0305] Mouse anti-human ASGPR antibody 5G3 (referred to as anti-ASGPR (5G3) or Ab1) hybridoma was obtained by immunization of mice with human ASGPR extracellular domain. Ab1 heavy chain variable region (Ab1 VH, SEQ ID NO: 11) or Ab1 light chain (Ab1 VL, SEQ ID NO: 13) variable region sequences were obtained by sequencing the Ab1 hybridoma cDNA. A mammalian expression vector encoding Ab1H (SEQ ID NO: 1) was generated by in-frame ligation of amplified Ab1 VH (SEQ ID NO: 11) and human IgG1 CH1 (SEQ ID NO: 12) to pFuse-hIgG1-Fc backbone vector (InvivoGen, CA). Genes encoding antibody Ab1 VL (SEQ ID NO: 13) and human Ig kappa CL (SEQ ID NO: 14) were amplified. The overlap-PCR product of Ab1 VL and human Ig kappa was cloned into the pFuse vector without hIgG1 Fc fragment to generate a mammalian expression vector encoding Ab1L (SEQ ID NO: 2). The gene sequence encoding a single chain insulin with a four-point mutation and a GGGPRR connecting peptide (Ins1, SEQ ID NO: 99) was synthesized by Integrated DNA Technologies, Inc. (IA, USA), and amplified by polymerase chain reaction (PCR). Nucleic acids encoding linker GGGGS (L1, SEQ ID NO: 141) were cloned between Ins1 and the N-terminus of Ab1H to generate Ins1-L1-Ab1H (SEQ ID NO: 57). Nucleic acids encoding linker GGGGS (L1, SEQ ID NO: 141) were cloned between Ins1 and the N-terminus of Ab1L to generate Ins1-L1-Ab1L (SEQ ID NO: 58). The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0306] ***Example 2: Expression and purification of Ins-L1-Ab1L IgG and Ins-L1-Ab1H fusion proteins***

[0307] Ins1-L1-Ab1L (SEQ ID NO: 79) and Ab1H (SEQ ID NO: 29), collectively, Ins1-L1-Ab1L IgG, was expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of Ab1H (SEQ ID NO: 1) and Ins1-L1-Ab1L (SEQ ID NO: 58), according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg of plasmid encoding Ins1-L1-Ab1L and 15 μg of plasmid encoding Ab1H diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO_2 environment at 37 °C. Culture medium containing secreted proteins (Ins1-L1-Ab1L IgG) were harvested every 48 hours, twice after transfection. Ins1-L1-Ab1L IgG was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE, as shown in FIG. 2. Ins1-L1-Ab1H (SEQ ID NO: 78) and Ab1L (SEQ ID NO: 30),

collectively, Ins1-L1-Ab1H IgG, was expressed and purified as described for Ins1-L1-Ab1L IgG and the purified fusion protein is shown in the SDS-PAGE gel of FIG. 2.

[0308] ***Example 3:Ins1-L1-Ab1L IgG and Ins-L1-Ab1H IgG fusion proteins binding assay for human ASGPR***

[0309] The activity of anti-ASGPR within the Ins1-L1-Ab1L IgG (SEQ ID NOS: 79, 29) and Ins1-L1-Ab1H IgG (SEQ ID NOS: 78, 30) fusion proteins for human ASGPR was tested by ELISA assay. Briefly, 100ng/well ASGPR antigen (human, rat and cyno monkey) was coated on 96-well plate in PBS at 4 °C overnight; the wells were blocked with 2% milk/PBST (0.5% Tween-20 in PBS) at room temperature for 1hr; antibodies were added in concentrations of 10 nM, 1 nM and 0.1 nM in 2% milk/PBST at room temperature for 2 hr; the wells were washed with PBST 4-5 times; anti-light chain kappa (sigma A7164) in 2% milk/PBST was added and the plate incubated at room temperature for 1 hr; the wells were washed with PBST 4-5 times; and the reaction was developed with QuantaBlu fluorogenic peroxidase substrate (Life technologies, 15169), and quantified using a Spectramax fluorescence plate reader with excitation at 325nm and emission at 420nm. FIG. 3 shows concentration dependent median fluorescence intensity for binding of Ab1 (anti-ASGPR antibody without a fusion therapeutic peptide (SEQ ID NOS: 29, 30)), Ins1-L1-Ab1L IgG, and Ins1-L1-Ab1H IgG with human ASGPR. FIG. 4 shows concentration dependent fluorescence intensity for binding of Ab1, Ins1-L1-Ab1L IgG, and Ins1-L1-Ab1H IgG with rat ASGPR. The figures illustrate that anti-ASGPR antibodies fused to insulin therapeutic peptides retain activity for their antigen ASGPR.

[0310] ***Example 4: Insulin fusion protein activity assay with HepG2 cells (Phospho-AKT (Ser473) Assay)***

[0311] HepG2, human hepatoma cells, were grown in Minimum Essential Medium (MEM)/F12 (1:1) containing 10% fetal bovine serum (FBS), 100 mM sodium pyruvate and antibiotics (M1). The cells were then seeded in a 384 well plate (15K cell/well) in 8 μL of Dulbecco's modified Eagle's medium (DMEM)/F12 (1:1) containing HEPES and L-glutamine (Life Technologies) FBS and phenol red (M2). The cells were grown overnight (~16 h) at 37°C in the presence of 5% CO_2 gas. The following day, activation of phosphorylated-AKT (Ser473) was evaluated following incubation in each well with various concentrations of insulin or insulin fusion proteins in M2 medium (incubation at 37°C in the presence of 5% CO_2 gas for 10 min). Phosphorylated AKT (Ser473) were detected using the Phospho-AKT (Ser473) Cellular Assay Kits (Cisbio Assay, Cat: 64AKSPEG) according to the manufacturer's protocol. Briefly, the cells were lysed directly in the assay plate by adding 4 μL of lysis buffer. Each well was then supplemented with 4 μL antibody solution containing two monoclonal antibodies that recognize the phosphorylated AKT and emit a time-resolved Fluorescence Resonance Energy Transfer (FRET) signal proportionate to the extent of phosphorylated AKT upon excitation at 320 nm. Emission was measured using an Envision plate reader at 665 nm and 615 nm. FIG. 5 shows the activity of insulin fusion proteins on HepG2 cells with a plot of the HTRF (homogeneous time-resolved fluorescence) ratio as a function of concentration of insulin (SEQ ID NO: 138), Ins1 fused to the amino-terminus of herceptin antibody (Ins1-herceptin comprising SEQ ID NO: 94), anti-ASGPR (SEQ ID NOS: 29, 30), Ins1-L1-

Ab1H IgG and Ins-L1-Ab1L IgG. FIG. 5 illustrates that the Ins1 fusion proteins have comparable or enhanced insulin activity on HepG2 cells. The EC_{50} values for test compounds were calculated as 103 nm for Ins1-L1-Ab1H IgG (SEQ ID NOS: 78, 30), 20 nm for Ins1-L1-Ab1L IgG (SEQ ID NOS: 79, 29), 118 nm for Ins1-herceptin IgG (SEQ ID NOS: 94), and 401 nm for wild type insulin (SEQ ID NO: 138). FIGS. 11, 15, 18, 20-22 illustrate that the Ins1, Ins2, Ins3 and Ins4 fusion proteins have comparable or enhanced insulin activity on HepG2 cells. The EC_{50} values for test compounds were calculated as 46 nm for Ins1-L1-Ab2 IgG (SEQ ID NOS: 80, 31), 3.8 nm for Ins3-L2-Ab3 IgG (SEQ ID NOS: 83, 33) +PC2, 4.4 nm for Ins3-L2-Ab3 IgG (SEQ ID NOS: 82, 33), 5.4 nm for Ins2-L2-Ab3 IgG (SEQ ID NOS: 81, 167) +PC2, 21 for Ins2-L2-Ab3 IgG (SEQ ID NOS: 81, 167) and 209 nm for wild type insulin (SEQ ID NO: 138); FIG. 11. The EC_{50} values for test compounds were calculated as 23 nm for Ins1-L3-Ab4 IgG (SEQ ID NOS: 84, 34), 187 nm for Ins1-L3-Ab4(Fab) (SEQ ID NOS: 84, 36) and 345 nm for wild type insulin (SEQ ID NO: 138); FIG. 15. The EC_{50} values for test compounds were calculated as 53 nm for Ins4-L3-Ab4 IgG (SEQ ID NOS: 85, 34), 175 nm for Ins4-L3-Ab2 IgG (SEQ ID NOS: 86, 31) and 569 nm for wild type insulin (SEQ ID NO: 138); FIG. 18. The EC_{50} values for test compounds were calculated as 40 nm for Ins4-L6-Ab4 IgG (SEQ ID NOS: 91, 34) and 345 nm for wild type insulin (SEQ ID NO: 138); FIG. 20. The EC_{50} values for test compounds were calculated as 223 nm for Ins4-L6-Ab4 (Fab) (SEQ ID NOS: 95, 36) IgG, >1580 nm for Ins5-L7-Ab4 IgG (SEQ ID NOS: 90, 34) and 426 nm for wild type insulin (SEQ ID NO: 138); FIG. 21. The EC_{50} values for test compounds were calculated as 8 nm for Ins1-L3-Ab4 IgG (SEQ ID NOS: 84, 34), 13 nm for Ins1-L4-Ab4 IgG (SEQ ID NOS: 87, 34), 6 nm for Ins1-L5-Ab4 IgG (SEQ ID NOS: 88, 34) and 282 nm for wild type insulin (SEQ ID NO: 138); FIG. 22.

[0312] ***Example 5: Flow cytometry analysis of the binding affinity of insulin fusion proteins with HepG2 cells***

[0313] HepG2 cells were harvested, washed and resuspended in PBS/1%BSA solution at a density of 5×10^6 cells/mL. The cell suspension was incubated at 4 °C for 1 hour. Various concentrations (40, 20, 10, 5, 2.5, 1.25, 0.625, 0 nM) of antibodies (Ab1 IgG (SEQ ID NOS: 29, 30), Ins1-L1-Ab1L IgG (SEQ ID NOS: 79, 29), Ins1-L1-Ab1H IgG (SEQ ID NOS: 78, 30), and Ins1-Herceptin (SEQ ID NOS: 94) were added to the cells for a 2-hour incubation at 4 °C with agitation. The cells were then washed 3 times with PBS/1%BSA. FITC-anti-human Kappa antibody (Life Technologies, Inc.) was diluted 500-fold with PBS/1%BSA and then added to the cells for incubation at 4 °C for another 2 hours. Following incubation, the cells were washed twice with PBS/1%BSA and resuspended in PBS/1%BSA solution. Flow cytometry was performed to analyze the amount of bound antibody. FIG. 6 shows binding of Ins1-L1-Ab1L IgG (panel A) and Ins1-L1-Ab1H IgG (panel B) on HepG2 cells. Mean cellular fluorescence (FITC channel) was used to quantify the binding affinity. FIG. 7 shows a plot of the mean fluorescence intensity (MFI) versus concentration for each antibody tested.

[0314] ***Example 6: Construction of insulin IgG fusion proteins for expression in mammalian cells***

[0315] The gene encoding the heavy chain of palivizumab (Ab2H, SEQ ID NO: 3) was cloned into a pFuse vector. Nucleic acids encoding Ins1, SEQ ID NO: 99, (as described in Example 1) were

synthesized by Integrated DNA Technologies, Inc. and amplified by PCR. A mammalian expression vector encoding Ins1-L1-Ab2L (SEQ ID NO: 59) was generated by cloning the gene encoding Ins1 (SEQ ID NO: 99) and the light chain of palivizumab (Ab2L, SEQ ID NO: 4) with nucleotides encoding the linker GGGGS (L1, SEQ ID NO: 141) into a pFuse vector. The resulting mammalian expression vector was confirmed by DNA sequencing.

[0316] To generate insulin, anti-ASGPR fusion proteins, a gene encoding a nucleic acid sequence of a heavy (SEQ ID NO: 1, 6, 8, 9, 10, 11 or 15) or light chain (SEQ ID NO: 2, 5, 7, 13, or 16) of anti-ASGPR was cloned into a pFuse vector. Nucleic acids encoding insulin selected from SEQ ID NOS: 109-140 were synthesized by Integrated DNA Technologies, Inc. and amplified by PCR. A mammalian expression vector encoding insulin and anti-ASGPR fusion protein was generated by cloning the nucleic acids encoding insulin and a linker into the pFuse vector. The resulting mammalian expression vector was confirmed by DNA sequencing.

[0317] ***Example 7: Expression and purification of insulin IgG fusion proteins***

[0318] Ins1-L1-Ab2L (SEQ ID NO: 59) and Ab2H (SEQ ID NO: 3), collectively, Ins1-L1-Ab2L IgG, were expressed through transient transfection of FreeStyle HEK 293 cells with expression vectors of Ab2H (SEQ ID NO: 3) and Ins1-L1-Ab2L (SEQ ID NO: 59), according to the manufacturer's protocol. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg of plasmid encoding Ins1-L1-Ab1L and 15 μg of plasmid encoding Ab1H diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO_2 environment at 37 °C. Culture medium containing secreted proteins Ins1-L1-Ab2L IgG (SEQ ID NOS: 80, 31) were harvested every 48 hours, twice after transfection. Ins1-L1-Ab2L IgG was purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE, as shown in FIG. 8.

[0319] To purify insulin fusion proteins, FreeStyle HEK 293 cells were first transiently transfected with mammalian expression vectors encoding for an insulin fusion protein. Optionally, the cells were co-transfected with a mammalian expression vector encoding a protease such as PC2 to cleave a protease cleavage site within a connecting peptide of the insulin, anti-ASGPR fusion protein. Briefly, 28 mL FreeStyle HEK 293 cells containing 3×10^7 cells were seeded in a 125 mL shaking flask. 15 μg of plasmid encoding insulin fusion proteins were diluted in 1 mL Opti-MEM medium were added in 1 mL Opti-MEM containing 60 μL 293fectin (Invitrogen, Inc). After the plasmids were incubated with 293fectin for 30 min, lipoplex mixture was added to the cell suspension. Cells were then shaken at 125 rpm in a 5% CO_2 environment at 37 °C. Culture medium containing secreted insulin fusion proteins were harvested every 48 hours, twice after transfection. Insulin fusion proteins were purified by Protein G chromatography (Thermo Fisher Scientific, IL). Purified proteins were analyzed by SDS-PAGE, as shown in FIGS. 9, 10, 12-14, 17 and 19. FIG. 9 shows an SDS-PAGE gel of purified Ins2-L2-Ab3L IgG (SEQ ID NO: 81) and Ab3H (SEQ ID NO: 167) fusion protein; with and without proteolytic cleavage by the enzyme PC2. FIG. 10 shows an SDS-PAGE gel of purified Ins3-L2-Ab3L IgG (Ins3-L2-Ab3L, SEQ

ID NO: 82; Ab3H, SEQ ID NO: 167) fusion protein. FIG. 12 shows an SDS-PAGE gel of purified Ins1-L3-Ab4L IgG (Ins1-L3-Ab4L, SEQ ID NO: 84; Ab4H, SEQ ID NO: 34) fusion protein. FIG. 13 shows an SDS-PAGE gel of purified Ins1-L3-Ab5L IgG (Ins1-L3-Ab5L, SEQ ID NO: 96; Ab5H, SEQ ID NO: 37) fusion protein. FIG. 14 shows an SDS-PAGE gel of purified Ins1-L3-Ab4L IgG (Ins1-L3-Ab4L, SEQ ID NO: 84; Ab4H(Fab), SEQ ID NO: 36) fusion protein. FIG. 17 shows an SDS-PAGE gel of purified Ins4-L3-Ab4L IgG (Ins4-L3-Ab4L, SEQ ID NO: 85; Ab4H, SEQ ID NO: 34) fusion protein and Ins4-L3-Ab2L IgG (Ins4-L3-Ab2L, SEQ ID NO: 86; Ab2H, SEQ ID NO: 31) fusion protein. FIG. 19 shows an SDS-PAGE gel of purified Ins4-L6-Ab4L IgG (Ins4-L6-Ab4L, SEQ ID NO: 91; Ab4H, SEQ ID NO: 34) fusion protein; Ins4-L6-Ab4L (Fab) (Ins4-L6-Ab4L, SEQ ID NO: 91; Ab4H(Fab), SEQ ID NO: 36) fusion protein; and Ins5-L7-Ab4L IgG (Ins5-L7-Ab4L, SEQ ID NO: 90; Ab4H, SEQ ID NO: 34) fusion protein.

[0320] ***Example 8: Construction, expression and purification of Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, Ins7-L3-Ab4 Fab, and Ins7-L3-Ab5 Fab fusion proteins for expression in mammalian cells***

[0321] Mouse anti-human ASGPR antibody 5G3 (referred to as anti-ASGPR (5G3) or Ab1) was humanized to obtain humanized anti-ASGPR or Ab4. To generate Ab5H, Ab4H was mutated to substitute an arginine for a tyrosine at amino acid position 50. The gene sequence encoding Ins1 (SEQ ID NO: 99) or Ins7 (SEQ ID NO: 108) was synthesized by Integrated DNA Technologies, Inc. (IA, USA), and amplified by polymerase chain reaction (PCR). Nucleic acids encoding linker L3 (SEQ ID NO: 143) were cloned between Ins1 or Ins7 and the N-terminus of Ab4L or Ab5L to generate Ins1-L3-Ab4L (SEQ ID NO: 63), Ins1-L3-Ab5L (SEQ ID NO: 75), Ins7-L3-Ab4L (SEQ ID NO: 76) or Ins7-L3-Ab5L (SEQ ID NO: 77). The resulting mammalian expression vectors were confirmed by DNA sequencing.

[0322] The fusion proteins were expressed and purified as described generally in Example 2. Purified proteins were analyzed by SDS-PAGE, as shown in FIGS. 23-26. Purified Ins1-L3-Ab4L (SEQ ID NO: 84) and Ab4H (SEQ ID NO: 36), collectively, Ins1-L3-Ab4 Fab, is shown in the SDS-PAGE gel of FIG. 23. Purified Ins1-L3-Ab5L (SEQ ID NO: 96) and Ab5H (SEQ ID NO: 38), collectively, Ins1-L3-Ab5 Fab, is shown in the SDS-PAGE gel of FIG. 24. Purified Ins7-L3-Ab4L (SEQ ID NO: 97) and Ab4H (SEQ ID NO: 36), collectively, Ins7-L3-Ab4 Fab, is shown in the SDS-PAGE gel of FIG. 25. Purified Ins7-L3-Ab5L (SEQ ID NO: 98) and Ab5H (SEQ ID NO: 38), collectively, Ins7-L3-Ab5 Fab, is shown in the SDS-PAGE gel of FIG. 26.

[0323] Following protein purification and analysis by SDS-PAGE, Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, and Ins7-L3-Ab5 Fab fusion proteins were further purified by Superdex 200 increase size exclusion gel filtration (GE HealthCare LifeSciences) as shown in FIGS. 27-29. As shown in FIG. 27, the major peak for purified Ins1-L3-Ab4L (SEQ ID NO: 84) and Ab4H (SEQ ID NO: 36), collectively, Ins1-L3-Ab4 Fab, was collected at 80-100 min. As shown in FIG. 28, the major peak for purified Ins1-L3-Ab5L **(SEQ ID NO: 96)** and Ab5H (SEQ ID NO: 38), collectively, Ins1-L3-Ab5 Fab, was collected at 80-100 min. As shown in FIG. 29, the major peak for purified Ins7-L3-Ab5L (SEQ ID NO: 98) and Ab5H (SEQ ID NO: 38), collectively, Ins7-L3-Ab5 Fab, was collected at 75-85 min.

[0324] ESI-MS was used to characterize Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab that was purified by Protein G chromatography (Thermo Fisher Scientific, IL) and gel filtration as shown in FIG. 30. The observance for Ins1-L3-Ab4 Fab, was 56209, and the observance for Ins1-L3-Ab5 Fab was 56239.

[0325] The thermal stability of A4Fab, Ins1-L3-Ab4 Fab, and Ins1-L3-Ab4 Fab gel filtration major peak collection was determined as shown in FIG. 31, panels A-C. 6.25 μg of fusion protein in 12.5 μL of DPBS (pH 7.5) were mixed with 2.5 μL of fresh-diluted thermal shift dye and 5.0 μL of shift buffer (Protein Thermal Shift™ Dye Kit, ThermoFisher Scientific, Cat. 4461146). The detection of fluorescence was coupled with the thermal scanning from 25°C to 99°C at a heating rate 0.05°C/s using ViiA™ 7 Real-Time PCR System. The melting temperature (Tm) was calculated by the analysis model "area under curve" in GraphPad Prism7. Assays were repeated 2 times to ensure reproducibility. As seen in FIG. 31, panel A, the Tm for A4 Fab was 76°C. As seen in FIG. 31, panel B, the Tm for Ins1-L3-Ab4 Fab was 74.67°C. The Tm for Ins1-L3-Ab4 Fab gel filtration major peak collection was 74.8°C.

[0326] ***Example 9: Insulin fusion protein activity assay with HepG2, A673, and SGBS cells (Phospho-AKT (Ser473) Assay)***

[0327] The activity of the insulin fusion proteins on AKT was described generally in Example 4. FIG. 32 and FIG. 33 illustrate that the Ins1 fusion proteins have comparable or enhanced insulin activity on HepG2 cells. The EC_{50} values for the fusion proteins were calculated as 30 nM for Ins1-L3-Ab4 Fab, 140 nM for Ins1-L3-Ab5 Fab, 73 nM for Ins7-L3-Ab4 Fab, and 231 nM for WT insulin as seen in FIG. 32 and FIG. 33.

[0328] The activity of the insulin fusion proteins on AKT on A673 cells was also measured as seen in FIG. 34. The EC_{50} values for were calculated as 581 nM for Ins1-L3-Ab4 Fab, 351 nM for Ins1-L3-Ab5 Fab, and 362 nM for WT insulin. As seen in FIG. 34, the insulin fusion proteins had comparable or enhanced insulin activity on A673 cells.

[0329] The activity of insulin fusion proteins on AKT on SGBS cells was also measured as seen in FIG. 35. The EC_{50} values for were calculated as 94 nM for Ins1-L3-Ab4 Fab, 206 nM for Ins1-L3-Ab5 Fab, and 176 nM for WT insulin. The insulin fusion proteins had comparable or enhanced insulin activity on SGBS cells as seen in FIG. 35.

[0330] ***Example 10: Flow cytometry analysis of the binding affinity of insulin fusion proteins with HepG2, A673, and SGBS cells***

[0331] Flow cytometry analysis of the binding affinity of insulin fusion proteins with HepG2 was generally described in Example 5. Briefly, 2×10^5 HepG2 cells were blocked with 2% FBS, 0.1% NaN_3/PBS at 4°C and mixed with antibodies or fusion proteins at 200 nM 4°C for 1hr. After the cells were washed three times with blocking buffer, HepG2 cells were incubated with anti-human FAB-FITC (1:1000, 109-095-006, Immuno JacksonResearch) at 4°C for 30 min. Following three washes with blocking buffer, FITC signal was obtained by BD Accuri™ 6 Flow Cytometer. Gating was applied to single cell suspension and mean fluorescent intensity (MFI) was plotted versus concentration for comparison. The MFI for Ins1-L3-Ab4 Fab was calculated as 21570 and for Ins1-L3-Ab5 Fab was 8523.

[0332] Flow cytometry was also performed to determine the binding affinity of insulin fusion proteins with A673 cells. The MFI for Ins1-L3-Ab4 Fab was calculated as 731 and for Ins1-L3-Ab5 Fab was 630.

[0333] Flow cytometry was performed of insulin fusion proteins with SGBS cells. The MFI for Ins1-L3-Ab4 Fab was calculated as 1411 and for Ins1-L3-Ab5 Fab was 1047.

[0334] FIG. 36 illustrates binding to HepG2 of Ins1-L3-Ab4, Ins1-L3-Ab5, Ab4, and Ab5. HepG2 cells, 2×10^5, were blocked with 2% FBS, 0.1% NaN_3/PBS at 4°C and mixed with antibodies or fusion proteins from 30 pM to 10 nM at 4°C for 1hr. After the cells were washed three times with blocking buffer, HepG2 cells were incubated with anti-human Fc-FITC (1:1000, 02-10-20, KPL) at 4°C for 30 min. Following three washes with blocking buffer, FITC signal was obtained by BD Accuri™ 6 Flow Cytometer. Gating was applied to single cell suspension and mean fluorescent intensity (MFI) was plotted versus concentration for comparison. FIG. 36 shows a plot of the mean fluorescence intensity (MFI) versus concentration for each antibody or fusion protein tested.

[0335] ***Example 11: Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab fusion proteins binding assay for human, rat, and monkey ASGPR***

[0336] The activity of anti-ASGPR within Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab fusion proteins for human, rat, and cyno monkey ASGPR was tested by ELISA assay as shown in FIGS. 37-39 as generally described in Example 3. 100ng/well ASGPR antigen (human, rat, and cyno monkey) was coated on 96-well plate in PBS 4°C over night, blocked with 2% milk/PBST (0.5% Tween-20 in PBS) at room temperature for 1 hr, and incubated with the fusion proteins at 4 nM, 20 nM, 100 nM, and 500 nM in 2% milk/PBST at room temperature for 2 hr. Wells were then washed with PBST for 4-5 times, incubated with mouse anti-insulin (MA5-12037, ThermoFisher Scientific) in 2% milk/PBST at room temperature for 2 hr, washed with PBST for 4-5 times, incubated with goat anti-mouse IgG-HRP (115-035-008, Jackson ImmunoResearch) for 30 min, and washed with PBST for 4-5 times The plates were developed with QuantaBlu fluorogenic peroxidase substrate (Life technologies, 15169), and quantified using Spectramax fluorescence plate reader with excitation at 325nm and emission at 420nm.

[0337] FIG. 37 shows concentration dependent median fluorescence intensity for binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab with human ASPGR. FIG. 38 shows concentration dependent median fluorescence intensity for binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab with rat ASGPR. FIG. 39 shows concentration dependent median fluorescence intensity for binding of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab with cyno monkey ASPGR. The figures illustrate that anti-ASGPR antibodies fused to insulin therapeutic peptides retain activity for their antigen ASGPR as determined by ELISA assay.

[0338] FIGS. 16, panels A-C are graphs showing the binding of insulin immunoglobulin fusion proteins (Ins1-L3-Ab4L and Ab4H; Ins1-L3-Ab4L and Ab4H(Fab)) to extracellular domains of human, rat or cynomolgus monkey ASGPR as determined by ELISA assay.

[0339] ***Example 12: Pharmacology kinetics and blood glucose of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in Streptozotocin (STZ) induced rats***

[0340] The pharmacology kinetics of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab was determined in STZ induced rats as seen in FIGS. 40, 42, and 44.

[0341] FIG. 40 illustrates the pharmacology kinetics in STZ induced rats following intravenous (IV) administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. 9 week old male Wistar rats were used. STZ was induced with 65mg/kg IV, and animals were monitored for 2 weeks with fasting blood glucose taken to confirm diabetes. On assay day, animals were fasted for 4 hrs prior to insulin and fusion proteins dose of 1mg/kg, IV. Pre-dosing, animals were assayed for baseline blood glucose and body weights and sorted (based on body weight and blood glucose) prior to insulin dose. After 8 hrs (12 hrs fasting), food was returned. Standard chow was fed to the rats. Anti-human IgG antibodies (ab98616, Abcam) was coated on 96-well ELISA plate, blocked with 2% milk, incubated with plasma, and then incubated with mouse anti-Insulin (MA5-12037, ThermoFisher Scientific). Signal was detected by goat anti-mouse IgG-HRP antibodies (115-035-008, Jackson ImmunoResearch). Fusion proteins' concentration in plasma were plotted versus time as shown in FIG. 40. As seen in FIG. 40, Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab resulted in a time dependent decrease in concentration of insulin in the plasma.

[0342] FIG. 41 illustrates the effect on blood glucose concentration in STZ induced rats following IV administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. Ins1-L3-Ab4 Fab was administered intravenously at either a 0.1 mg/kg or 1 mg/kg dose. Ins1-L3-Ab5 Fab was administered intravenously at either a 0.1 mg/kg or 1 mg/kg dose. Levimir was administered subcutaneously at 6U/kg. FIG. 41 illustrates the effects of Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, Levimir, Vehicle, and Naïve control on blood glucose concentration over time.

[0343] FIG. 42 illustrates the pharmacology kinetics in STZ induced rats following IV administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. 9 week old male Wistar rats were used. STZ was induced with 65mg/kg IV, and animals were monitored for 2 weeks with fasting blood glucose taken to confirm diabetes. On assay day, animals were fasted for 4 hrs prior to insulin and fusion proteins dose of 20 mg/kg intravenously. Pre-dosing, animals were assayed for baseline blood glucose and body weights and sorted (based on body weight and blood glucose) prior to insulin dose. After 8 hrs (12 hrs fasting), food was returned. Standard chow was fed to the rats. Anti-human Fab antibodies (109-005-097, Jackson ImmunoResearch) was coated on 96-well ELISA plate, blocked with 2% milk, incubated with plasma, and then incubated with mouse anti-Insulin (MA5-12037, ThermoFisher Scientific). Signal was detected by goat anti-mouse IgG-HRP antibodies (115-035-008, Jackson ImmunoResearch). Fusion proteins' concentration in plasma were plotted versus time as shown in FIG. 42 and pharmacokinetic parameters were analyzed by Winnolin. $T_{1/2}$ for Ins1-L3-Ab4 Fab was determined to be 4.8 hr and for Ins1-L3-Ab5 Fab, it was determined to be 4.2 hr. The C_{max} for Ins1-L3-Ab4 Fab was determined to be 2541 nM and for Ins1-L3-Ab5 Fab, it was determined to be 5917 nM. The T_{max} for Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab was 0.5 hr. The area under the curve (AUC) was calculated to be 5145 hr·nM for Ins1-L3-Ab4 Fab and 11886 hr·nM for Ins1-L3-Ab5 Fab.

[0344] FIG. 43 illustrates the effect on blood glucose concentration in STZ induced rats following IV administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. 20 mg/kg dose of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab were administered intravenously to STD induced rats. Levimir was administered

subcutaneously at 6U/kg. FIG. 43 illustrates the effects of Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, Levimir, Vehicle (HBSS), and Naïve control on blood glucose concentration over time.

[0345] FIG. 44 illustrates the pharmacology kinetics in STZ induced rats following subcutaneous (SC) administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. Similar to the methods described in this example, rats were administered 10 mg/kg SC of Ins1-L3-Ab4 Fab or Ins1-L3-Ab5 Fab. Fusion proteins' concentration in plasma were plotted versus time as shown in FIG. 44. As seen in FIG. 44, Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab resulted in a time dependent decrease in concentration of insulin in the plasma following 30 hrs.

[0346] FIG. 45 illustrates the effect on blood glucose concentration in STZ induced rats following SC administration of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab. 10 mg/kg dose of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab were administered subcutaneously to STD induced rats. Levimir was administered subcutaneously at 6U/kg. FIG. 45 illustrates the effects of Ins1-L3-Ab4 Fab, Ins1-L3-Ab5 Fab, Levimir, Vehicle (HBSS), and Naïve control on blood glucose concentration over time.

[0347] ***Example 13: Bio-distribution of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in normal rats***

[0348] FIGS. 46A-46C illustrate the bio-distribution of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in normal rats. 9 week old male Wistar rats were fasted for 4 hrs prior to fusion proteins dose (5mg/kg, IV). Pre-dosing, animals were assayed for baseline blood glucose and body weights and sorted (based on body weight and blood glucose) prior to insulin dose. After 1hr post dosing, rats were sacrificed, and liver, muscle (quadriceps femoris), and fat (epididymal white adipose) tissue were extracted. Extracted tissue were homogenized as 300mg/mL in PBS with 1x protease inhibitor, 1mM EDTA and 0.5% Triton-100. Anti-human Fab antibodies (109-005-097, Jackson ImmunoResearch) was coated on 96-well ELISA plate, blocked with 2% milk, incubated with plasma, and then incubated with mouse anti-Insulin (MA5-12037, ThermoFisher Scientific). Signal was detected by goat anti-mouse IgG-HRP antibodies (115-035-008, Jackson ImmunoResearch).

[0349] As seen in FIG. 46A, the amount of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in the liver was 7.98 for Ins1-L3-Ab4 Fab and 3.12 for Ins1-L3-Ab5 Fab. As seen in FIG. 46B, the amount of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab in the fat was 0.08 for Ins1-L3-Ab4 Fab and 0.23 for Ins1-L3-Ab5 Fab. As seen in FIG. 46C, the amount of Ins1-L3-Ab4 Fab and Ins1-L3-Ab5 Fab protein in the muscle was 0.08 for Ins1-L3-Ab4 Fab and 0.27 for Ins1-L3-Ab5 Fab.

[0350] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known

equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of the present invention is embodied by the appended claims.

[0351] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0352] All references cited herein are incorporated by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

Table 1. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Nucleic acid sequence

NAME	SEQ ID NO	SEQUENCE
Ab1H (murine anti-ASGPR HC)	1	CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTTGTGAAGCCTG GGGCTTCAGTGAAACTGTCCTGCAAGGCTTCTGGCTATACCTT CACCAACTACTGGATGCACTGGGTGAAACAGAGGCCTGGACG AGGCCTTGAGTGGATTGGAAGGATTGATCTTAATAGTGGTGGT ACTAATTACAATTACAATGAGAAGTTCAAGACCAAGGCCACA CTGACTGTAGACAAACCCTCCAGCACAGCCTACATGCAGCTCA GCAGCCTGACATCTGAGGACTCTGCGGTCTATTATTGTGCAAA TTACTACGGTAGTAGCTGGTTTGCTTACTGGGGCCAAGGGACC ACTCTCACAGTCTCCTCAGCTAAAACAACAGCCCCATCGGTCT ATCCACTGGCCCCTGTGTGTGGAGATACAACTGGCTCCTCGGT GACTCTAGGATGCCTGGTCAAGGGTTATTTCCCTGAGCCAGTG ACCTTGACCTGGAACTCTGGATCCCTGTCCAGTGGTGTGCACA CCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACCCTCAGCAGC TCAGTGACTGTAACCTCGAGCACCTGGCCCAGCCAGTCCATCA CCTGCAATGTGGCCCACCCGGCAAGCAGCACCAAGGTGGACA AGAAAATTGAGCCCAGAGGGCCCACAATCAAGCCCTGTCCTCC ATGCAAATGCCCAGCACCTAACCTCTTGGGTGGACCATCCGTC TTCATCTTCCCTCCAAAGATCAAGGATGTACTCATGATCTCCCT GAGCCCCATAGTCACATGTGTGGTGGTGGATGTGAGCGAGGAT GACCCAGATGTCCAGATCAGCTGGTTTGTGAACAACGTGGAAG TACACACAGCTCAGACACAAACCCATAGAGAGGATTACAACA GTACTCTCCGGGTGGTCAGTGCCCTCCCCATCCAGCACCAGGA CTGGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACAACAA AGACCTCCCAGCGCCCATCGAGAGAACCATCTCAAAACCCAA AGGGTCAGTAAGAGCTCCACAGGTATATGTCTTGCCTCCACCA GAAGAAGAGATGACTAAGAAACAGGTCACTCTGACCTGCATG GTCACAGACTTCATGCCTGAAGACATTTACGTGGAGTGGACCA ACAACGGGAAAACAGAGCTAAACTACAAGAACACTGAACCAG

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NAME	SEQ ID NO	SEQUENCE
		TCCTGGACTCTGATGGTTCTTACTTCATGTACAGCAAGCTGAG AGTGGAAAAGAAGAACTGGGTGGAAAGAAATAGCTACTCCTG TTCAGTGGTCCACGAGGGTCTGCACAATCACCACACGACTAAG AGCTTCTCCCGGACTCCGGGTAAA
Ab1L (murine anti- ASGPR LC)	2	GAAACTGTACTCACCCAGTCTCCAACCACCATGGCTACATCTC CCGGGGAGAAGATCACTATCACCTGCAGTGCCAGCTCAACTAT AAGTTCCAATTACTTGCATTGGTATCAGCAGAAGCCAGGATTC TCCCCTAAACTCTTGATTTATAGGACATCCGATCTGGCTTCTGG AGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTAC TCTCTCACAATTGGCACCATGGAGGCTGAAGATGTTGCCACTT ACTACTGCCAGCAGGGTAGTAGTATACCATTCACGTTCGGCTC GGGGACAAAGCTGGAGATTAACCGGGCAGATACAGCACCAAC TGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGA GGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAAAG ACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAA ATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACA GCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACG AGTATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAA GACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAATGAG TGT
Ab2H (Palivizumab HC)	3	CAGGTGACCCTGCGCGAGTCCGGCCCTGCACTGGTGAAGCCCA CCCAGACCCTGACCCTGACCTGCACCTTCTCCGGCTTCTCCCTG TCCACCTCCGGCATGTCCGTGGGCTGGATCCGGCAGCCTCCCG GCAAGGCCCTGGAGTGGCTGGCTGACATCTGGTGGGACGACA AGAAGGACTACAACCCCTCCCTGAAGTCCCGCCTGACCATCTC CAAGGACACCTCCAAGAACCAGGTGGTGCTGAAGGTGACCAA CATGGACCCCGCCGACACCGCCACCTACTACTGCGCCCGCTCA ATGATTACCAACTGGTACTTCGACGTGTGGGGAGCCGGTACCA CCGTGACCGTGTCTTCCGCCTCCACCAAGGGCCCATCGGTCTT CCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCA GCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTA CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGA CAAGAAAGTTGAACCCAAATCTTGCGACAAAACTCACACATG CCCACCGTGCCCAGCACCTCCAGTCGCCGGACCGTCAGTCTTC CTCTTCCCTCCAAAACCCAAGGACACCCTCATGATCTCCCGGA CCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAG ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAG CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC TGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA GGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAAAGCCAAA GGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCTCCATCCC GGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGG TCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAG

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NAME	**SEQ ID NO**	**SEQUENCE**
		CAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGC TCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGA GCCTCTCCCTGTCTCCGGGTAAATGATAA
Ab2L (Palivizumab LC)	4	GACATCCAGATGACCCAGTCCCCCTCCACCCTGTCCGCCTCCG TGGGCGACCGCGTGACCATCACCTGCAAGTGCCAGCTGTCCGT GGGCTACATGCACTGGTACCAGCAGAAGCCCGGCAAGGCCCC CAAGCTGCTGATCTACGACACCTCCAAGCTGGCCTCCGGCGTG CCCTCCCGCTTCTCCGGCTCCGGCTCCGGCACCGAGTTCACCCT GACCATCTCCTCCCTGCAGCCCGACGACTTCGCCACCTACTAC TGCTTCCAGGGCTCCGGCTACCCCTTCACCTTCGGCGGCGGCA CCAAGCTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTT CATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCC TCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT CCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCT ACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACG AGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC TGTCCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTG A
Ab3L (chimeric anti-ASGPR)	5	GAAACTGTACTCACCCAGTCTCCAACCACCATGGCTACATCTC CCGGGGAGAAGATCACTATCACCTGCAGTGCCAGCTCAACTAT AAGTTCCAATTACTTGCATTGGTATCAGCAGAAGCCAGGATTC TCCCCTAAACTCTTGATTTATAGGACATCCGATCTGGCTTCTGG AGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTAC TCTCTCACAATTGGCACCATGGAGGCTGAAGATGTTGCCACTT ACTACTGCCAGCAGGGTAGTAGTATACCATTCACGTTCGGCTC GGGGACAAAGTTGGAAATTAAACGAACTGTGGCTGCACCATC TGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAG AGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGG GTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGTTGA
Ab4H (anti-ASGPR HC, humanized)	6	CAGGTGCAGCTGGTCCAGTCCGGCGCAGAGGTGAAGAAACCC GGGGCCTCCGTGAAGGTCTCTTGCAAAGCTAGTGGGTACACCT TCACAAACTATTGGATGCACTGGGTGCGACAGGCACCTGGACA GGGCCTGGAATGGATGGGAAGAATCGACCTGAACAGCGGCGG GACTAACTACAATTATGCCCAGAAGTTTCAGGGCAGGGTGACT ATGACCCGCGATACCTCAATTAGCACAGCTTACATGGAGCTGT CACGGCTGAGAAGCGACGATACAGCCGTCTACTATTGTGCTCG GTACTATGGCAGCTCCTGGTTCGCCTATTGGGGGCAGGGAACA CTGGTGACTGTCTCTAGTGCATCAACAAAGGGACCAAGCGTGT TTCCACTGGCCCCCTCAAGCAAGAGCACCTCCGGAGGGACAGC

Table 1. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Nucleic acid sequence		
NAME	SEQ ID NO	SEQUENCE
		CGCTCTGGGATGTCTGGTGAAAGACTACTTCCCCGAGCCTGTG ACTGTCTCTTGGAATAGTGGCGCTCTGACCTCCGGGGTGCACA CATTTCCAGCAGTCCTGCAGTCCTCTGGACTGTATTCTCTGAGT TCAGTGGTCACCGTGCCCAGCTCCTCTCTGGGCACTCAGACCT ACATCTGCAATGTCAACCATAAGCCTAGTAACACAAAAGTGG ATAAGAAAGTCGAACCAAAGAGCTGTGACAAAACTCACACAT GCCCACCGTGCCCAGCACCTCCAGTCGCCGGACCGTCAGTCTT CCTCTTCCCTCCAAAACCCAAGGACACCCTCATGATCTCCCGG ACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG ACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA AAGGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAAAGCCA AAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCTCCATC CCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCT GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCA CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAA GAGCCTCTCCCTGTCTCCGGGTAAA
Ab4L (anti-ASGPR LC, humanized)	7	GAGATCGTGCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCTC CAGGAGAACGAGCCACCCTGTCCTGCTCCGCCTCATCAACAAT TTCTAGTAACTACCTGCACTGGTATCAGCAGAAGCCAGGACAG GCACCTCGACTGCTGATCTACAGAACTAGTGACCTGGCCTCTG GCATTCCCGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACTT TACCCTGACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGTC TACTATTGTCAGCAGGGCTCAAGCATCCCATTCACATTTGGCC AGGGGACTAAGCTGGAGATCAAGCGCACAGTGGCAGCCCCCA GCGTCTTCATTTTTCCCCCTTCCGATGAACAGCTGAAGTCCGGC ACTGCTTCTGTGGTCTGTCTGCTGAACAATTTCTATCCCAGAGA GGCCAAGGTGCAGTGGAAAGTGGACAACGCTCTGCAGTCCGG CAACAGCCAGGAGAGTGTGACCGAACAGGATAGTAAGGACAG CACATATTCTCTGTCTAGTACCCTGACACTGAGTAAGGCAGAT TACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACTCATCAG GGACTGTCAAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAG TGT
Ab4H Fab (anti-ASGPR HC, humanized, Fab)	8	CAGGTGCAGCTGGTCCAGTCCGGCGCAGAGGTGAAGAAACCC GGGGCCTCCGTGAAGGTCTCTTGCAAAGCTAGTGGGTACACCT TCACAAACTATTGGATGCACTGGGTGCGACAGGCACCTGGACA GGGCCTGGAATGGATGGGAAGAATCGACCTGAACAGCGGCGG GACTAACTACAATTATGCCCAGAAGTTTCAGGGCAGGGTGACT ATGACCCGCGATACCTCAATTAGCACAGCTTACATGGAGCTGT CACGGCTGAGAAGCGACGATACAGCCGTCTACTATTGTGCTCG GTACTATGGCAGCTCCTGGTTCGCCTATTGGGGGCAGGGAACA CTGGTGACTGTCTCTAGTGCATCAACAAAGGGACCAAGCGTGT

Table 1. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		TTCCACTGGCCCCCTCAAGCAAGAGCACCTCCGGAGGGACAGC CGCTCTGGGATGTCTGGTGAAAGACTACTTCCCCGAGCCTGTG ACTGTCTCTTGGAATAGTGGCGCTCTGACCTCCGGGGTGCACA CATTTCCAGCAGTCCTGCAGTCCTCTGGACTGTATTCTCTGAGT TCAGTGGTCACCGTGCCCAGCTCCTCTCTGGGCACTCAGACCT ACATCTGCAATGTCAACCATAAGCCTAGTAACACAAAAGTGG ATAAGAAAGTCGAACCAAAGAGCTGTGGACAAAACTCACACA
Ab5H (anti-ASGPR HC, humanized, R50W)	9	CAGGTGCAGCTGGTCCAGTCCGGCGCAGAGGTGAAGAAACCC GGGGCCTCCGTGAAGGTCTCTTGCAAAGCTAGTGGGTACACCT TCACAAACTATTGGATGCACTGGGTGCGACAGGCACCTGGACA GGGCCTGGAATGGATGGGATGGATCGACCTGAACAGCGGCGG GACTAACTACAATTATGCCCAGAAGTTTCAGGGCAGGGTGACT ATGACCCGCGATACCTCAATTAGCACAGCTTACATGGAGCTGT CACGGCTGAGAAGCGACGATACAGCCGTCTACTATTGTGCTCG GTACTATGGCAGCTCCTGGTTCGCCTATTGGGGGCAGGGAACA CTGGTGACTGTCTCTAGTGCATCAACAAAGGGACCAAGCGTGT TTCCACTGGCCCCCTCAAGCAAGAGCACCTCCGGAGGGACAGC CGCTCTGGGATGTCTGGTGAAAGACTACTTCCCCGAGCCTGTG ACTGTCTCTTGGAATAGTGGCGCTCTGACCTCCGGGGTGCACA CATTTCCAGCAGTCCTGCAGTCCTCTGGACTGTATTCTCTGAGT TCAGTGGTCACCGTGCCCAGCTCCTCTCTGGGCACTCAGACCT ACATCTGCAATGTCAACCATAAGCCTAGTAACACAAAAGTGG ATAAGAAAGTCGAACCAAAGAGCTGTGACAAAACTCACACAT GCCCACCGTGCCCAGCACCTCCAGTCGCCGGACCGTCAGTCTT CCTCTTCCCTCCAAAACCCAAGGACACCCTCATGATCTCCCGG ACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGG ACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA AAGGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAAAGCCA AAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCTCCATC CCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCT GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCC GTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCA CCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAA GAGCCTCTCCCTGTCTCCGGGTAAA
Ab5H Fab (anti-ASGPR HC, humanized, R50W, Fab)	10	CAGGTGCAGCTGGTCCAGTCCGGCGCAGAGGTGAAGAAACCC GGGGCCTCCGTGAAGGTCTCTTGCAAAGCTAGTGGGTACACCT TCACAAACTATTGGATGCACTGGGTGCGACAGGCACCTGGACA GGGCCTGGAATGGATGGGATGGATCGACCTGAACAGCGGCGG GACTAACTACAATTATGCCCAGAAGTTTCAGGGCAGGGTGACT ATGACCCGCGATACCTCAATTAGCACAGCTTACATGGAGCTGT CACGGCTGAGAAGCGACGATACAGCCGTCTACTATTGTGCTCG GTACTATGGCAGCTCCTGGTTCGCCTATTGGGGGCAGGGAACA

Table 1. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		CTGGTGACTGTCTCTAGTGCATCAACAAAGGGACCAAGCGTGT TTCCACTGGCCCCCTCAAGCAAGAGCACCTCCGGAGGGACAGC CGCTCTGGGATGTCTGGTGAAAGACTACTTCCCCGAGCCTGTG ACTGTCTCTTGGAATAGTGGCGCTCTGACCTCCGGGGTGCACA CATTTCCAGCAGTCCTGCAGTCCTCTGGACTGTATTCTCTGAGT TCAGTGGTCACCGTGCCCAGCTCCTCTCTGGGCACTCAGACCT ACATCTGCAATGTCAACCATAAGCCTAGTAACACAAAAGTGG ATAAGAAAGTCGAACCAAAGAGCTGTGACAAAACTCACACA
Ab1 VH	11	CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTTGTGAAGCCTG GGGCTTCAGTGAAACTGTCCTGCAAGGCTTCTGGCTATACCTT CACCAACTACTGGATGCACTGGGTGAAACAGAGGCCTGGACG AGGCCTTGAGTGGATTGGAAGGATTGATCTTAATAGTGGTGGT ACTAATTACAATTACAATGAGAAGTTCAAGACCAAGGCCACA CTGACTGTAGACAAACCCTCCAGCACAGCCTACATGCAGCTCA GCAGCCTGACATCTGAGGACTCTGCGGTCTATTATTGTGCAAA TTACTACGGTAGTAGCTGGTTTGCTTACTGGGGCCAAGGGACC ACTCTCACAGTCTCCTCA
human IgG1 CH1	12	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCT CCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTAC AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACTGTGCC CTCTAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAACCC AAATCTTGC
Ab1 VL	13	GAAACTGTACTCACCCAGTCTCCAACCACCATGGCTACATCTC CCGGGGAGAAGATCACTATCACCTGCAGTGCCAGCTCAACTAT AAGTTCCAATTACTTGCATTGGTATCAGCAGAAGCCAGGATTC TCCCCTAAACTCTTGATTTATAGGACATCCGATCTGGCTTCTGG AGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTAC TCTCTCACAATTGGCACCATGGAGGCTGAAGATGTTGCCACTT ACTACTGCCAGCAGGGTAGTAGTATACCATTCACGTTCGGCTC GGGGACAAAGTTGGAAATTAAA
human Ig kappa CL	14	CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGA TGAGCAGTTGAAATCTGGAACTGCCTCTGTCGTGTGCCTGCTG AATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTG GATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACG CCTGCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAA GAGCTTCAACAGGGGAGAGTGT
Ab4 VH	15	CAGGTGCAGCTGGTCCAGTCCGGCGCAGAGGTGAAGAAACCC GGGGCCTCCGTGAAGGTCTCTTGCAAAGCTAGTGGGTACACCT TCACAAACTATTGGATGCACTGGGTGCGACAGGCACCTGGACA GGGCCTGGAATGGATGGGAAGAATCGACCTGAACAGCGGCGG GACTAACTACAATTATGCCCAGAAGTTTCAGGGCAGGGTGACT ATGACCCGCGATACCTCAATTAGCACAGCTTACATGGAGCTGT

Table 1. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Nucleic acid sequence		
NAME	SEQ ID NO	SEQUENCE
		CACGGCTGAGAAGCGACGATACAGCCGTCTACTATTGTGCTCG GTACTATGGCAGCTCCTGGTTCGCCTATTGGGGGCAGGGAACA CTGGTGACTGTCTCTAGT
Ab4 VL	16	GAGATCGTGCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCTC CAGGAGAACGAGCCACCCTGTCCTGCTCCGCCTCATCAACAAT TTCTAGTAACTACCTGCACTGGTATCAGCAGAAGCCAGGACAG GCACCTCGACTGCTGATCTACAGAACTAGTGACCTGGCCTCTG GCATTCCCGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACTT TACCCTGACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGTC TACTATTGTCAGCAGGGCTCAAGCATCCCATTCACATTTGGCC AGGGGACTAAGCTGGAGATCAAG
Ab1 VH CDR1	17	GGCTATACCTTCACCAACTACTGGATGCAC
Ab1 VH CDR2	18	AGGATTGATCTTAATAGTGGTGGTACTAATTACAATTACAATG AGAAGTTCAAGACC
Ab1 VH CDR3	19	TACTACGGTAGTAGCTGGTTTGCTTAC
Ab1 VL CDR1	20	AGTGCCAGCTCAACTATAAGTTCCAATTACTTGCAT
Ab1 VL CDR2	21	AGGACATCCGATCTGGCTTCT
Ab1 VL CDR3	22	CAGCAGGGTAGTAGTATACCATTCACG
Ab4L CDR1	23	TCCGCCTCATCAACAATTTCTAGTAACTACCTGCAC
Ab4L CDR2	24	AGAACTAGTGACCTGGCCTCT
Ab4L CDR3	25	CAGCAGGGCTCAAGCATCCCATTCACA
Ab4H CDR1	26	GGGTACACCTTCACAAACTATTGGATGCAC
Ab4H CDR2	27	AGAATCGACCTGAACAGCGGCGGGACTAACTACAATTATGCC CAGAAGTTTCAGGGCA
Ab4H CDR3	28	TACTATGGCAGCTCCTGGTTCGCCTAT

Table 2. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Amino Acid Sequence		
Ab1H (murine anti-ASGPR, HC)	29	QVQLQQPGAELVKPGASVKLSCKASGYTFTNYWMHWVKQRPG RGLEWIGRIDLNSGGTNYNYNEKFKTKATLTVDKPSSTAYMQLS SLTSEDSAVYYCANYYGSSWFAYWGQGTTLTVSSAKTTAPSVYP LAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRG PTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDV SEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQH QDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPE EEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVL DSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFS RTPGK
Ab1L (murine anti-ASGPR, LC)	30	ETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKL LIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGS SIPFTFGSGTKLEINRADTAPTVSIFPPSSEQLTSGGASVVCFLNNF YPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTK DEYERHNSYTCEATHKTSTSPIVKSFNRNEC
Ab2H (Palivizumab HC)	31	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGK ALEWLADIWWDDKKDYNPSLKSRLTISKDTSKNQVVLKVTNMD PADTATYYCARSMITNWYFDVWGAGTTVTVSSASTKGPSVFPLA

Table 2. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Amino Acid Sequence		
		PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
Ab2L (Palivizumab LC)	32	DIQMTQSPSTLSASVGDRVTITCKCQLSVGYMHWYQQKPGKAPK LLIYDTSKLASGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCFQGS GYPFTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ab3L (chimeric anti-ASGPR)	33	ETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKL LIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGS SIPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ab4H (anti-ASGPR HC, humanized)	34	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGRIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
Ab4L (anti-ASGPR LC, humanized)	35	EIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPR LLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGS SIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ab4H Fab (anti-ASGPR HC, humanized, Fab)	36	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGRIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT
Ab5H (anti-ASGPR HC, humanized, R50W)	37	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGWIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL

Table 2. Immunoglobulin Light Chain (LC) and Heavy Chain (HC)–Amino Acid Sequence		
		TVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
Ab5H Fab (anti-ASGPR HC, humanized, R50W, Fab)	38	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGWIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT
Ab1 VH	39	QVQLQQPGAELVKPGASVKLSCKASGYTFTNYWMHWVKQRPG RGLEWIGRIDLNSGGTNYNYNEKFKTKATLTVDKPSSTAYMQLS SLTSEDSAVYYCANYYGSSWFAYWGQGTLVTVSA
human IgG1 CH1	40	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSC
Ab1 VL	41	ETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKL LIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGS SIPFTFGSGTKLEIK
human Ig kappa CL	42	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
Ab4 VH	43	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGRIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSS
Ab4 VL	44	EIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPR LLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGS SIPFTFGQGTKLEIK
Ab1 VH CDR1	45	GYTFTNYWMH
Ab1 VH CDR2	46	RIDLNSGGTNYNYNEKFKT
Ab1 VH CDR3	47	YYGSSWFAY
Ab1 VL CDR1	48	SASSTISSNYLH
Ab1 VL CDR2	49	RTSDLAS
Ab1 VL CDR3	50	QQGSSIPFT
Ab4L CDR1	51	SASSTISSNYLH
Ab4L CDR2	52	RTSDLAS
Ab4L CDR3	53	QQGSSIPFT
Ab4H CDR1	54	GYTFTNYWMH
Ab4H CDR2	55	RIDLNSGGTNYNYAQKFQG
Ab4H CDR3	56	YYGSSWFAY

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
Ins1-L1-Ab1H Single chain	57	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTCACAGC*

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
(insulin1 with connecting peptide C1 connecting insulin B chain and insulin A chain; L1 linker; murine anti-ASGPR LC)		*ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGAGGCAGCCAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTTGTGAAGCCTGGGGCTTCAGTGAAACTGTCCTGCAAGGCTTCTGGCTATACCTTCACCAACTACTGGATGCACTGGGTGAAACAGAGGCCTGGACGAGGCCTTGAGTGGATTGGAAGGATTGATCTTAATAGTGGTGGTACTAATTACAATTACAATGAGAAGTTCAAGACCAAGGCCACACTGACTGTAGACAAACCCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTATTGTGCAAATTACTACGGTAGTAGCTGGTTTGCTTACTGGGGCCAAGGGACCACTCTCACAGTCTCCTCAGCTAAAACAACAGCCCCATCGGTCTATCCACTGGCCCCTGTGTGTGGAGATACAACTGGCTCCTCGGTGACTCTAGGATGCCTGGTCAAGGGTTATTTCCCTGAGCCAGTGACCTTGACCTGGAACTCTGGATCCCTGTCCAGTGGTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACCCTCAGCAGCTCAGTGACTGTAACCTCGAGCACCTGGCCCAGCCAGTCCATCACCTGCAATGTGGCCCACCCGGCAAGCAGCACCAAGGTGGACAAGAAAATTGAGCCCAGAGGGCCCACAATCAAGCCCTGTCCTCCATGCAAATGCCCAGCACCTAACCTCTTGGGTGGACCATCCGTCTTCATCTTCCCTCCAAAGATCAAGGATGTACTCATGATCTCCCTGAGCCCCATAGTCACATGTGTGGTGGTGGATGTGAGCGAGGATGACCCAGATGTCCAGATCAGCTGGTTTGTGAACAACGTGGAAGTACACACAGCTCAGACACAAACCCATAGAGAGGATTACAACAGTACTCTCCGGGTGGTCAGTGCCCTCCCCATCCAGCACCAGGACTGGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACAACAAAGACCTCCCAGCGCCCATCGAGAGAACCATCTCAAAACCCAAAGGGTCAGTAAGAGCTCCACAGGTATATGTCTTGCCTCCACCAGAAGAAGAGATGACTAAGAAACAGGTCACTCTGACCTGCATGGTCACAGACTTCATGCCTGAAGACATTTACGTGGAGTGGACCAACAACGGGAAAACAGAGCTAAACTACAAGAACACTGAACCAGTCCTGGACTCTGATGGTTCTTACTTCATGTACAGCAAGCTGAGAGTGGAAAAGAAGAACTGGGTGGAAAGAAATAGCTACTCCTGTTCAGTGGTCCACGAGGGTCTGCACAATCACCACACGACTAAGAGCTTCTCCCGGACTCCGGGTAA
Ins1-L1-Ab1L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L1 linker; murine anti-ASGPR LC)	58	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCTACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG GCGGAGGGCCCCGCCGG*GGCATTGTGGAACAATGCTGTCACAGC*ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGAGGCAGCGAAACTGTACTCACCCAGTCTCCAACCACCATGGCTACATCTCCCGGGGAGAAGATCACTATCACCTGCAGTGCCAGCTCAACTATAAGTTCCAATTACTTGCATTGGTATCAGCAGAAGCCAGGATTCTCCCCTAAACTCTTGATTTATAGGACATCCGATCTGGCTTCTGGAGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATTGGCACCATGGAGGCTGAAGATGTTGCCACTTACTACTGCCAGCAGGGTAGTAGTATACCATTCACGTTCGGCTCGGGGACAAAGCTGGAGATTAACCGGGCAGATACAGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCC

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		CAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACG ACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAGCAA AGACAGCACCTACAGCATGAGCAGCACCCTCACGTTGACCAA GGACGAGTATGAACGACATAACAGCTATACCTGTGAGGCCAC TCACAAGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGG AATGAGTGT
Ins1-L1-Ab2L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L1 linker; palivizumab LC)	59	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* *GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTCACAGC* *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGA GGCAGCGACATCCAGATGACCCAGTCCCCCTCCACCCTGTCCG CCTCCGTGGGCGACCGCGTGACCATCACCTGCAAGTGCCAGCT GTCCGTGGGCTACATGCACTGGTACCAGCAGAAGCCCGGCAA GGCCCCCAAGCTGCTGATCTACGACACCTCCAAGCTGGCCTCC GGCGTGCCCTCCCGCTTCTCCGGCTCCGGCTCCGGCACCGAGT TCACCCTGACCATCTCCTCCCTGCAGCCCGACGACTTCGCCAC CTACTACTGCTTCCAGGGCTCCGGCTACCCCTTCACCTTCGGCG GCGGCACCAAGCTGGAGATCAAACGAACTGTGGCTGCACCAT CTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCAGAG AGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGG GTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACA GCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAG ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC AGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGTTGA
Ins2-L2-Ab3L Dual chain (insulin2 B chain with C3 connecting peptide, n=4; insulin2 A chain; L2 linker; chimeric anti-ASGPR LC)	60	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* *GCGGGGGAGGCAGCGGGGGAGGCGGGTCCGGAGGCGGGGGAT* *CTGGCGGGGGAGGCAGTCGGAAAAAGCGTGGCATTGTGGAACAA* *TGCTGTCACAGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGCA* *AC*GGAGGCCCTTCCTCCGGAGCTCCACCTCCGTCCGGGGGTGG CGGAGGCGAAACTGTACTCACCCAGTCTCCAACCACCATGGCT ACATCTCCCGGGGAGAAGATCACTATCACCTGCAGTGCCAGCT CAACTATAAGTTCCAATTACTTGCATTGGTATCAGCAGAAGCC AGGATTCTCCCCTAAACTCTTGATTTATAGGACATCCGATCTG GCTTCTGGAGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGA CCTCTTACTCTCTCACAATTGGCACCATGGAGGCTGAAGATGT TGCCACTTACTACTGCCAGCAGGGTAGTAGTATACCATTCACG TTCGGCTCGGGGACAAAGTTGGAAATTAAACGAACTGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA TCTGGAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCC CAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCA ATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAA GGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAC CCATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGG

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		GGAGAGTGTTGA
Ins3-L2-Ab3L Single chain (insulin3 chain with C2 connecting peptide, n=2, connecting B chain and A chain; L2 linker; chimeric anti-ASGPR LC)	61	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G GAGGCGGGGGGATCTGGCGGGGGGAGGCAGT*GGCATTGTGGAACA ATGCTGTCACAGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGC AAC*GGAGGCCCTTCCTCCGGAGCTCCACCTCCGTCCGGGGGTG GCGGAGGCGAAACTGTACTCACCCAGTCTCCAACCACCATGGC TACATCTCCCGGGGAGAAGATCACTATCACCTGCAGTGCCAGC TCAACTATAAGTTCCAATTACTTGCATTGGTATCAGCAGAAGC CAGGATTCTCCCCTAAACTCTTGATTTATAGGACATCCGATCTG GCTTCTGGAGTCCCAACTCGCTTCAGTGGCAGTGGGTCTGGGA CCTCTTACTCTCTCACAATTGGCACCATGGAGGCTGAAGATGT TGCCACTTACTACTGCCAGCAGGGTAGTAGTATACCATTCACG TTCGGCTCGGGGACAAAGTTGGAAATTAAACGAACTGTGGCTG CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA TCTGGAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCC CAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCA ATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAA GGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAA AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAC CCATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGG GGAGAGTGTTGA*
Ins3-L2-Ab3L Dual chain (insulin 3 B chain with C3 connecting peptide, n=4; insulin3 A chain; L2 linker; anti-ASGPR LC)	62	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G *GAGGCGGGGGGATCTGGCGGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTCACAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*GGAGGCCCTTCCTCCGGAGCTCCACCTCC GTCCGGGGGTGGCGGAGGCGAAACTGTACTCACCCAGTCTCCA ACCACCATGGCTACATCTCCCGGGGAGAAGATCACTATCACCT GCAGTGCCAGCTCAACTATAAGTTCCAATTACTTGCATTGGTA TCAGCAGAAGCCAGGATTCTCCCCTAAACTCTTGATTTATAGG ACATCCGATCTGGCTTCTGGAGTCCCAACTCGCTTCAGTGGCA GTGGGTCTGGGACCTCTTACTCTCTCACAATTGGCACCATGGA GGCTGAAGATGTTGCCACTTACTACTGCCAGCAGGGTAGTAGT ATACCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATTAAAC GAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT GAGCAGTTGAAATCTGGAACTGCCTCTGTCGTGTGCCTGCTGA ATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGA GCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCT GACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGC CTGCGAAGTCACCCATCAGGGCCTGTCCTCGCCCGTCACAAAG AGCTTCAACAGGGGAGAGTGTTGA*
Ins1-L3-Ab4L Single chain (insulin1 with	63	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G GCGGAGGGCCCCGCCGG*GGCATTGTGGAACAATGCTGTCACAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGGGGTGGC

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)		GAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCTGCA AAGGCAGGAGGCGAGATCGTGCTGACTCAGAGCCCAGGAACC CTGTCCCTGTCTCCAGGAGAACGAGCCACCCTGTCCTGCTCCG CCTCATCAACAATTTCTAGTAACTACCTGCACTGGTATCAGCA GAAGCCAGGACAGGCACCTCGACTGCTGATCTACAGAACTAG TGACCTGGCCTCTGGCATTCCCGATAGGTTCAGCGGCTCCGGG TCTGGAACAGACTTTACCCTGACAATCTCCCGCCTGGAGCCTG AAGATTTCGCTGTCTACTATTGTCAGCAGGGCTCAAGCATCCC ATTCACATTTGGCCAGGGGACTAAGCTGGAGATCAAGCGCAC AGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTTCCGATGAAC AGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCTGCTGAACAA TTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAAAGTGGACAA CGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGTGACCGAACA GGATAGTAAGGACAGCACATATTCTCTGTCTAGTACCCTGACA CTGAGTAAGGCAGATTACGAGAAGCACAAAGTGTATGCCTGC GAAGTCACTCATCAGGGACTGTCAAGCCCCGTGACCAAGAGCT TCAACCGGGGCGAGTGT
Ins4-L3-Ab4L Dual chain (insulin4 B chain with C3 connecting peptide, n=2; insulin4 A chain; L3 linker; anti-ASGPR, humanized LC)	64	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GAGGCGGGGGGATCTGGCGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*GGGGGTGGCGAAGCAGCTGCTAAGGAGG CAGCCGCAAAGGAAGCAGCTGCAAAGGCAGGAGGCGAGATCG TGCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCTCCAGGAGA ACGAGCCACCCTGTCCTGCTCCGCCTCATCAACAATTTCTAGT AACTACCTGCACTGGTATCAGCAGAAGCCAGGACAGGCACCT CGACTGCTGATCTACAGAACTAGTGACCTGGCCTCTGGCATTC CCGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACTTTACCCT GACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGTCTACTAT TGTCAGCAGGGCTCAAGCATCCCATTCACATTTGGCCAGGGGA CTAAGCTGGAGATCAAGCGCACAGTGGCAGCCCCCAGCGTCTT CATTTTTCCCCCTTCCGATGAACAGCTGAAGTCCGGCACTGCTT CTGTGGTCTGTCTGCTGAACAATTTCTATCCCAGAGAGGCCAA GGTGCAGTGGAAAGTGGACAACGCTCTGCAGTCCGGCAACAG CCAGGAGAGTGTGACCGAACAGGATAGTAAGGACAGCACATA TTCTCTGTCTAGTACCCTGACACTGAGTAAGGCAGATTACGAG AAGCACAAAGTGTATGCCTGCGAAGTCACTCATCAGGGACTGT CAAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGT
Ins4-L3-Ab2L Dual chain (insulin4 B chain with C3 connecting peptide, n=2; insulin4 A chain; L3 linker;	65	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GAGGCGGGGGGATCTGGCGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*GGGGGTGGCGAAGCAGCTGCTAAGGAGG CAGCCGCAAAGGAAGCAGCTGCAAAGGCAGGAGGCGACATCC AGATGACCCAGTCCCCCTCCACCCTGTCCGCCTCCGTGGGCGA CCGCGTGACCATCACCTGCAAGTGCCAGCTGTCCGTGGGCTAC ATGCACTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
palivizumab LC)		CTGATCTACGACACCTCCAAGCTGGCCTCCGGCGTGCCCTCCC GCTTCTCCGGCTCCGGCTCCGGCACCGAGTTCACCCTGACCAT CTCCTCCCTGCAGCCCGACGACTTCGCCACCTACTACTGCTTCC AGGGCTCCGGCTACCCCTTCACCTTCGGCGGCGGCACCAAGCT GGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTCG TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGA GAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACA CAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGTCCTCG CCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
Ins1-L4-Ab4L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L4 linker; anti-ASGPR, humanized LC)	66	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G GCGGAGGGCCCCGCCGG*GGCATTGTGGAACAATGCTGTCACAGC* *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGA GGCAGCGGGGGTGGCGAAGCAGCTGCTAAGGAGGCAGCCGCA AAGGAAGCAGCTGCAAAGGCAGGAGGCGAGATCGTGCTGACT CAGAGCCCAGGAACCCTGTCCCTGTCTCCAGGAGAACGAGCC ACCCTGTCCTGCTCCGCCTCATCAACAATTTCTAGTAACTACCT GCACTGGTATCAGCAGAAGCCAGGACAGGCACCTCGACTGCT GATCTACAGAACTAGTGACCTGGCCTCTGGCATTCCCGATAGG TTCAGCGGCTCCGGGTCTGGAACAGACTTTACCCTGACAATCT CCCGCCTGGAGCCTGAAGATTTCGCTGTCTACTATTGTCAGCA GGGCTCAAGCATCCCATTCACATTTGGCCAGGGGACTAAGCTG GAGATCAAGCGCACAGTGGCAGCCCCCAGCGTCTTCATTTTTC CCCCTTCCGATGAACAGCTGAAGTCCGGCACTGCTTCTGTGGT CTGTCTGCTGAACAATTTCTATCCCAGAGAGGCCAAGGTGCAG TGGAAAGTGGACAACGCTCTGCAGTCCGGCAACAGCCAGGAG AGTGTGACCGAACAGGATAGTAAGGACAGCACATATTCTCTGT CTAGTACCCTGACACTGAGTAAGGCAGATTACGAGAAGCACA AAGTGTATGCCTGCGAAGTCACTCATCAGGGACTGTCAAGCCC CGTGACCAAGAGCTTCAACCGGGGCGAGTGT
Ins1-L5-Ab4L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L5 linker; anti-ASGPR, humanized LC)	67	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G GCGGAGGGCCCCGCCGG*GGCATTGTGGAACAATGCTGTCACAGC* *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGGGGTGGC GAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCTGCA AAGGCAGGTGGCGGAGGCAGCGGAGGCGAGATCGTGCTGACT CAGAGCCCAGGAACCCTGTCCCTGTCTCCAGGAGAACGAGCC ACCCTGTCCTGCTCCGCCTCATCAACAATTTCTAGTAACTACCT GCACTGGTATCAGCAGAAGCCAGGACAGGCACCTCGACTGCT GATCTACAGAACTAGTGACCTGGCCTCTGGCATTCCCGATAGG TTCAGCGGCTCCGGGTCTGGAACAGACTTTACCCTGACAATCT CCCGCCTGGAGCCTGAAGATTTCGCTGTCTACTATTGTCAGCA GGGCTCAAGCATCCCATTCACATTTGGCCAGGGGACTAAGCTG GAGATCAAGCGCACAGTGGCAGCCCCCAGCGTCTTCATTTTTC

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		CCCCTTCCGATGAACAGCTGAAGTCCGGCACTGCTTCTGTGGT CTGTCTGCTGAACAATTTCTATCCCAGAGAGGCCAAGGTGCAG TGGAAAGTGGACAACGCTCTGCAGTCCGGCAACAGCCAGGAG AGTGTGACCGAACAGGATAGTAAGGACAGCACATATTCTCTGT CTAGTACCCTGACACTGAGTAAGGCAGATTACGAGAAGCACA AAGTGTATGCCTGCGAAGTCACTCATCAGGGACTGTCAAGCCC CGTGACCAAGAGCTTCAACCGGGGCGAGTGT
Ins1-L6-Ab4L (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L6 linker; anti-ASGPR, humanized LC)	68	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACC*G GCGGAGGGCCCCGCCGG*GGCATTGTGGAACAATGCTGTCACAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGA GGCAGCGGGGGTGGCGAAGCAGCTGCTAAGGAGGCAGCCGCA AAGGAAGCAGCTGCAAAGGCAGGTGGCGGAGGCAGCGGAGG CGAGATCGTGCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCT CCAGGAGAACGAGCCACCCTGTCCTGCTCCGCCTCATCAACAA TTTCTAGTAACTACCTGCACTGGTATCAGCAGAAGCCAGGACA GGCACCTCGACTGCTGATCTACAGAACTAGTGACCTGGCCTCT GGCATTCCCGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACT TTACCCTGACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGT CTACTATTGTCAGCAGGGCTCAAGCATCCCATTCACATTTGGC CAGGGGACTAAGCTGGAGATCAAGCGCACAGTGGCAGCCCCC AGCGTCTTCATTTTTCCCCCTTCCGATGAACAGCTGAAGTCCGG CACTGCTTCTGTGGTCTGTCTGCTGAACAATTTCTATCCCAGAG AGGCCAAGGTGCAGTGGAAAGTGGACAACGCTCTGCAGTCCG GCAACAGCCAGGAGAGTGTGACCGAACAGGATAGTAAGGACA GCACATATTCTCTGTCTAGTACCCTGACACTGAGTAAGGCAGA TTACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACTCATCAG GGACTGTCAAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAG TGT*
Ab4-L7-Ins5 Single chain (anti-ASGPR, humanized LC; L7 linker; insulin5 within C4 connecting peptide connecting insulin A chain to insulin B chain)	69	GAGATCGTGCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCTC CAGGAGAACGAGCCACCCTGTCCTGCTCCGCCTCATCAACAAT TTCTAGTAACTACCTGCACTGGTATCAGCAGAAGCCAGGACAG GCACCTCGACTGCTGATCTACAGAACTAGTGACCTGGCCTCTG GCATTCCCGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACTT TACCCTGACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGTC TACTATTGTCAGCAGGGCTCAAGCATCCCATTCACATTTGGCC AGGGGACTAAGCTGGAGATCAAGCGCACAGTGGCAGCCCCCA GCGTCTTCATTTTTCCCCCTTCCGATGAACAGCTGAAGTCCGGC ACTGCTTCTGTGGTCTGTCTGCTGAACAATTTCTATCCCAGAGA GGCCAAGGTGCAGTGGAAAGTGGACAACGCTCTGCAGTCCGG CAACAGCCAGGAGAGTGTGACCGAACAGGATAGTAAGGACAG CACATATTCTCTGTCTAGTACCCTGACACTGAGTAAGGCAGAT TACGAGAAGCACAAAGTGTATGCCTGCGAAGTCACTCATCAG GGACTGTCAAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAG TGTGGCGGAGGTGGTTCTGGGGGAAGCCCC*GGAATCGTAGAGC AGTGTTGTACCAGTATTTGCAGCCTCTATCAGCTCGAGAACTATTGT AATGGCGGAGGGTCCGGCGGTGGGAGCGGCTTCGTGAATCAACA*

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		CCTGTGCGGGTCCCACCTGGTGGAAGCGTTGTATCTTGTCTGCGG GGAAAGGGGTTTCTTCTACACACCGAAGACC
Ins4-L6-Ab4 Dual chain (insulin4 B chain with C3 connecting peptide, n=2; insulin4 A chain; L6 linker; anti-ASGPR, humanized LC)	70	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GAGGCGGGGGGATCTGGCGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*GGTGGCGGAGGCAGCGGGGGTGGCGAAG CAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCTGCAAAGG CAGGTGGCGGAGGCAGCGGAGGCGAGATCGTGCTGACTCAGA GCCCAGGAACCCTGTCCCTGTCTCCAGGAGAACGAGCCACCCT GTCCTGCTCCGCCTCATCAACAATTTCTAGTAACTACCTGCACT GGTATCAGCAGAAGCCAGGACAGGCACCTCGACTGCTGATCT ACAGAACTAGTGACCTGGCCTCTGGCATTCCCGATAGGTTCAG CGGCTCCGGGTCTGGAACAGACTTTACCCTGACAATCTCCCGC CTGGAGCCTGAAGATTTCGCTGTCTACTATTGTCAGCAGGGCT CAAGCATCCCATTCACATTTGGCCAGGGGACTAAGCTGGAGAT CAAGCGCACAGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTT CCGATGAACAGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCT GCTGAACAATTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAA AGTGGACAACGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGT GACCGAACAGGATAGTAAGGACAGCACATATTCTCTGTCTAGT ACCCTGACACTGAGTAAGGCAGATTACGAGAAGCACAAAGTG TATGCCTGCGAAGTCACTCATCAGGGACTGTCAAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGT
Ins6-L6-Ab4 Dual chain (insulin6 B chain with C7 connecting peptide, n=2; insulin6 A chain; L6 linker; anti-ASGPR, humanized LC)	71	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCC GGAAAAAGCGTGGCGGGGGAGGCAGCGGGGGAGGCGGGTCCCG GAAAAAGCGTGGCATTGTGGAACAATGCTGTACCAGCATCTGCTCC CTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGAGGCAGCGG GGGTGGCGAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGC AGCTGCAAAGGCAGGTGGCGGAGGCAGCGGAGGCGAGATCGT GCTGACTCAGAGCCCAGGAACCCTGTCCCTGTCTCCAGGAGAA CGAGCCACCCTGTCCTGCTCCGCCTCATCAACAATTTCTAGTA ACTACCTGCACTGGTATCAGCAGAAGCCAGGACAGGCACCTC GACTGCTGATCTACAGAACTAGTGACCTGGCCTCTGGCATTCC CGATAGGTTCAGCGGCTCCGGGTCTGGAACAGACTTTACCCTG ACAATCTCCCGCCTGGAGCCTGAAGATTTCGCTGTCTACTATT GTCAGCAGGGCTCAAGCATCCCATTCACATTTGGCCAGGGGAC TAAGCTGGAGATCAAGCGCACAGTGGCAGCCCCCAGCGTCTTC ATTTTTCCCCCTTCCGATGAACAGCTGAAGTCCGGCACTGCTTC TGTGGTCTGTCTGCTGAACAATTTCTATCCCAGAGAGGCCAAG GTGCAGTGGAAAGTGGACAACGCTCTGCAGTCCGGCAACAGC CAGGAGAGTGTGACCGAACAGGATAGTAAGGACAGCACATAT TCTCTGTCTAGTACCCTGACACTGAGTAAGGCAGATTACGAGA AGCACAAAGTGTATGCCTGCGAAGTCACTCATCAGGGACTGTC AAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGT
Ins1-L1-	72	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT*

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
herceptin HC single chain (insulin1 with connecting peptide C1 connecting insulin B chain and insulin A chain; L1 linker; herceptin HC)		*ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* *GCGGAGGGCCCCCGCCGGGGCATTGTGGAACAATGCTGTCACAGC* *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGA GGCAGCGAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGGTC CAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGGT TCAATATTAAGGACACTTACATCCACTGGGTCCGCCAGGCTCC AGGGAAGGGGCTGGAGTGGGTCGCACGTATTTATCCTACCAAT GGTTACACACGCTACGCAGACTCCGTGAAGGGCCGATTCACCA TCTCCGCAGACACTTCCAAGAACACGGCGTATCTTCAAATGAA CAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTTCGAGA TGGGGCGGTGACGGCTTCTATGCCATGGACTACTGGGGCCAAG GAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATC GGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAAC CGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGT GCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCA GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAA GGTGGACAAGAAAGTTGAACCCAAATCTTGCGACAAAACTCA CACATGCCCACCGTGCCCAGCACCTCCAGTCGCCGGACCGTCA GTCTTCCTCTTCCCTCCAAAACCCAAGGACACCCTCATGATCTC CCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCA ACAAAGGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAAAG CCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCTC CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCC TCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGC TCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCA GAAGAGCCTCTCCCTGTCTCCGGGTAAA
Ins1-L1-herceptin LC single chain (insulin1 with connecting peptide C1 connecting insulin B chain and insulin A chain; L1 linker; herceptin LC)	73	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* *GCGGAGGGCCCCCGCCGGGGCATTGTGGAACAATGCTGTCACAGC* *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGTGGCGGA GGCAGCGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTG CATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA GGATGTGAATACCGCGGTCGCATGGTATCAGCAGAAACCAGG GAAAGCCCCTAAGCTCCTGATCTATTCTGCATCCTTCTTGTATA GTGGGGTCCCATCAAGGTTCAGTGGCAGTAGATCTGGGACAG ATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGC AACTTACTACTGTCAACAGCATTACACTACCCCTCCGACGTTC GGCCAAGGTACCAAGGTTGAGATCAAACGAACTGTGGCTGCA

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATC TGGAACTGCCTCTGTCGTGTGCCTGCTGAATAACTTCTATCCCA GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT CGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAG CAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC ATCAGGGCCTGTCCTCGCCCGTCACAAAGAGCTTCAACAGGGG AGAGTGT
Ins4-L6-Ab4L (Fab) (insulin4 B chain after RKKR cleavage of C3 connecting peptide, n=2; insulin4 A chain; L6 linker; anti-ASGPR, humanized LC)	74	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG* *GCGGGGGAGGCAGCGGGGGAGGCGGGTCCCGGAAAAAGCGTGG* *CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG* *GAGAACTACTGCAAC*GGTGGCGGAGGCAGCGGGGGTGGCGAAG CAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCTGCAAAGG CAGGTGGCGGAGGCAGCGGAGGCGAGATCGTGCTGACTCAGA GCCCAGGAACCCTGTCCCTGTCTCCAGGAGAACGAGCCACCCT GTCCTGCTCCGCCTCATCAACAATTTCTAGTAACTACCTGCACT GGTATCAGCAGAAGCCAGGACAGGCACCTCGACTGCTGATCT ACAGAACTAGTGACCTGGCCTCTGGCATTCCCGATAGGTTCAG CGGCTCCGGGTCTGGAACAGACTTTACCCTGACAATCTCCCGC CTGGAGCCTGAAGATTTCGCTGTCTACTATTGTCAGCAGGGCT CAAGCATCCCATTCACATTTGGCCAGGGGACTAAGCTGGAGAT CAAGCGCACAGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTT CCGATGAACAGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCT GCTGAACAATTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAA AGTGGACAACGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGT GACCGAACAGGATAGTAAGGACAGCACATATTCTCTGTCTAGT ACCCTGACACTGAGTAAGGCAGATTACGAGAAGCACAAAGTG TATGCCTGCGAAGTCACTCATCAGGGACTGTCAAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGT
Ins1-L3-Ab5L single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	75	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT* *ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* *GCGGAGGGCCCCGCCGG**GGCATTGTGGAACAATGCTGTCACAGC*** *ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*GGGGGTGGC GAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCTGCA AAGGCAGGAGGCGAGATCGTGCTGACTCAGAGCCCAGGAACC CTGTCCCTGTCTCCAGGAGAACGAGCCACCCTGTCCTGCTCCG CCTCATCAACAATTTCTAGTAACTACCTGCACTGGTATCAGCA GAAGCCAGGACAGGCACCTCGACTGCTGATCTACAGAACTAG TGACCTGGCCTCTGGCATTCCCGATAGGTTCAGCGGCTCCGGG TCTGGAACAGACTTTACCCTGACAATCTCCCGCCTGGAGCCTG AAGATTTCGCTGTCTACTATTGTCAGCAGGGCTCAAGCATCCC ATTCACATTTGGCCAGGGGACTAAGCTGGAGATCAAGCGCAC AGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTTCCGATGAAC AGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCTGCTGAACAA TTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAAAGTGGACAA CGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGTGACCGAACA

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
		GGATAGTAAGGACAGCACATATTCTCTGTCTAGTACCCTGACA CTGAGTAAGGCAGATTACGAGAAGCACAAAGTGTATGCCTGC GAAGTCACTCATCAGGGACTGTCAAGCCCCGTGACCAAGAGCT TCAACCGGGGCGAGTGT
Ins7-L3-Ab4L single chain (insulin7 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	76	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTACCAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC***GGGGGTGG CGAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCT GCAAAGGCAGGAGGC***GAGATCGTGCTGACTCAGAGCCCAGG AACCCTGTCCCTGTCTCCAGGAGAACGAGCCACCCTGTCCTGC TCCGCCTCATCAACAATTTCTAGTAACTACCTGCACTGGTATCA GCAGAAGCCAGGACAGGCACCTCGACTGCTGATCTACAGAAC TAGTGACCTGGCCTCTGGCATTCCCGATAGGTTCAGCGGCTCC GGGTCTGGAACAGACTTTACCCTGACAATCTCCCGCCTGGAGC CTGAAGATTTCGCTGTCTACTATTGTCAGCAGGGCTCAAGCAT CCCATTCACATTTGGCCAGGGGACTAAGCTGGAGATCAAGCGC ACAGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTTCCGATGA ACAGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCTGCTGAAC AATTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAAAGTGGAC AACGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGTGACCGAA CAGGATAGTAAGGACAGCACATATTCTCTGTCTAGTACCCTGA CACTGAGTAAGGCAGATTACGAGAAGCACAAAGTGTATGCCT GCGAAGTCACTCATCAGGGACTGTCAAGCCCCGTGACCAAGA GCTTCAACCGGGGCGAGTGT*
Ins7-L3-Ab5L single chain (insulin7 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	77	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTACCAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC***GGGGGTGG CGAAGCAGCTGCTAAGGAGGCAGCCGCAAAGGAAGCAGCT GCAAAGGCAGGAGGC***GAGATCGTGCTGACTCAGAGCCCAGG AACCCTGTCCCTGTCTCCAGGAGAACGAGCCACCCTGTCCTGC TCCGCCTCATCAACAATTTCTAGTAACTACCTGCACTGGTATCA GCAGAAGCCAGGACAGGCACCTCGACTGCTGATCTACAGAAC TAGTGACCTGGCCTCTGGCATTCCCGATAGGTTCAGCGGCTCC GGGTCTGGAACAGACTTTACCCTGACAATCTCCCGCCTGGAGC CTGAAGATTTCGCTGTCTACTATTGTCAGCAGGGCTCAAGCAT CCCATTCACATTTGGCCAGGGGACTAAGCTGGAGATCAAGCGC ACAGTGGCAGCCCCCAGCGTCTTCATTTTTCCCCCTTCCGATGA ACAGCTGAAGTCCGGCACTGCTTCTGTGGTCTGTCTGCTGAAC AATTTCTATCCCAGAGAGGCCAAGGTGCAGTGGAAAGTGGAC AACGCTCTGCAGTCCGGCAACAGCCAGGAGAGTGTGACCGAA CAGGATAGTAAGGACAGCACATATTCTCTGTCTAGTACCCTGA CACTGAGTAAGGCAGATTACGAGAAGCACAAAGTGTATGCCT GCGAAGTCACTCATCAGGGACTGTCAAGCCCCGTGACCAAGA GCTTCAACCGGGGCGAGTGT*
For SEQ ID NOS: 57-77		

Table 3. Immunoglobulin fusion protein –Nucleic acid sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
Immunoglobulin region = dashed underline Therapeutic peptide = *italic* Therapeutic peptide connecting peptide = *italic* Linker = bold, thick underline		

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
Ins1-L1-Ab1H Single chain (insulin1 with connecting peptide GGGPRR connecting insulin B chain and insulin A chain; GGGGS linker; murine anti-ASGPR HC)	78	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGGSQVQLQQPGAELVKPGASVKLSCKASGYTFT NYWMHWVKQRPGRGLEWIGRIDLNSGGTNYNYNEKFKTKATLT VDKPSSTAYMQLSSLTSEDSAVYYCANYYGSSWFAYWGQGTTL TVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTW NSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVL MISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKG SVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNG KTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVV HEGLHNHHTTKSFSRTPGK
Ins1-L1-Ab1L Single chain (insulin1 with connecting peptide GGGPRR connecting insulin B chain and insulin A chain; GGGGS linker; murine anti-ASGPR LC)	79	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGGSETVLTQSPTTMATSPGEKITITCSASSTISSNY LHWYQQKPGFSPKLLIYRTSDLASGVPTRFSGSGSGTSYSLTIGTM EAEDVATYYCQQGSSIPFTFGSGTKLEINRADTAPTVSIFPPSSEQL TSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSK DSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC
Ins1-L1-Ab2L Single chain (insulin1 with connecting peptide GGGPRR connecting insulin B chain and insulin A chain; GGGGS linker;	80	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGGSDIQMTQSPSTLSASVGDRVTITCKCQLSVGY MHWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTEFTLTISSL QPDDFATYYCFQGSGYPFTFGGGTKLEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
palivizumab LC)		
Ins2-L2-Ab3L Dual chain (insulin2 B chain with C3 connecting peptide, n=4, after proteolytic cleavage at RKKR; insulin2 A chain; CEX5G linker; chimeric anti-ASGPR LC)	81	B CHAIN: *FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGSGGGGSGGGGS* A CHAIN: *GIVEQCCHSICSLYQLENYCN*GGPSSGAPPPSGGGGGETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKLLIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGSSIPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins3-L2-Ab3L Single chain (insulin3 chain with C2 connecting peptide, n=2, connecting B chain and A chain; CEX5G linker; chimeric anti-ASGPR LC)	82	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGSGIVEQCCHSICSLYQLENYCN*GGPSSGAPPPSGGGGGETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKLLIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGSSIPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins3-L2-Ab3L Dual chain (insulin3 B chain with C3 connecting peptide, n=2, after proteolytic cleavage at RKKR; insulin3 A chain; CEX5G linker; chimeric anti-ASGPR LC)	83	B CHAIN: *FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGS* A CHAIN: *GIVEQCCHSICSLYQLENYCN*GGPSSGAPPPSGGGGGETVLTQSPTTMATSPGEKITITCSASSTISSNYLHWYQQKPGFSPKLLIYRTSDLASGVPTRFSGSGSGTSYSLTIGTMEAEDVATYYCQQGSSIPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins1-L3-Ab4L Single chain (insulin1 with C1 connecting	84	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSICSLYQLENYCN*GGGEAAAKEAAAKEAAAKAGGEIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)		NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
Ins4-L3-Ab4L Dual chain (insulin4 B chain with C3 connecting peptide, n=2, after proteolytic cleavage at RKKR; L3 linker; anti-ASGPR, humanized LC)	85	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*GGGEAAAKEAAAKEAAAKAGGEIVL TQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIY RTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPF TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins4-L3-Ab2L Dual chain (insulin4 B chain with C3 connecting peptide, n=2, after proteolytic cleavage at RKKR; insulin4 A chain; L3 linker; palivizumab LC)	86	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*GGGEAAAKEAAAKEAAAKAGGDIQ MTQSPSTLSASVGDRVTITCKCQLSVGYMHWYQQKPGKAPKLLI YDTSKLASGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCFQGSGY PFTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins1-L4-Ab4L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L4 linker; anti-ASGPR, humanized LC)	87	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGGSGGGEAAAKEAAAKEAAAKAGGEIVLTQSP GTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSD LASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC
Ins1-L5-Ab4L Single chain	88	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGEAAAKEAAAKEAAAKAGGGGSGGEIVLTQSP

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
(insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L5 linker; anti-ASGPR, humanized LC)		GTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSD LASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC
Ins1-L6-Ab4L Single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L6 linker; anti-ASGPR, humanized LC)	89	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*GGGGSGGGEAAAKEAAAKEAAAKAGGGGSGGEIV LTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLI YRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIP FTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ab4L-L7-Ins5 Single chain (anti-ASGPR, humanized LC; L7 linker; insulin5 within C4 connecting peptide connecting insulin A chain to insulin B chain)	90	EIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPR LLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGS SIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSGGSP*GIVE QCCTSICSLYQLENYCNGGGSGGGSGFVNQHLCGSHLVEALYLVCGE RGFFYTPKT*
Ins4-L6-Ab4 Dual chain (insulin4 B chain with C3 connecting peptide, n=2, after proteolytic cleavage at RKKR; insulin4 A chain; L6 linker; anti-	91	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*GGGGSGGGEAAAKEAAAKEAAAKA GGGGSGGEIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQ KPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAV YYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
ASGPR, humanized LC)		
Ins6-L6-Ab4 Dual chain (insulin6 B chain after RKKR cleavage of C7 connecting peptide; insulin6 A chain; L6 linker; anti-ASGPR, humanized LC)	92	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKT* A CHAIN: *GIVEQCCTSICSLYQLENYCN*GGGGSGGGEAAAKEAAAKEAAAKA GGGGSGGEIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQ KPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAV YYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins1-L1-herceptin HC single chain (insulin1 with connecting peptide C1 connecting insulin B chain and insulin A chain; L1 linker; herceptin HC)	93	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC* *SLYQLENYCN*GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNIK DTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADT SKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
Ins1-L1-herceptin LC single chain (insulin1 with connecting peptide C1 connecting insulin B chain and insulin A chain; L1 linker; herceptin LC)	94	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC* *SLYQLENYCN*GGGGSDIQMTQSPSSLSASVGDRVTITCRASQDVNT AVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISS LQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
Ins4-L6-Ab4L (Fab) (insulin4 B chain after RKKR cleavage of C3 connecting	95	HEAVY CHAIN: QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPG QGLEWMGRIDLNSGGTNYNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARYYGSSWFAYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT LIGHT CHAIN:

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
peptide, n=2; insulin4 A chain; L6 linker; anti-ASGPR, humanized LC)		B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCNGGGGS*GGGEAAAKEAAAKEAAAKAGGGGSGGEIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins1-L3-Ab5L (Fab) single chain (insulin1 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	96	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSICSLYQLENYCN*GGGEAAAKEAAAKEAAAKAGGEIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins7-L3-Ab4L Single chain (insulin7 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	97	*FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGPRRGIVEQCCTSICSLYQLENYCN***GGGEAAAKEAAAKEAAAKAGG**EIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Ins7-L3-Ab5L Single chain (insulin7 with C1 connecting peptide connecting insulin B chain and insulin A chain; L3 linker; anti-ASGPR, humanized LC)	98	*FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGPRRGIVEQCCTSICSLYQLENYCN***GGGEAAAKEAAAKEAAAKAGG**EIVLTQSPGTLSLSPGERATLSCSASSTISSNYLHWYQQKPGQAPRLLIYRTSDLASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQGSSIPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
For SEQ ID NOS: 78-98		

Table 4. Immunoglobulin fusion protein – Protein Sequence		
NAME	**SEQ ID NO**	**SEQUENCE**
Immunoglobulin region = dashed underline Therapeutic peptide = *italic* Therapeutic peptide connecting peptide = *italic* Linker = **bold, thick underline**		

Table 5. Therapeutic Peptides–Nucleic acid sequence		
Name	**SEQ ID NO**	**Sequence**
Ins1 with C1 connecting peptide Single chain	99	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTCACAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*
Ins2 with C3 connecting peptide Dual chain	100	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG GCGGGGGAGGCAGCGGGGGAGGCGGGTCCGGAGGCGGGGGAT CTGGCGGGGGAGGCAGTCGGAAAAAGCGTGGCATTGTGGAACAA TGCTGTCACAGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGCA AC*
Ins3 with C2 connecting peptide Single chain	101	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG* **GAGGCGGGGGATCTGGCGGGGGAGGCAGT***GGCATTGTGGAACA ATGCTGTCACAGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGC AAC*
Ins3 with C3 connecting peptide Dual chain	102	*TTTGTGAACCAACACCTGTGCGGCTCAGACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACAGACCCCACCG GAGGCGGGGGATCTGGCGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTCACAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*
Ins4 with C3 connecting peptide (n=2) Dual chain	103	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GAGGCGGGGGATCTGGCGGGGGAGGCAGTCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*
Ins4 with C7 connecting peptide, n=2 Dual chain	104	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCC GGAAAAAGCGTGGCGGGGGAGGCAGCGGGGGAGGCGGGTCCCG GAAAAAGCGTGGCATTGTGGAACAATGCTGTACCAGCATCTGCTCC CTCTACCAGCTGGAGAACTACTGCAAC*
Ins4 Dual chain	105	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GCGGGGGAGGCAGCGGGGGAGGCGGGTCCCGGAAAAAGCGTGG CATTGTGGAACAATGCTGTACCAGCATCTGCTCCCTCTACCAGCTG GAGAACTACTGCAAC*
Ins5 with C4 connecting peptide Single chain	106	*GGAATCGTAGAGCAGTGTTGTACCAGTATTTGCAGCCTCTATCAGC TCGAGAACTATTGTAATGGCGGAGGGTCCGGCGGTGGGAGCGGC TTCGTGAATCAACACCTGTGCGGGTCCCACCTGGTGGAAGCGTTG TATCTTGTCTGCGGGGAAAGGGGTTTCTTCTACACACCGAAGACC*
Ins6 with C7	107	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT*

Table 5. Therapeutic Peptides–Nucleic acid sequence		
Name	**SEQ ID NO**	**Sequence**
connecting peptide, n=2 Dual chain		*ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCC GGAAAAAGCGTGGCGGGGGAGGCAGCGGGGGAGGCGGGTCCCG GAAAAAGCGTGGCATTGTGGAACAATGCTGTACCAGCATCTGCTCC CTCTACCAGCTGGAGAACTACTGCAAC*
Ins7 with C1 connecting peptide Single chain	108	*TTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCT ACCTAGTGTGCGGGGAACGAGGCTTCTTCTACACACCCAAGACCG GCGGAGGGCCCCGCCGGGGCATTGTGGAACAATGCTGTACCAGC ATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAAC*
Therapeutic peptide = *italic* Therapeutic peptide connecting peptide = *italic*		

Table 6. Therapeutic Peptides -Amino Acid Sequence		
Name	**SEQ ID NO**	**Sequence**
Ins1 with C1 connecting peptide Single chain	109	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGPRRGIVEQCCHSIC SLYQLENYCN*
Ins2 with cleaved C3 connecting peptide, n=4 Dual chain	110	B CHAIN: *FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGSGGGGS GGGGS* A CHAIN: *GIVEQCCHSICSLYQLENYCN*
Ins3 with C2 connecting peptide Single chain	111	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGSGIVEQC CHSICSLYQLENYCN*
Ins3 with cleaved C3 connecting peptide, n=2 Dual chain	112	B CHAIN: *FVNQHLCGSDLVEALYLVCGERGFFYTDPTGGGGSGGGGS* A CHAIN: *GIVEQCCHSICSLYQLENYCN*
Ins4 with cleaved C3 connecting peptide, n=2 Dual chain	113	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*
Ins4 with cleaved C3 connecting peptide, n=2 Dual chain	114	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*
Ins4 Dual chain	115	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGGSGGGGS* A CHAIN: *GIVEQCCTSICSLYQLENYCN*
Ins5 with C4 connecting	116	*GIVEQCCTSICSLYQLENYCNGGGSGGGSGFVNQHLCGSHLVEALYL VCGERGFFYTPKT*

Table 6. Therapeutic Peptides -Amino Acid Sequence		
Name	**SEQ ID NO**	**Sequence**
peptide Single chain		
Ins6 with cleaved C7 connecting peptide Dual chain	117	B CHAIN: *FVNQHLCGSHLVEALYLVCGERGFFYTPKT* A CHAIN: *GIVEQCCTSICSLYQLENYCN*
Ins7 with C1 connecting peptide Single chain	118	*FVNQHLCGSHLVEALYLVCGERGFFYTPKTGGGPRRGIVEQCCTSICSLYQLENYCN*
InsX Single Chain	119	*FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$TX$_n$GIVEQCCX$_D$SICSLYQLENYCN* X_A is D or H, X_B is D or P, X_C is P or K, X_D is H or T, X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX1: X_A is D, X_B is D, X_C is P and X_D is H	120	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX2: X_A is D, X_B is D, X_C is P and X_D is T	121	*FVNQHLCGSDLVEALYLVCGERGFFYTDPTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX3: X_A is D, X_B is D, X_C is K and X_D is H	122	*FVNQHLCGSDLVEALYLVCGERGFFYTDKTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX4: X_A is D, X_B is D, X_C is K and X_D is T	123	*FVNQHLCGSDLVEALYLVCGERGFFYTDKTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX5: X_A is D, X_B is P, X_C is P and X_D is H	124	*FVNQHLCGSDLVEALYLVCGERGFFYTPPTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX6: X_A is D, X_B is P, X_C is P and X_D is T	125	*FVNQHLCGSDLVEALYLVCGERGFFYTPPTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX7: X_A is D, X_B is P, X_C is K and X_D is H	126	*FVNQHLCGSDLVEALYLVCGERGFFYTPKTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid

Table 6. Therapeutic Peptides -Amino Acid Sequence		
Name	**SEQ ID NO**	**Sequence**
InsX8: X_A is D, X_B is P, X_C is K and X_D is T	127	*FVNQHLCGSDLVEALYLVCGERGFFYTPKTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX9: X_A is H, X_B is D, X_C is P and X_D is H	128	*FVNQHLCGSHLVEALYLVCGERGFFYTDPTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX10: X_A is H, X_B is D, X_C is P and X_D is T	129	*FVNQHLCGSHLVEALYLVCGERGFFYTDPTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX11: X_A is H, X_B is D, X_C is K and X_D is H	130	*FVNQHLCGSHLVEALYLVCGERGFFYTDKTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX12: X_A is H, X_B is D, X_C is K and X_D is T	131	*FVNQHLCGSHLVEALYLVCGERGFFYTDKTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX13: X_A is H, X_B is P, X_C is P and X_D is H	132	*FVNQHLCGSHLVEALYLVCGERGFFYTPPTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX14: X_A is H, X_B is P, X_C is P and X_D is T	133	*FVNQHLCGSHLVEALYLVCGERGFFYTPPTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX15: X_A is H, X_B is P, X_C is K and X_D is H	134	*FVNQHLCGSHLVEALYLVCGERGFFYTPKTX$_n$GIVEQCCHSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX16: X_A is H, X_B is P, X_C is P and X_D is T	135	*FVNQHLCGSHLVEALYLVCGERGFFYTPPTX$_n$GIVEQCCTSICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX17: Xn is GGGPGG	136	*FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$TGGGPGGGIVEQCCX$_D$SICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
InsX18: Xn is GGGPKK	137	*FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$TGGGPKKGIVEQCCX$_D$SICSLYQLENYCN* X_n is n number of amino acids, wherein each X is independently any natural or non-naturally occurring amino acid
Mature human insulin	138	FVNQHLCGSHLVEALYLVCGERGFFYTPKT GIVEQCCTSICSLYQLENYCN
Mature bovine	139	FVNQHLCGSHLVEALYLVCGERGFFYTPKA

Table 6. Therapeutic Peptides -Amino Acid Sequence		
Name	**SEQ ID NO**	**Sequence**
insulin		GIVEQCCASVCSLYQLENYCN
Mature porcine insulin	140	FVNQHLCGSHLVEALYLVCGERGFFYTPKA GIVEQCCTSICSLYQLENYCN
Therapeutic peptide = *italic* Therapeutic peptide connecting peptide = *italic*		

Table 7. Linker Sequences		
Name	**SEQ ID NO**	**Sequence**
L1	141	GGGGS
L2 (CEX5G)	142	GGPSSGAPPPSGGGGG
L3 (EAK)	143	GGGEAAAKEAAAKEAAAKAGG
L4 (GGGGSEAK)	144	GGGGSGGGEAAAKEAAAKEAAAKAGG
L5 (EAKGGGGS)	145	GGGEAAAKEAAAKEAAAKAGGGGSGG
L6 (GGGGSEAKGGGGS)	146	GGGGSGGGEAAAKEAAAKEAAAKAGGGGSGG
L7 (GGGGSGGSP)	147	GGGGSGGSP

Table 8. Connecting Peptide Sequences		
Name	**SEQ ID NO**	**Sequence**
C1	148	GGGPRR
C2	149	$(GGGGS)_n$ (n = 1-10)
C3	150	$(GGGGS)_n$RKKR (n = 1-10)
C4	151	GGGSGGGSG
C5	152	GGGPGG
C6	153	GGGPKK
C7	154	RKKR(GGGGS)nRKKR (n=1-10)

Table 9. Additional Sequences		
Name	**SEQ ID NO**	**Sequence**
Amino terminus of anti-ASGPR VH	155	QVQLX$_1$QX$_2$GAE, wherein X$_1$ and X$_2$ are independently selected from a naturally or non-naturally occurring amino acid
Amino terminus of anti-ASGPR VL	156	EX$_1$VLTQSPX$_2$T, wherein X$_1$ and X$_2$ are independently selected from a naturally or non-naturally occurring amino acid
insulin B peptide	157	FVNQHLCGSX$_A$LVEALYLVCGERGFFYTX$_B$X$_C$T, wherein X$_A$, X$_B$, X$_C$ and X$_D$ are independently selected from a naturally or non-naturally occurring amino acid
insulin A peptide	158	GIVEQCCX$_D$SICSLYQLENYCN, wherein X$_D$ is a naturally or non-naturally occurring amino acid
connecting peptide	159	GGGX$_1$X$_2$, wherein X$_1$ and X$_2$ are independently selected from a naturally or non-naturally occurring amino acid
insulin B chain	160	FVNQHLCGSHLVEALYLVCGERGFFYT
insulin A chain	161	GIVEQCCTSICSLYQLENYC
human ASGPR	162	QNSQLQEELRGLRETFSNFTASTEAQVKGLSTQGGNVGRK MKSLESQLEK QQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSER

Table 9. Additional Sequences		
Name	**SEQ ID NO**	**Sequence**
		TCCPVNWVEH ERSCYWFSRSGKAWADADNYCRLEDAHLVVVTSWEEQKF VQHHIGPVNTW MGLHDQNGPWKWVDGTDYETGFKNWRPEQPDDWYGHGL GGGEDCAHFTDD GRWNDDVCQRPYRWVCETELDKASQEPPLL
Cyno Monkey ASGPR	163	QNAQLQRELRGLRETLSNFTASTEAQVKGLSTQGGNVGRK MKSLESQLEK QQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSER ACCPVNWVEH ERSCYWFSRSGKAWADADNYCRLEDAHLVVVTSWEEQKF VQHHIGPVNTW MGLHDQNGPWKWVDGTDYETGFKNWRPEQPDDWYGHGL GGGEDCAHFTDD GRWNDDVCQRPYRWVCETELHKASQEPPLL
rat ASGPR	164	QNSQLREDLRVLRQNFSNFTVSTEDQVKALTTQGERVGRK MKLVESQLEK HQEDLREDHSRLLLHVKQLVSDVRSLSCQMAALRGNGSERI CCPINWVEY EGSCYWFSSSVKPWTEADKYCQLENAHLVVVTSWEEQRFV QQHMGPLNTW IGLTDQNGPWKWVDGTDYETGFKNWRPGQPDDWYGHGL GGGEDCAHFTTD GHWNDDVCRRPYRWVCETELGKAN
mouse ASGPR	165	QNSQLREDLLALRQNFSNLTVSTEDQVKALSTQGSSVGRK MKLVESKLEK QQKDLTEDHSSLLLHVKQLVSDVRSLSCQMAAFRGNGSER TCCPINWVEY EGSCYWFSSSVRPWTEADKYCQLENAHLVVVTSRDEQNFL QRHMGPLNTW IGLTDQNGPWKWVDGTDYETGFQNWRPEQPDNWYGHGL GGGEDCAHFTTD GRWNDDVCRRPYRWVCETKLDKAN
Ab3H (anti-ASGPR, chimeric HC)	166	CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTTGTGAAG CCTGGGGCTTCAGTGAAACTGTCCTGCAAGGCTTCTGGCT ATACCTTCACCAACTACTGGATGCACTGGGTGAAACAGA GGCCTGGACGAGGCCTTGAGTGGATTGGAAGGATTGATC TTAATAGTGGTGGTACTAATTACAATTACAATGAGAAGT TCAAGACCAAGGCCACACTGACTGTAGACAAACCCTCCA GCACAGCCTACATGCAGCTCAGCAGCCTGACATCTGAGG ACTCTGCGGTCTATTATTGTGCAAATTACTACGGTAGTAG CTGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTC TCTGCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGG CACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCC TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGC ACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTC

Table 9. Additional Sequences		
Name	**SEQ ID NO**	**Sequence**
		CCTCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAG CAACACCAAGGTGGACAAGAAAGTTGAACCCAAATCTTG CGACAAAACTCACACATGCCCACCGTGCCCAGCACCTCC AGTCGCCGGACCGTCAGTCTTCCTCTTCCCTCCAAAACCC AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACA TGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTC AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAAT GCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAC GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGA CTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAA CAAAGGCCTCCCAAGCTCCATCGAGAAAACCATCTCCAA AGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCTCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAG CCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATC GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTC CTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAG GTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC CCTGTCTCCGGGTAAA
Ab3H (anti-ASGPR, chimeric HC)	167	QVQLQQPGAELVKPGASVKLSCKASGYTFTNYWMHWVKQ RPGRGLEWIGRIDLNSGGTNYNYNEKFKTKATLTVDKPSST AYMQLSSLTSEDSAVYYCANYYGSSWFAYWGQGTLVTVS AASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

CLAIMS

What is claimed is:

1. An insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell.
2. The insulin immunoglobulin fusion protein of claim 1, wherein the antigen is asialoglycoprotein receptor (ASGPR).
3. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the first immunoglobulin region comprises a CDR having an amino acid sequence that differs from a sequence selected from SEQ ID NOS: 45-47 and 55 by no more than 2 amino acids.
4. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the first immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.
5. The insulin immunoglobulin fusion protein of any of claims 1-4, further comprising a second immunoglobulin region.
6. The insulin immunoglobulin fusion protein of claim 5, wherein the second immunoglobulin region comprises a CDR having an amino acid sequence that differs from a sequence selected from SEQ ID NOS: 48-50 by no more than 2 amino acids.
7. The insulin immunoglobulin fusion protein of claim 5, wherein the second immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.
8. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the first immunoglobulin region comprises a CDR having an amino acid sequence that differs from a sequence selected from SEQ ID NOS: 48-50 by no more than 2 amino acids.
9. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the first immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.
10. The insulin immunoglobulin fusion protein of claim 8 or claim 9, further comprising a second immunoglobulin region.
11. The insulin immunoglobulin fusion protein of claim 10, wherein the second immunoglobulin region comprises a CDR having an amino acid sequence that differs from a sequence selected from SEQ ID NOS: 45-47 and 55 by no more than 2 amino acids.
12. The insulin immunoglobulin fusion protein of claim 10, wherein the second immunoglobulin region comprises an amino acid sequence at least about 85% homologous to an amino acid sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.
13. The insulin immunoglobulin fusion protein of any of claims 1-12, wherein the insulin therapeutic peptide is connected to the amino-terminus of the first immunoglobulin region.

14. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the insulin therapeutic peptide is connected to the amino-terminus of the first immunoglobulin region; and wherein the first immunoglobulin region comprises SEQ ID NO: 155 ($QVQLX_1QX_2GAE$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid.
15. The insulin immunoglobulin fusion protein of claim 14, wherein X_1 is Q or V.
16. The insulin immunoglobulin fusion protein of claim 14 or claim 15, wherein X_2 is P or S.
17. The insulin immunoglobulin fusion protein of claim 1 or claim 2, wherein the insulin therapeutic peptide is connected to the amino-terminus of the first immunoglobulin region; and wherein the first immunoglobulin region comprises SEQ ID NO: 156 ($EX_1VLTQSPX_2T$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid.
18. The insulin immunoglobulin fusion protein of claim 17, wherein X_1 is T or I.
19. The insulin immunoglobulin fusion protein of claim 17 or claim 18, wherein X_2 is T or G.
20. The insulin immunoglobulin fusion protein of any of claims 1-19, wherein the insulin therapeutic peptide is connected to the first immunoglobulin region by a linker peptide.
21. The insulin immunoglobulin fusion protein of claim 20, wherein the linker peptide comprises between 3 and 50 amino acids, and the linker peptide comprises an amino acid sequence selected from: (a) an amino acid sequence having at least about 50% glycine, serine, or glycine and serine amino acids; and (b) an amino acid sequence having at least about 50% glycine, alanine, or glycine and alanine amino acids.
22. The insulin immunoglobulin fusion protein of claim 20 or claim 21, wherein the linker peptide comprises an amino acid sequence at least about 90% identical to any one of SEQ ID NOS: 141-147.
23. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises a single amino acid chain having the formula B-C-A or A-C-B; wherein B comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT); A comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC); and C comprises a connecting peptide.
24. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises a single amino acid chain having the formula: B-C-A or A-C-B;
wherein B comprises SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); A comprises SEQ ID NO 158: $GIVEQCCX_DSICSLYQLENYCN$; and C comprises a connecting peptide; and
wherein X_A, X_B, X_C and X_D are independently selected from a naturally or non-naturally occurring amino acid.
25. The insulin immunoglobulin fusion protein of claim 24, wherein the X_A is D or H.
26. The insulin immunoglobulin fusion protein of claim 24 or claim 25, wherein the X_B is D or P.
27. The insulin immunoglobulin fusion protein of any of claims 24-26, wherein the X_C is P or K.

28. The insulin immunoglobulin fusion protein of any of claims 24-27, wherein the X_D is H or T.
29. The insulin immunoglobulin fusion protein of any of claims 23-28, wherein the connecting peptide comprises an amino acid sequence comprising at least 50% glycine amino acids.
30. The insulin immunoglobulin fusion protein of any of claims 23-28, wherein the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid.
31. The insulin immunoglobulin fusion protein of claim 30, wherein X_1 is P, G or S.
32. The insulin immunoglobulin fusion protein of any of claim 30 or claim 31, wherein X_2 is R, S, G or K.
33. The insulin immunoglobulin fusion protein of any of claims 23-32, wherein C comprises a protease cleavage site.
34. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises an A peptide comprising an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC).
35. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises an A peptide comprising SEQ ID NO: 158 ($GIVEQCCX_DSICSLYQLENYCN$), and X_D is a naturally or non-naturally occurring amino acid.
36. The insulin immunoglobulin fusion protein of claim 35, wherein X_D is selected from H and T.
37. The insulin immunoglobulin fusion protein of any of claims 34-36, wherein one or more cysteine amino acids of the A peptide is present in a disulfide bond with a cysteine amino acid of a B peptide.
38. The insulin immunoglobulin fusion protein of claim 37, wherein the B peptide comprises SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid.
39. The insulin immunoglobulin fusion protein of claim 38, wherein the X_A is D or H.
40. The insulin immunoglobulin fusion protein of claim 38 or claim 39, wherein the X_B is D or P.
41. The insulin immunoglobulin fusion protein of any of claims 38-40, wherein the X_C is P or K.
42. The insulin immunoglobulin fusion protein of claim 37, wherein the B peptide comprises an amino acid sequence having no more than 2 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT).
43. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises an amino acid sequence having no more than 2 amino acid differences from a sequence selected from SEQ ID NOS: 109-140, 157, 158, 160 and 161.
44. The insulin immunoglobulin fusion protein of any of claims 1-22, wherein the insulin therapeutic peptide comprises an amino acid sequence having at least 85% sequence homology to any of SEQ ID NOS: 109-140, 157, 158, 160 and 161.

45. The insulin immunoglobulin fusion protein of claim 1, wherein the insulin immunoglobulin fusion protein comprises an amino acid sequence having no more than 5 amino acid differences from any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98.

46. The insulin immunoglobulin fusion protein of claim 1, wherein the insulin immunoglobulin fusion protein comprises an amino acid sequence having at least 75% sequence identity to any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98.

47. The insulin immunoglobulin fusion protein of claim 1, wherein the insulin immunoglobulin fusion protein comprises an amino acid sequence having at least 85% sequence homology to any of SEQ ID NOS: 78, 79, 81-85, 87-92, 95-98.

48. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the insulin immunoglobulin fusion protein of any of claims 1-47.

49. The method claim 48, further comprising administering to the subject an additional therapeutic peptide.

50. The method of claim 49, wherein the additional therapeutic peptide comprises insulin or an insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver or to a hepatocyte.

51. The method of claim 49 or claim 50, wherein the additional therapeutic agent is administered in a composition with the insulin immunoglobulin fusion protein.

52. The method of claim 49 or claim 50, wherein the additional therapeutic agent is administered in a composition separate from the insulin immunoglobulin fusion protein.

53. The method of any of claims 49-52, wherein the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

54. The method of any of claims 48-53, wherein the insulin immunoglobulin fusion protein is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

55. The method of any of claims 48-54, wherein the disease or condition is diabetes.

56. A composition comprising a molecule of Formula XVII:

I-L-G (Formula XVII)

wherein:

I has the formula B-A, A-B, B-C-A, or A-C-B; wherein B comprises an insulin B chain; A comprises an insulin A chain; if present, C comprises a connecter connecting B and A; and B-A, A-B, or both B-A and A-B are linked by a moiety or disulfide bond;

L comprises a linker; and

G comprises an immunoglobulin, immunoglobulin fragment, peptide or other ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte.

57. The composition of claim 56, wherein I has the formula B-A or A-B, and B-A or A-B are linked by a disulfide bond.

58. The composition of claim 56, wherein I has the formula B-C-A or A-C-B, and the connecter is a connecting peptide.

59. The composition of claim 58, wherein the connecting peptide comprises SEQ ID NO: 159 ($GGGX_1X_2$), wherein X_1 and X_2 are independently selected from a naturally or non-naturally occurring amino acid.

60. The composition of claim 59, wherein X_1 is P, G or S.

61. The composition of claim 59 or claim 60, wherein X_2 is R, S, G or K.

62. The composition of any of claims 56-61, wherein C comprises a protease cleavage site.

63. The composition of any of claims 56-62, wherein the insulin B chain comprises a sequence of SEQ ID NO: 157 ($FVNQHLCGSX_ALVEALYLVCGERGFFYTX_BX_CT$); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid.

64. The composition of claim 63, wherein the X_A is D or H.

65. The composition of claim 63 or claim 64, wherein the X_B is D or P.

66. The composition of any of claims 63-65, wherein the X_C is P or K.

67. The composition of any of claims 56-62, wherein the insulin B chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT).

68. The composition of any of claims 56-62, wherein the insulin B chain comprises a sequence at least about 85% identical to an insulin B chain in any one of SEQ ID NOS: 109-140, 157, 160.

69. The composition of any of claims 56-62, wherein insulin B chain is selected from human insulin B chain, porcine insulin B chain and bovine insulin B chain.

70. The composition of any of claims 56-69, wherein the insulin A chain comprises a sequence of SEQ ID NO: 158 ($GIVEQCCX_DSICSLYQLENYCN$), and X_D is a naturally or non-naturally occurring amino acid.

71. The composition of claim 70, wherein X_D is selected from H and T.

72. The composition of any of claims 56-69, wherein the insulin A chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC).

73. The composition of any of claims 56-69, wherein the insulin A chain comprises a sequence at least about 85% identical to an insulin A chain in any one of SEQ ID NOS: 109-140, 158, 161.

74. The composition of any of claims 56-69, wherein insulin A chain is selected from human insulin A chain, porcine insulin A chain and bovine insulin A chain.

75. The composition of any of claims 56-74, wherein the linker comprises a linker peptide.

76. The composition of claim 75, wherein the linker peptide comprises an amino acid sequence selected from: (a) an amino acid sequence having at least 50% glycine, serine, or glycine and serine amino acids; and (b) an amino acid sequence having at least 50% glycine, alanine, or glycine and alanine amino acids.

77. The composition of any of claims 56-76, wherein the antigen is ASGPR.

78. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising:
    a) a heavy chain variable region sequence comprising SEQ ID NO: 45;
    b) a heavy chain variable region sequence comprising SEQ ID NO: 46;
    c) a heavy chain variable region sequence comprising SEQ ID NO: 55;
    d) a heavy chain variable region sequence comprising SEQ ID NO: 47;
    e) a light chain variable region sequence comprising SEQ ID NO: 48;
    f) a light chain variable region sequence comprising SEQ ID NO: 49;
    g) a light chain variable region sequence comprising SEQ ID NO: 50;
    h) a combination of (a), (b) and (d);
    i) a combination of (a), (c) and (d);
    j) a combination of (e), (f) and (g);
    k) a combination of (h) and (j); or
    l) a combination of (i) and (j).
79. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising a sequence that differs from a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43 by no more than 2 amino acids.
80. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.
81. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising a sequence that differs from a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44 by no more than 2 amino acids.
82. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.
83. The composition of any of claims 56-77, wherein G comprises an immunoglobulin or immunoglobulin fragment comprising a CH1 domain.
84. The composition of any of claims 56-77, wherein G comprises a humanized immunoglobulin or fragment thereof.
85. The composition of any of claims 56-77, wherein G binds to one or more amino acids of an epitope of ASGPR having SEQ ID NO: 162, wherein the one or more amino acids is selected from R10, G11, F19, G35, N36, Q47, S56, L83, W134, E135, K138, V140, H142, and K173.
86. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the composition of any of claims 56-85.
87. The method claim 86, further comprising administering to the subject an additional therapeutic peptide.

88. The method of claim 87, wherein the additional therapeutic peptide comprises insulin or an insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver or to a hepatocyte.

89. The method of claim 87 or claim 88, wherein the additional therapeutic agent is administered in a composition with the insulin immunoglobulin fusion protein.

90. The method of claim 87 or claim 88, wherein the additional therapeutic agent is administered in a composition separate from the insulin immunoglobulin fusion protein.

91. The method of any of claims 87-90, wherein the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

92. The method of any of claims 86-91, wherein the insulin immunoglobulin fusion protein is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

93. The method of any of claims 86-92, wherein the disease or condition is diabetes.

94. An immunoglobulin for specific binding to asialoglycoprotein receptor (ASGPR), the immunoglobulin comprising:

a) a heavy chain variable region sequence comprising SEQ ID NO: 45;
b) a heavy chain variable region sequence comprising SEQ ID NO: 46;
c) a heavy chain variable region sequence comprising SEQ ID NO: 55;
d) a heavy chain variable region sequence comprising SEQ ID NO: 47;
e) a light chain variable region sequence comprising SEQ ID NO: 48;
f) a light chain variable region sequence comprising SEQ ID NO: 49;
g) a light chain variable region sequence comprising SEQ ID NO: 50;
h) a combination of (a), (b) and (d);
i) a combination of (a), (c) and (d);
j) a combination of (e), (f) and (g);
k) a combination of (h) and (j); or
l) a combination of (i) and (j).

95. The immunoglobulin of claim 94, comprising a sequence that differs from a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43 by no more than 2 amino acids.

96. The immunoglobulin of claim 94, comprising a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 34, 36-40 and 43.

97. The immunoglobulin of any of claims 94-96, comprising a CH1 domain.

98. The immunoglobulin of claim 97, wherein the CH1 domain comprises a sequence at least about 85% homologous to SEQ ID NO: 40.

99. The immunoglobulin of claim 94, comprising a sequence that differs from a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44 by no more than 2 amino acids.

100. The immunoglobulin of claim 94, comprising a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 30, 33, 35, 41, 42, and 44.

101. The immunoglobulin of any of claims 94-100, wherein the immunoglobulin is humanized.

102. An immunoglobulin that competes with the immunoglobulin of any of claims 94-101 for binding to ASGPR.

103. A method of targeting a molecule to a hepatocyte in a subject in need thereof, the method comprising administering to the subject a composition comprising the molecule and the immunoglobulin of any of claims 94-103.

104. The method of claim 103, wherein the molecule is fused or linked to the immunoglobulin.

105. The method of claim 103 or claim 104, wherein the molecule comprises a human insulin B chain, human insulin A chain, or a derivative or combination thereof.

106. The method of any of claims 103-105, wherein the subject has diabetes.

107. The method any of claims 103-106, further comprising administering to the subject an additional therapeutic peptide.

108. The method of claim 107, wherein the additional therapeutic peptide comprises insulin or an insulin containing molecule lacking a moiety that targets the additional therapeutic agent to the liver or to a hepatocyte.

109. A method of treating a disease or condition associated with glucose metabolism in a subject in need thereof, the method comprising administering an effective amount of an insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide and an immunoglobulin region comprising an antigen binding domain, wherein the antigen binding domain targets an antigen expressed or displayed by a hepatocyte.

110. The method of claim 109, wherein the antigen is ASGPR.

111. The method claim 109 or claim 110, further comprising administering to the subject an additional therapeutic peptide.

112. The method of claim 111, wherein the additional therapeutic peptide comprises insulin or an insulin containing molecule.

113. The method of claim 112, wherein the insulin or insulin containing molecule lacks a moiety that targets the additional therapeutic agent to the liver or to a hepatocyte.

114. The method of any of claims 111-113, wherein the additional therapeutic agent is administered in a composition with the insulin immunoglobulin fusion protein.

115. The method of any of claims 111-113, wherein the additional therapeutic agent is administered in a composition separate from the insulin immunoglobulin fusion protein.

116. The method of any of claims 111-115, wherein the additional therapeutic agent is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

117. The method of any of claims 110-116, wherein the insulin immunoglobulin fusion protein is administered via a subcutaneous, intravenous, intramuscular, infusion, transdermal, oral or nasal route.

118. The method of any of claims 109-117, wherein the disease or condition is diabetes.

119. The method of any of claims 109-118, wherein the insulin therapeutic peptide has the formula B-A, A-B, B-C-A, or A-C-B; wherein B comprises an insulin B chain; A comprises an insulin A chain; if present, C comprises a connecter connecting B and A; and B-A, A-B, or both B-A and A-B are linked by a moiety or disulfide bond.

120. The method of claim 119, wherein B-A or A-B are linked by a disulfide bond.

121. The method of claim 119 or claim 120, wherein the connecter is a connecting peptide.

122. The method of any of claims 119-121, wherein C comprises a protease cleavage site.

123. The method of any of claims 119-122, wherein the insulin B chain comprises a sequence of SEQ ID NO: 157 (FVNQHLCGSX_ALVEALYLVCGERGFFYT$X_B$$X_C$T); and X_A, X_B, and X_C are independently selected from a naturally or non-naturally occurring amino acid.

124. The method of claim 123, wherein the X_A is D or H.

125. The method of claim 123 or claim 124, wherein the X_B is D or P.

126. The method of any of claims 123-125, wherein the X_C is P or K.

127. The method of any of claims 119-122, wherein the insulin B chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 160 (FVNQHLCGSHLVEALYLVCGERGFFYT).

128. The method of any of claims 119-122, wherein the insulin B chain comprises a sequence at least about 85% identical to an insulin B chain in any one of SEQ ID NOS: 109-140.

129. The method of any of claims 119-122, wherein insulin B chain is selected from human insulin B chain, porcine insulin B chain and bovine insulin B chain.

130. The method of any of claims 119-129, wherein the insulin A chain comprises a sequence of SEQ ID NO: 158 (GIVEQCCX_DSICSLYQLENYCN), and X_D is a naturally or non-naturally occurring amino acid.

131. The method of claim 130, wherein X_D is selected from H and T.

132. The method of any of claims 119-129, wherein the insulin A chain comprises an amino acid sequence having no more than 1, 2, 3 or 4 amino acid differences from SEQ ID NO: 161 (GIVEQCCTSICSLYQLENYC).

133. The method of any of claims 119-129, wherein the insulin A chain comprises a sequence at least about 85% identical to an insulin A chain in any one of SEQ ID NOS: 109-140.

134. The method of any of claims 119-129, wherein insulin A chain is selected from human insulin A chain, porcine insulin A chain and bovine insulin A chain.

135. The method of any of claims 109-134, wherein the immunoglobulin region comprises:

a) a heavy chain variable region sequence comprising SEQ ID NO: 45;

b) a heavy chain variable region sequence comprising SEQ ID NO: 46;

c) a heavy chain variable region sequence comprising SEQ ID NO: 55;

d) a heavy chain variable region sequence comprising SEQ ID NO: 47;

e) a light chain variable region sequence comprising SEQ ID NO: 48;

f) a light chain variable region sequence comprising SEQ ID NO: 49;

g) a light chain variable region sequence comprising SEQ ID NO: 50;

h) a combination of (a), (b) and (d);

i) a combination of (a), (c) and (d);

j) a combination of (e), (f) and (g);

k) a combination of (h) and (j); or

l) a combination of (i) and (j).

136. The method of any of claims 109-134, wherein the immunoglobulin region comprises a sequence at least about 85% homologous to a sequence selected from SEQ ID NOS: 29, 30 and 33-44.

FIG. 1A

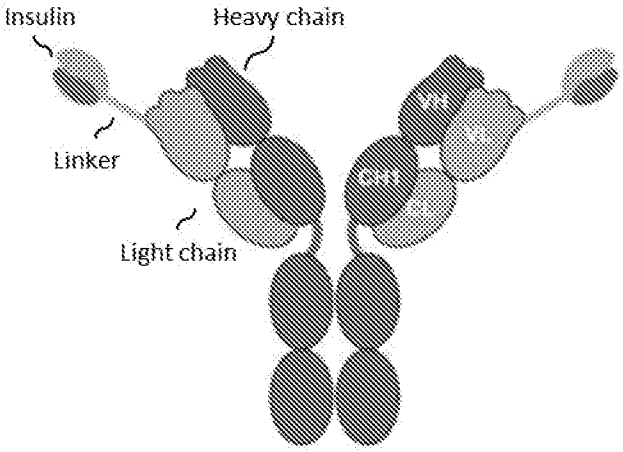

Insulin
Heavy chain
Linker
Light chain
VH
VL
CH1
CL

FIG. 1B

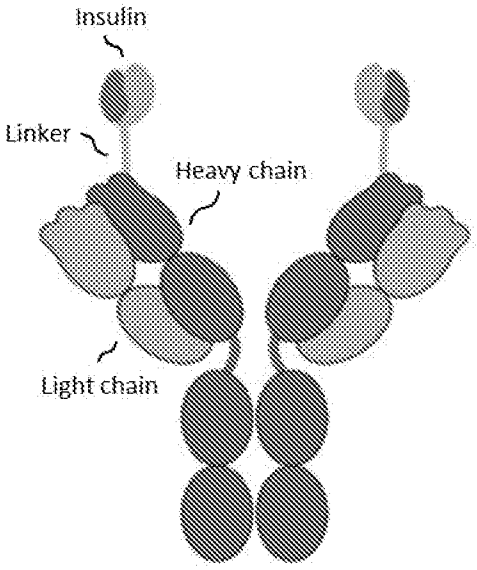

Insulin
Linker
Heavy chain
Light chain

FIG. 2

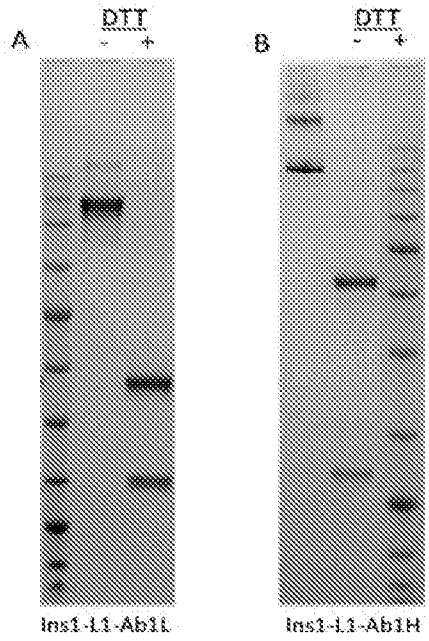

A
DTT
- +
B
DTT
- +
Ins1-L1-Ab1L
Ins1-L1-Ab1H

FIG. 3

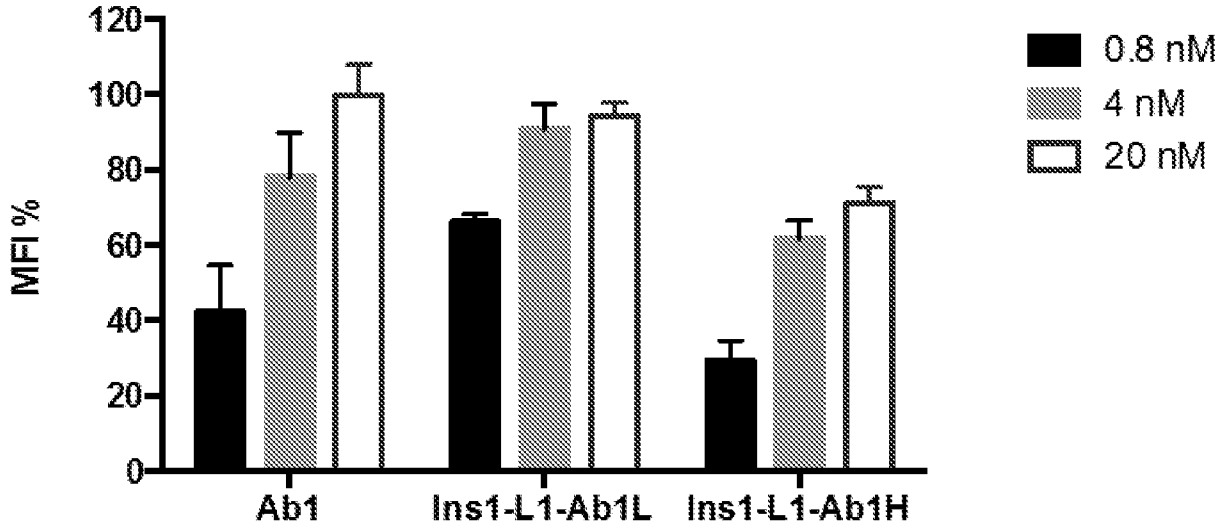

120
100
80
60
40
20
0
MFI %
Ab1
Ins1-L1-Ab1L
Ins1-L1-Ab1H
0.8 nM
4 nM
20 nM

FIG. 4

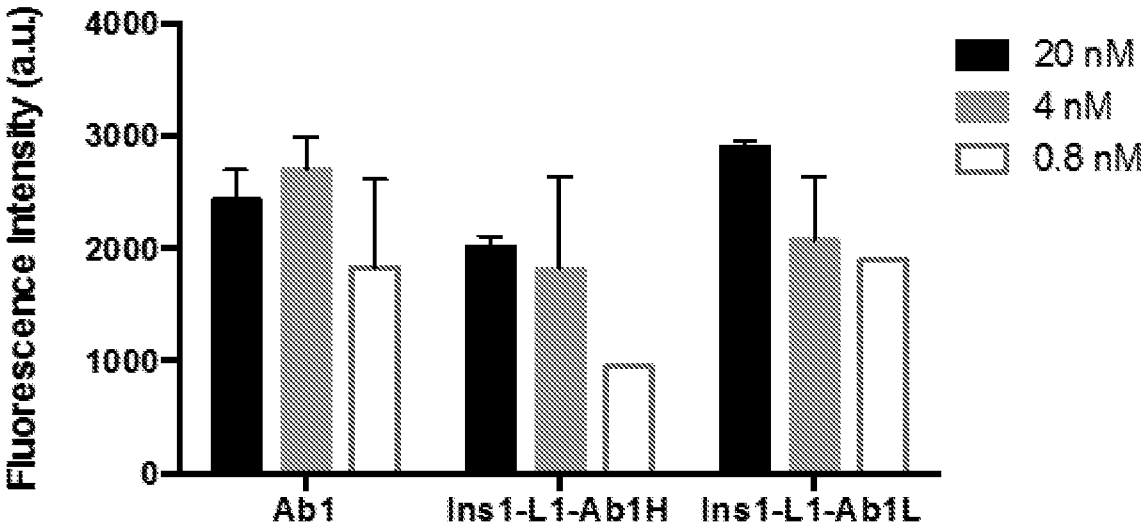

Fluorescence Intensity (a.u.)
4000
3000
2000
1000
0
Ab1
Ins1-L1-Ab1H
Ins1-L1-Ab1L
20 nM
4 nM
0.8 nM

FIG. 5

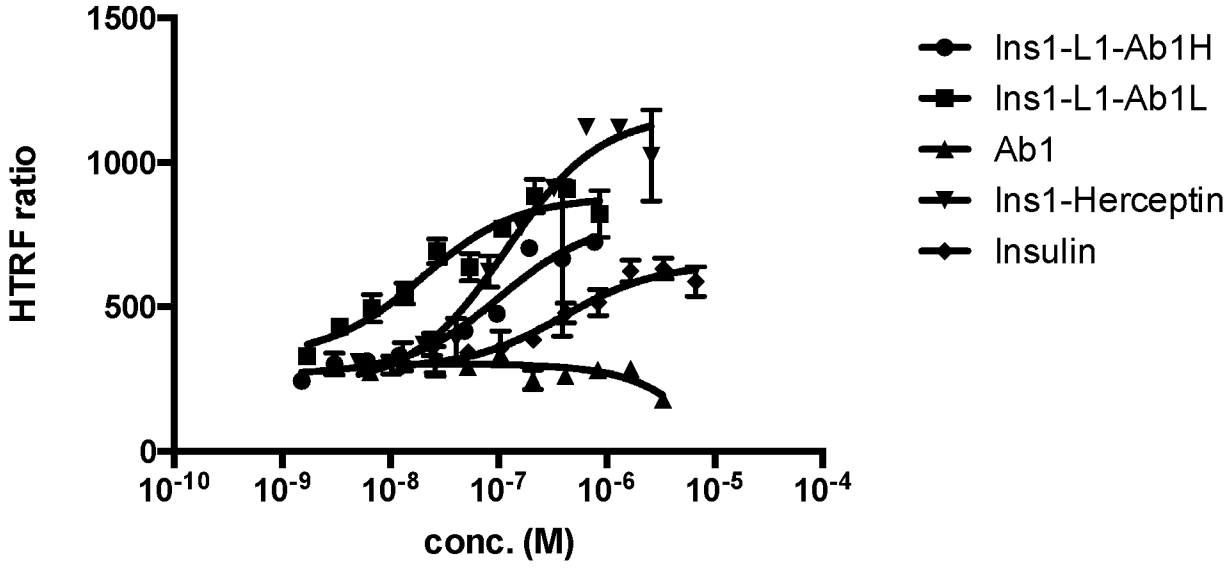

HTRF ratio
1500
1000
500
0
10-10
10-9
10-8
10-7
10-6
10-5
10-4
conc. (M)
Ins1-L1-Ab1H
Ins1-L1-Ab1L
Ab1
Ins1-Herceptin
Insulin

FIG. 6

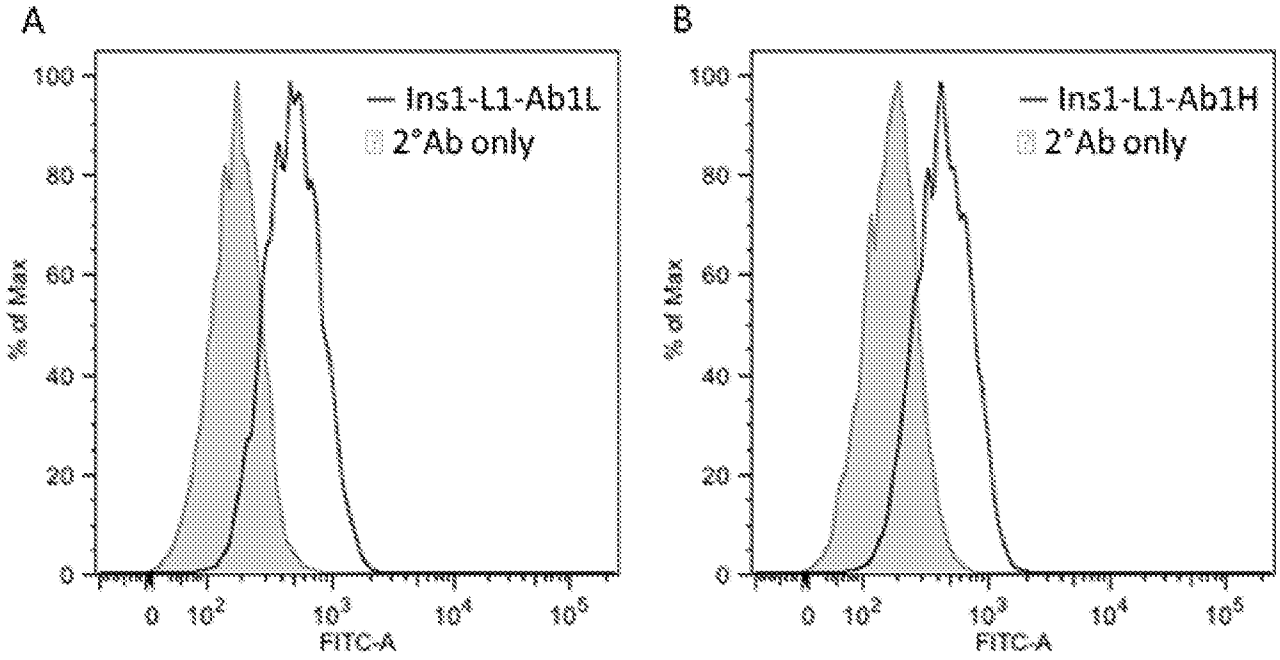

A
B
Ins1-L1-Ab1L
2°Ab only
Ins1-L1-Ab1H
2°Ab only
% of Max
FITC-A

FIG. 7

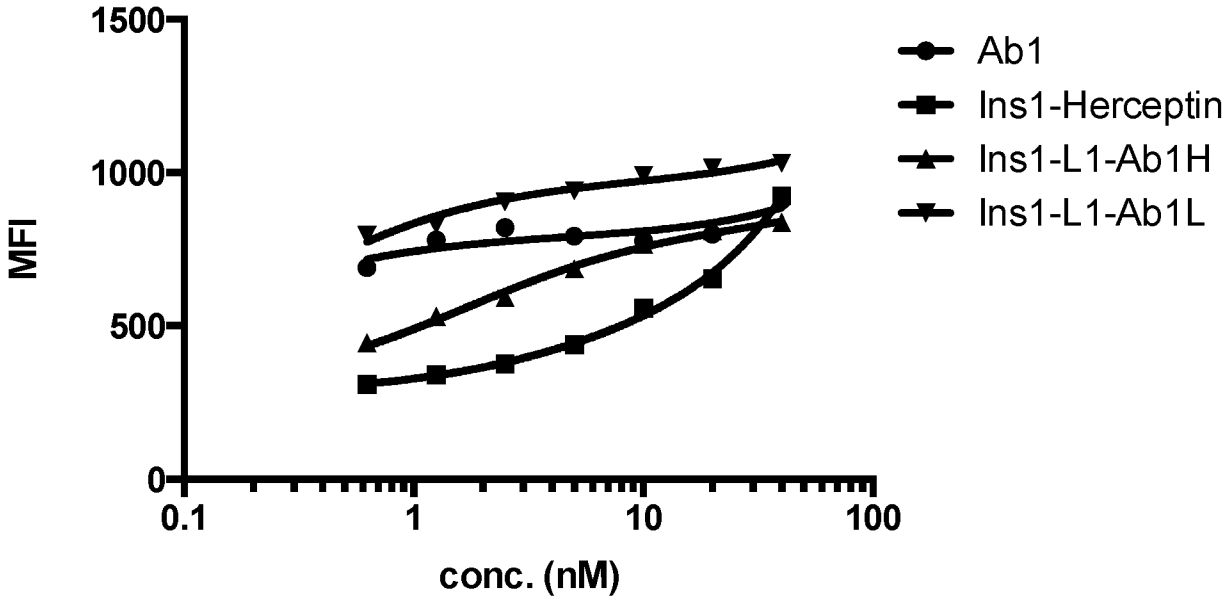

MFI
conc. (nM)
Ab1
Ins1-Herceptin
Ins1-L1-Ab1H
Ins1-L1-Ab1L

FIG. 8

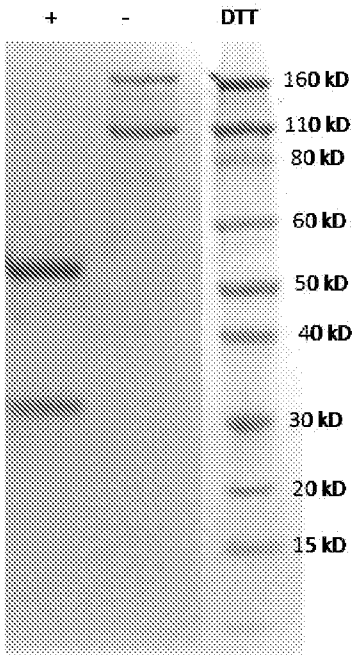
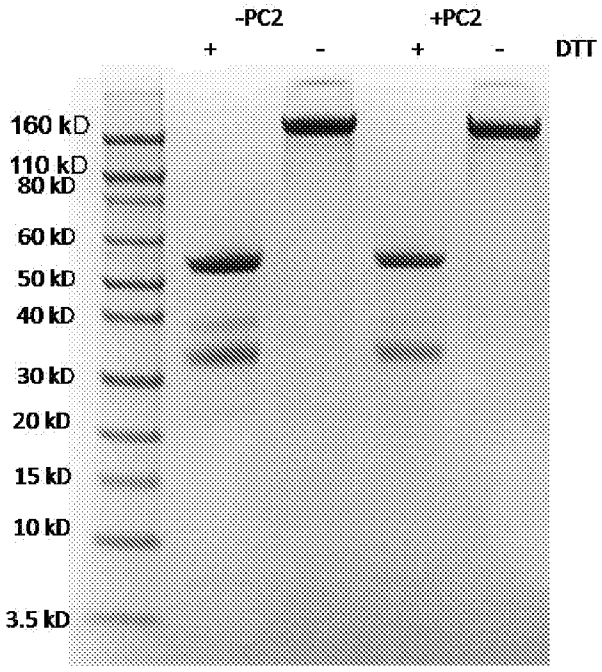
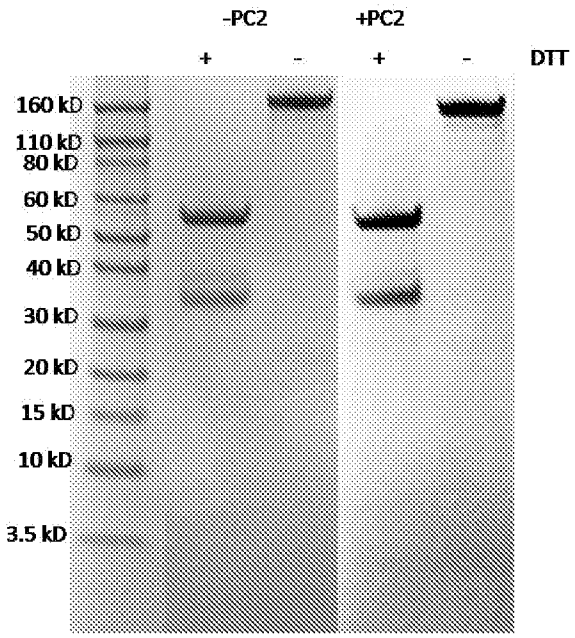


FIG. 9



Ins2-L2-Ab3

FIG. 10



Ins3-L2-Ab3

FIG. 11

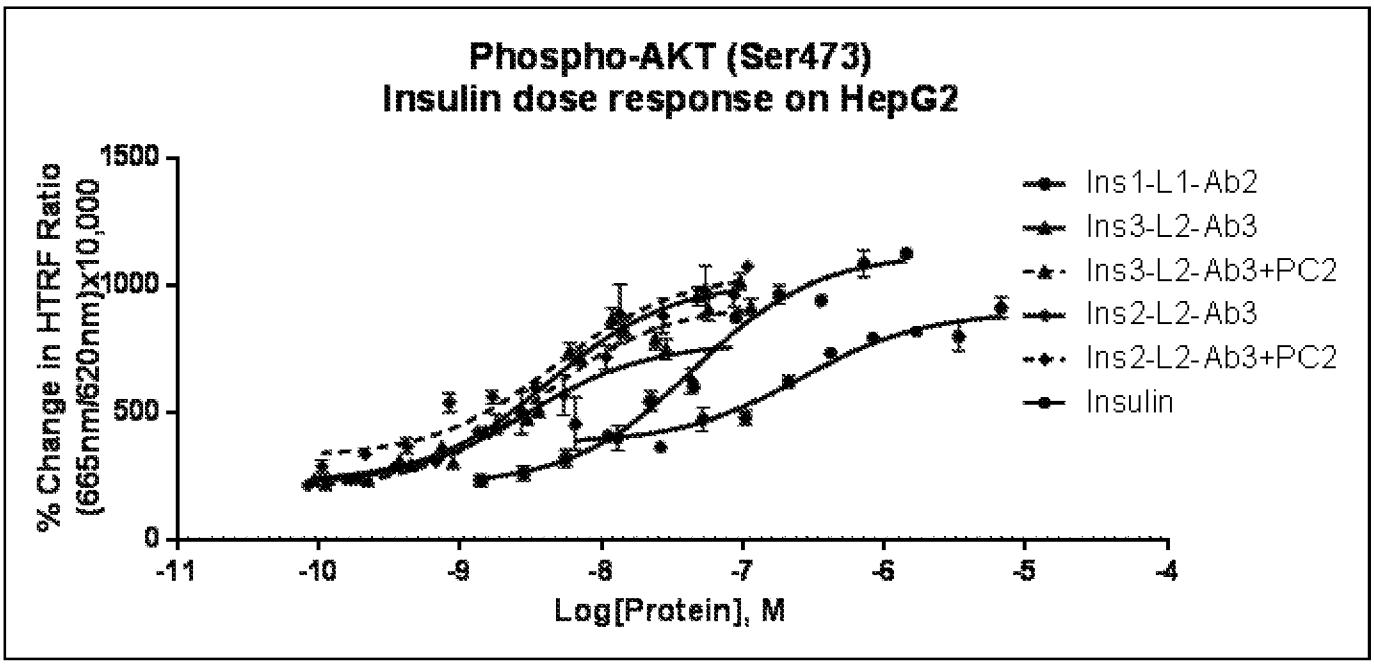
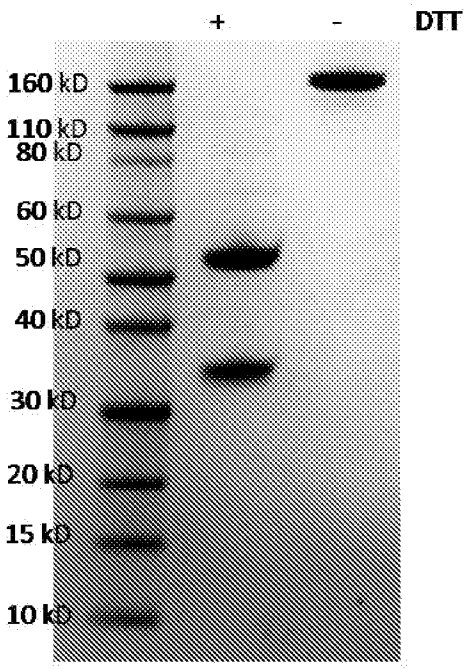
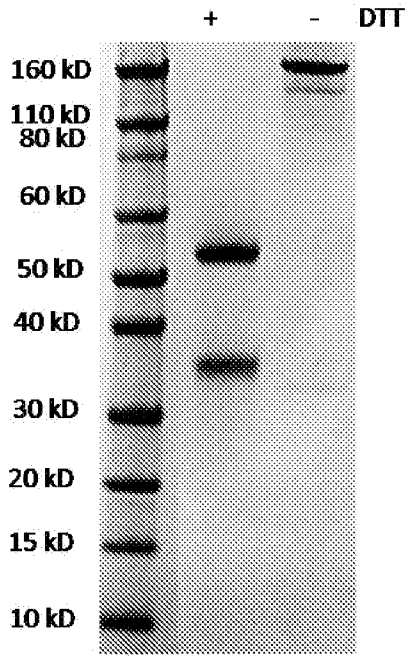


FIG. 12



Ins1-L3-Ab4

FIG. 13



Ins1-L3-Ab5

FIG. 14

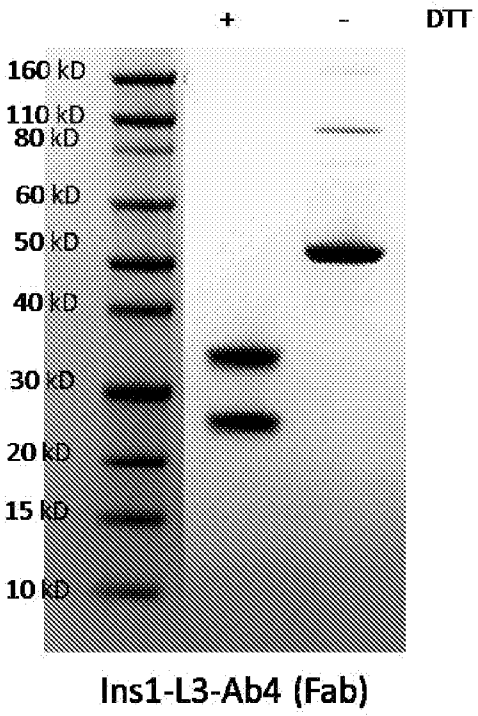

+
-
DTT
160 kD
110 kD
80 kD
60 kD
50 kD
40 kD
30 kD
20 kD
15 kD
10 kD
Ins1-L3-Ab4 (Fab)

FIG. 15

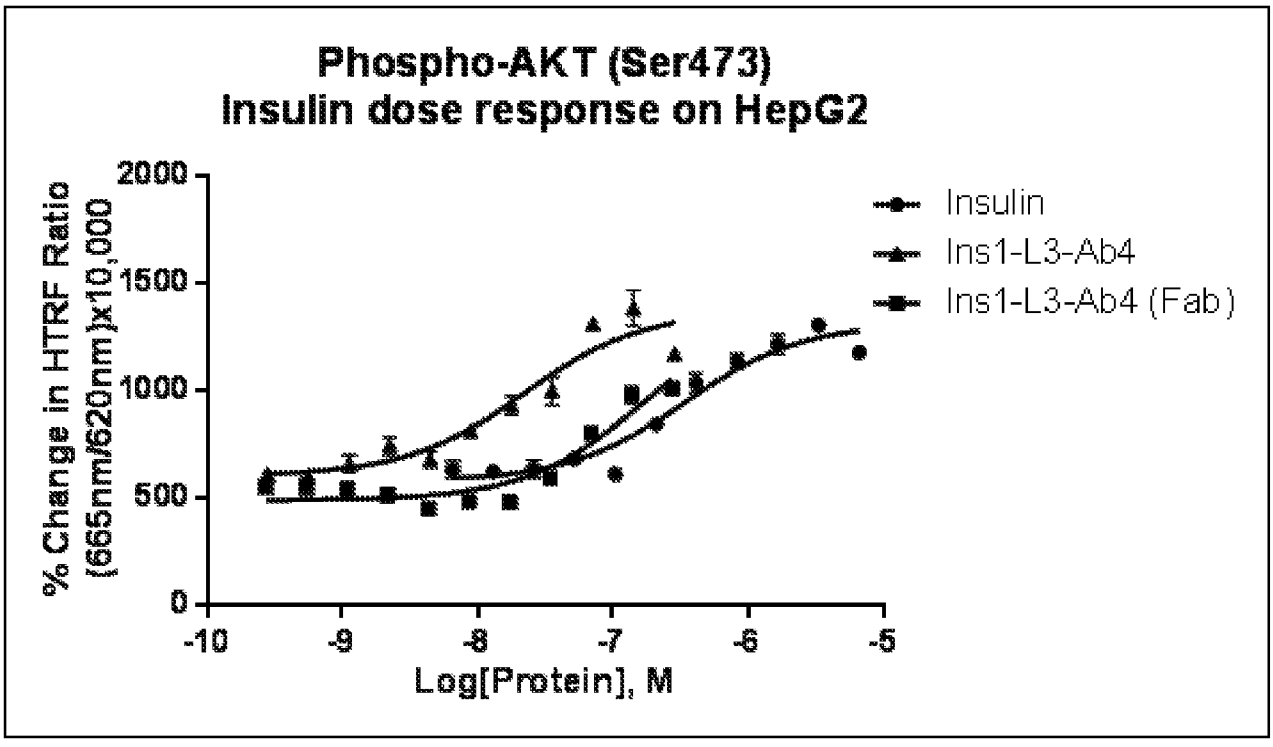

Phospho-AKT (Ser473)
Insulin dose response on HepG2
% Change in HTRF Ratio (665nm/620nm)x10,000
2000
1500
1000
500
0
-10
-9
-8
-7
-6
-5
Log[Protein], M
Insulin
Ins1-L3-Ab4
Ins1-L3-Ab4 (Fab)

FIG. 16

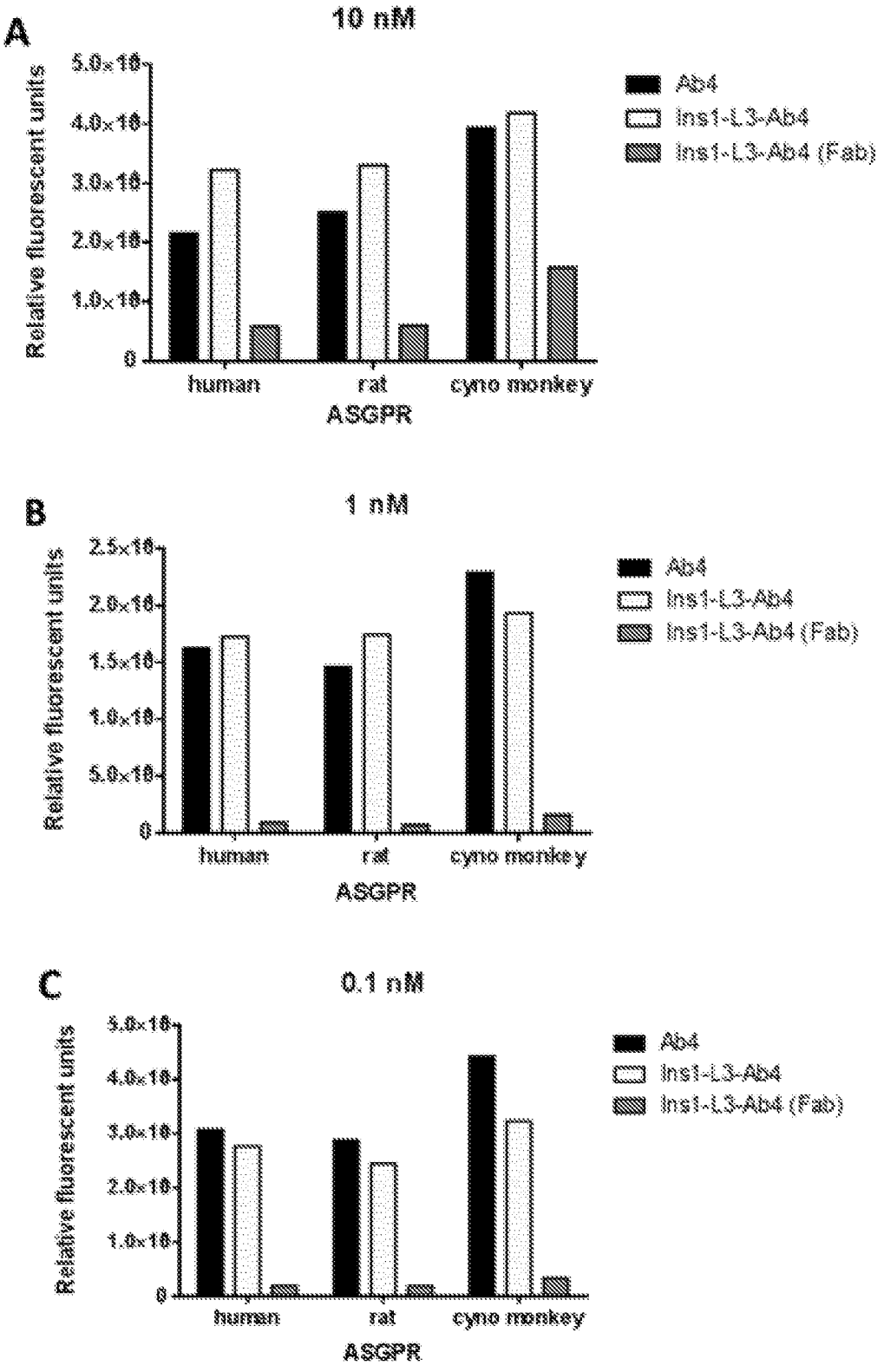

A
10 nM
Relative fluorescent units
5.0x10
4.0x10
3.0x10
2.0x10
1.0x10
0
human
rat
cyno monkey
ASGPR
Ab4
Ins1-L3-Ab4
Ins1-L3-Ab4 (Fab)
B
1 nM
Relative fluorescent units
2.5x10
2.0x10
1.5x10
1.0x10
5.0x10
0
human
rat
cyno monkey
ASGPR
Ab4
Ins1-L3-Ab4
Ins1-L3-Ab4 (Fab)
C
0.1 nM
Relative fluorescent units
5.0x10
4.0x10
3.0x10
2.0x10
1.0x10
0
human
rat
cyno monkey
ASGPR
Ab4
Ins1-L3-Ab4
Ins1-L3-Ab4 (Fab)

FIG. 17

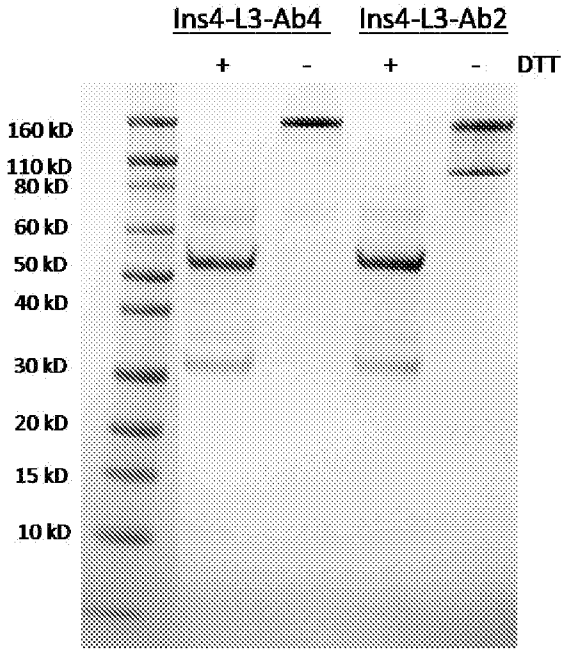

Ins4-L3-Ab4
Ins4-L3-Ab2
+
-
+
-
DTT
160 kD
110 kD
80 kD
60 kD
50 kD
40 kD
30 kD
20 kD
15 kD
10 kD

FIG. 18

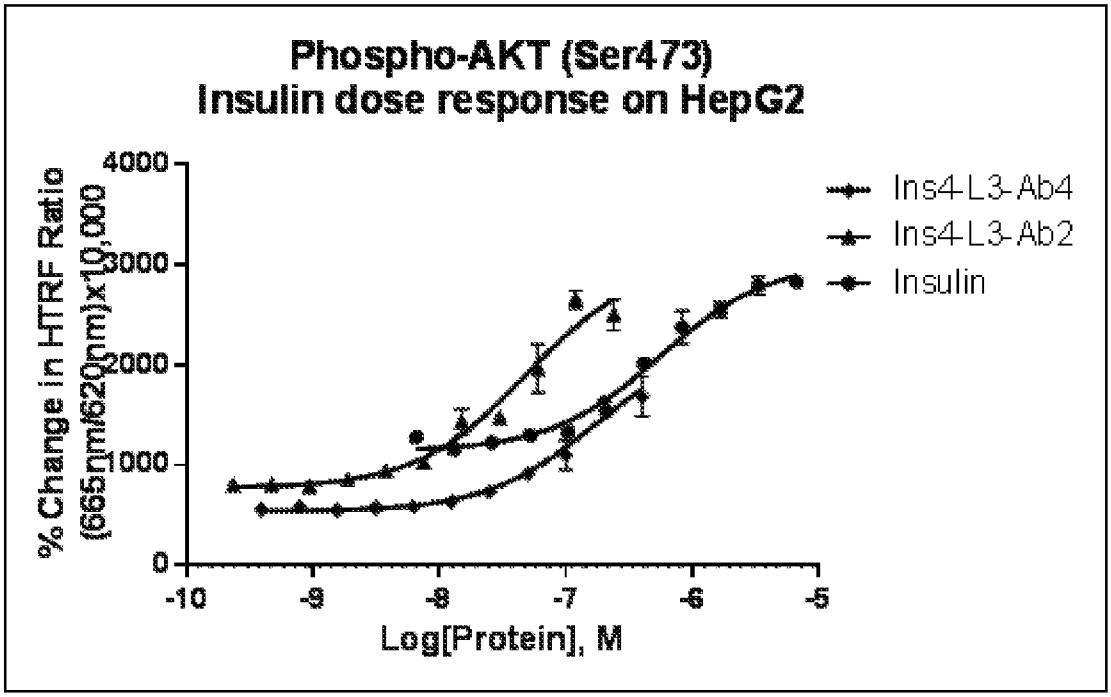

Phospho-AKT (Ser473)
Insulin dose response on HepG2
% Change in HTRF Ratio (665nm/620nm)x10,000
4000
3000
2000
1000
0
-10
-9
-8
-7
-6
-5
Log[Protein], M
Ins4-L3-Ab4
Ins4-L3-Ab2
Insulin

FIG. 19

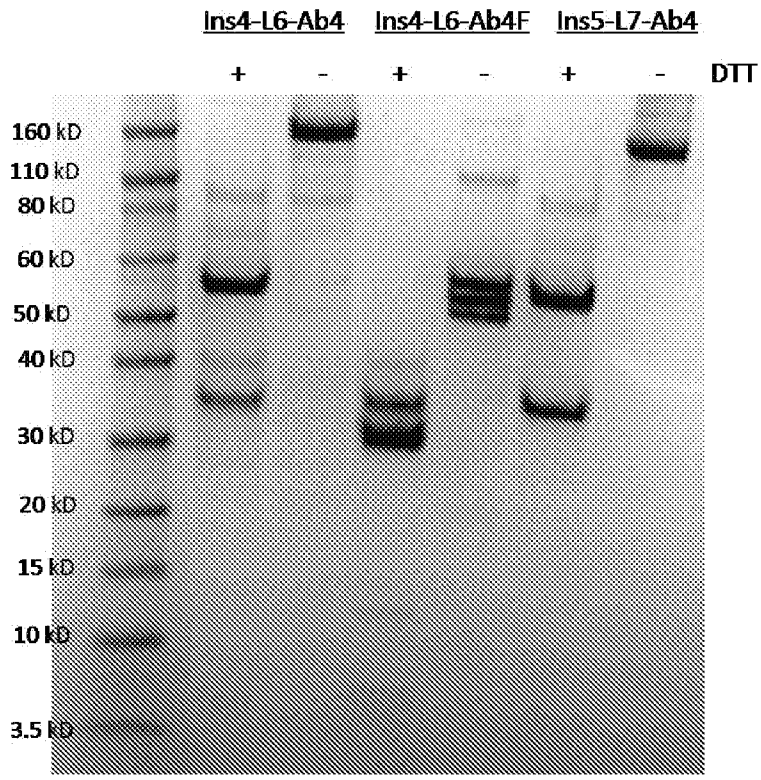

Ins4-L6-Ab4
Ins4-L6-Ab4F
Ins5-L7-Ab4
+ - + - + - DTT
160 kD
110 kD
80 kD
60 kD
50 kD
40 kD
30 kD
20 kD
15 kD
10 kD
3.5 kD

FIG. 20

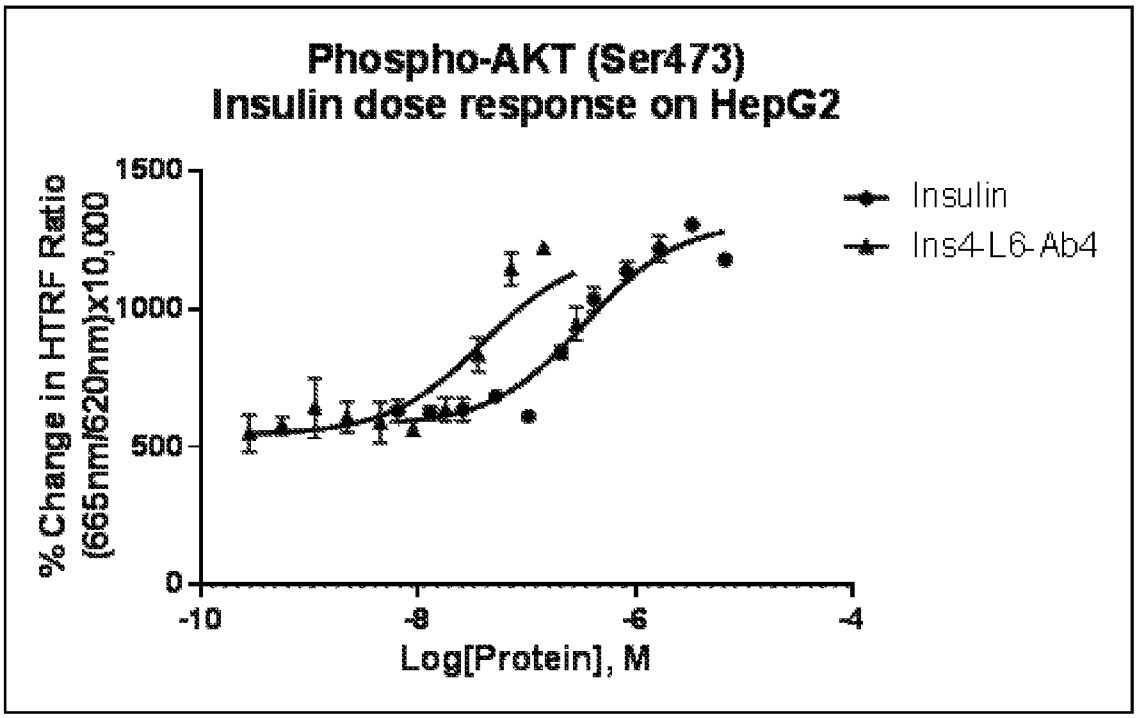

Phospho-AKT (Ser473)
Insulin dose response on HepG2
% Change in HTRF Ratio (665nm/620nm)x10,000
1500
1000
500
0
-10
-8
-6
-4
Log[Protein], M
Insulin
Ins4-L6-Ab4

FIG. 21

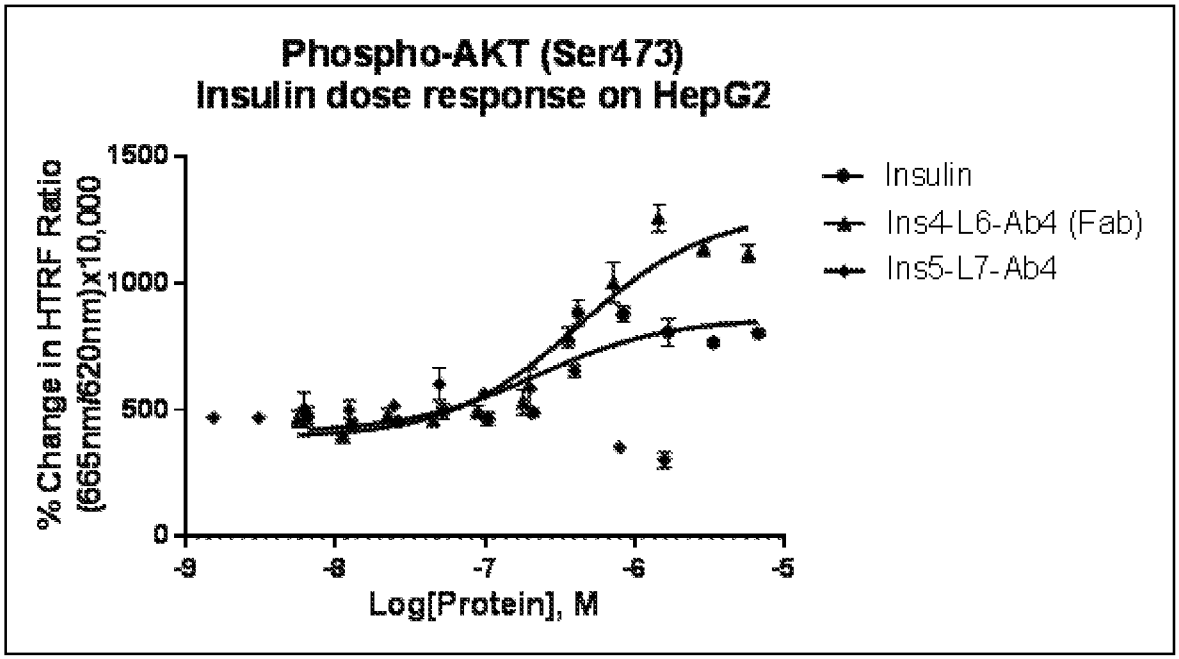

Phospho-AKT (Ser473)
Insulin dose response on HepG2
% Change in HTRF Ratio (665nm/620nm)x10,000
1500
1000
500
0
-9
-8
-7
-6
-5
Log[Protein], M
Insulin
Ins4-L6-Ab4 (Fab)
Ins5-L7-Ab4

FIG. 22

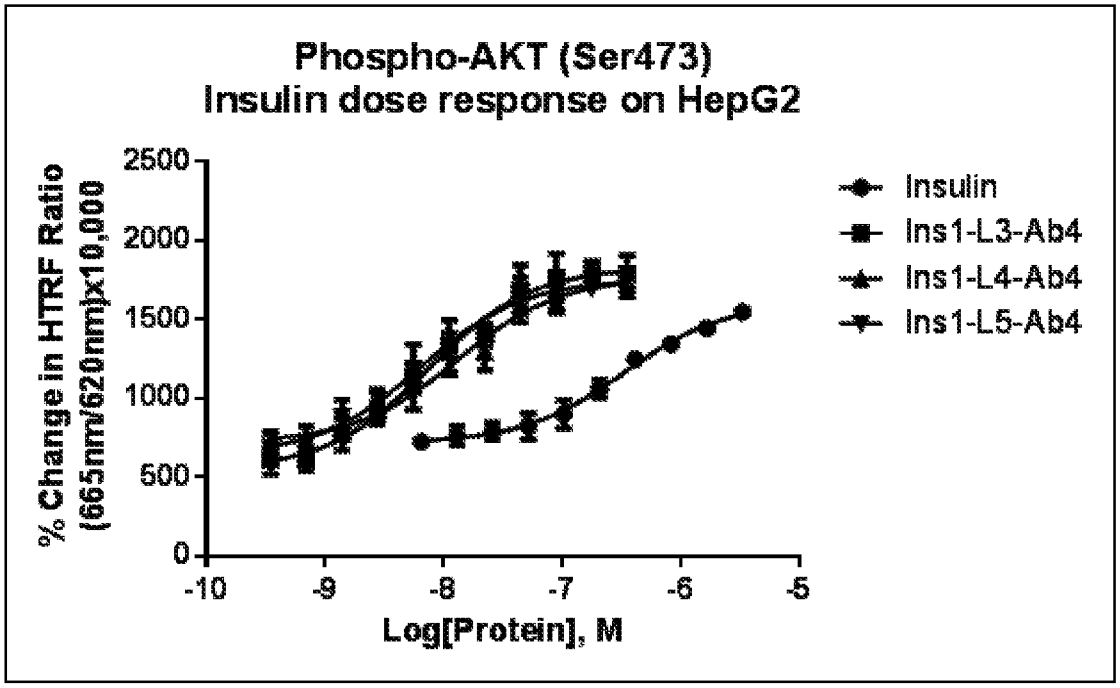
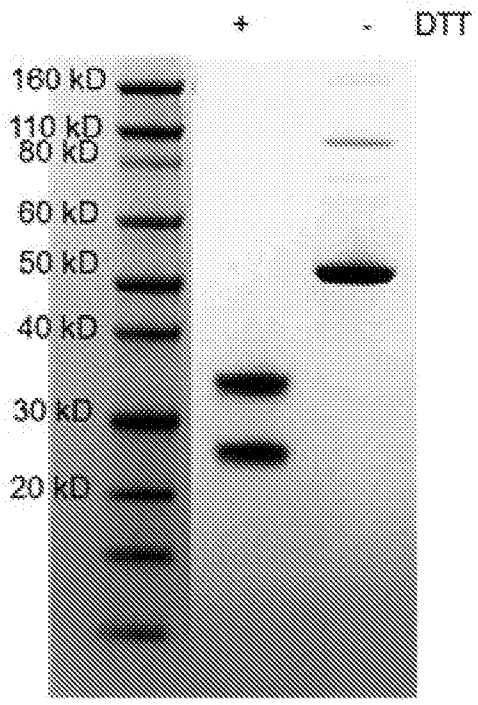
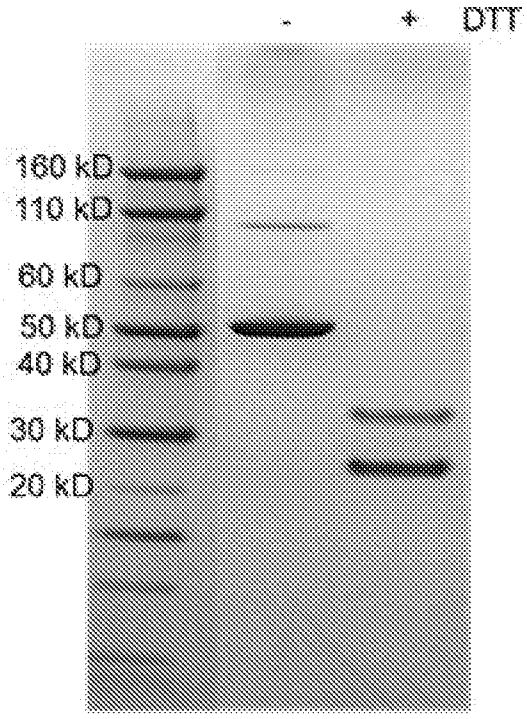

Phospho-AKT (Ser473)
Insulin dose response on HepG2
% Change in HTRF Ratio (665nm/620nm)x10,000
2500
2000
1500
1000
500
0
-10
-9
-8
-7
-6
-5
Log[Protein], M
Insulin
Ins1-L3-Ab4
Ins1-L4-Ab4
Ins1-L5-Ab4

FIG. 23



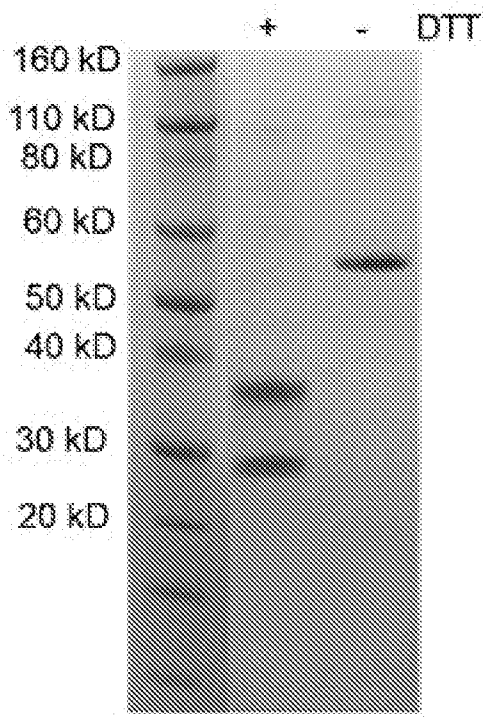
Ins1-L3-Ab4 Fab

FIG. 24



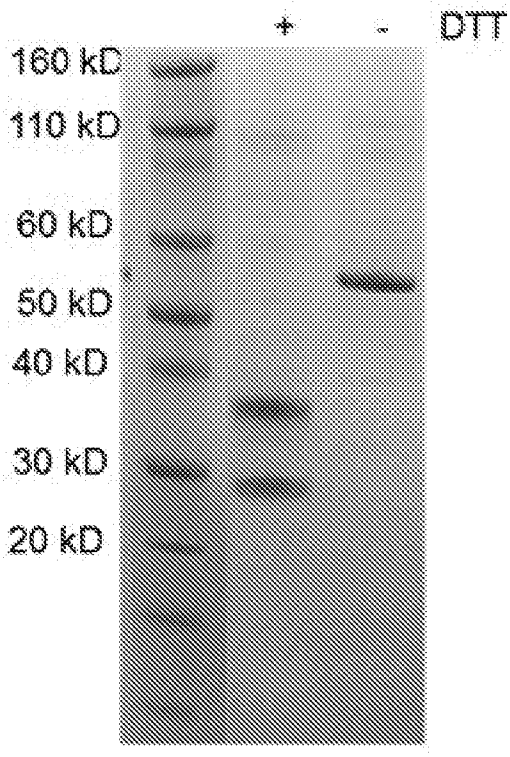
Ins1-L3-Ab5 Fab

FIG. 25



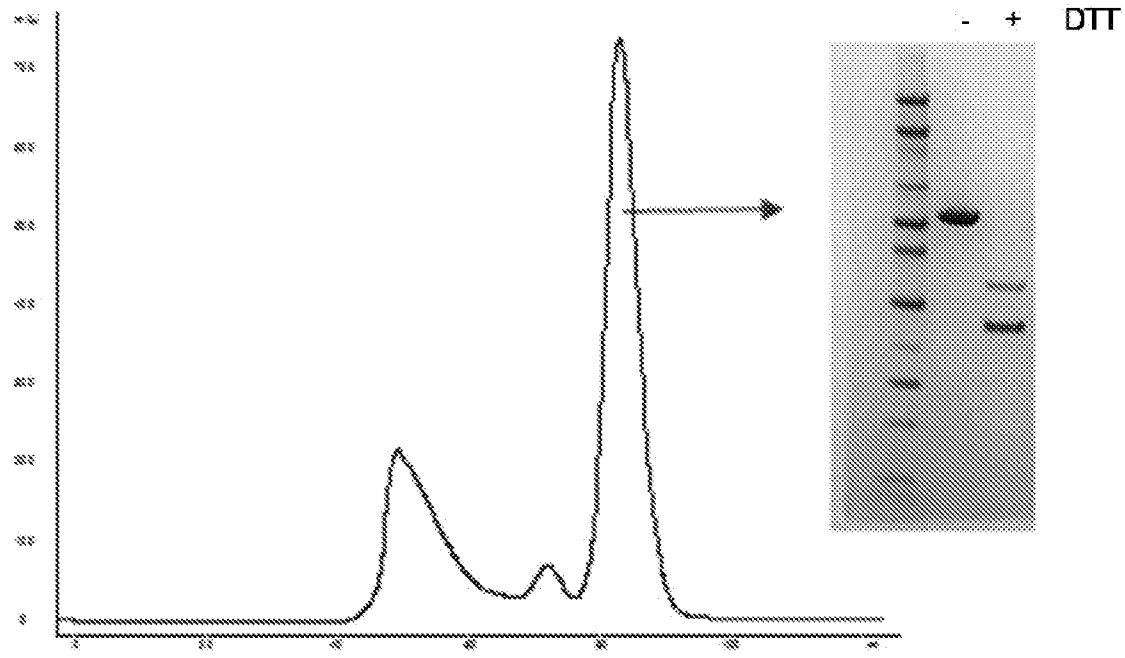
Ins7-L3-Ab4 Fab

FIG. 26



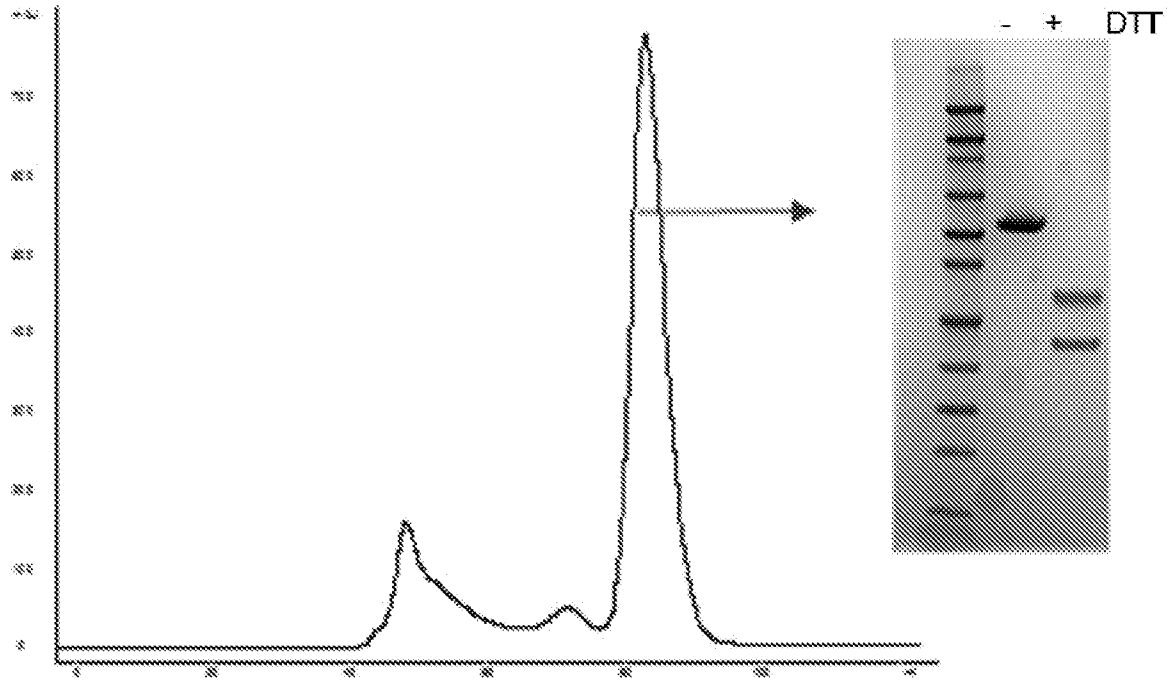
Ins7-L3-Ab5 Fab

FIG. 27



Ins1-L3-Ab4 Fab

FIG. 28



Ins1-L3-Ab5 Fab

FIG. 29

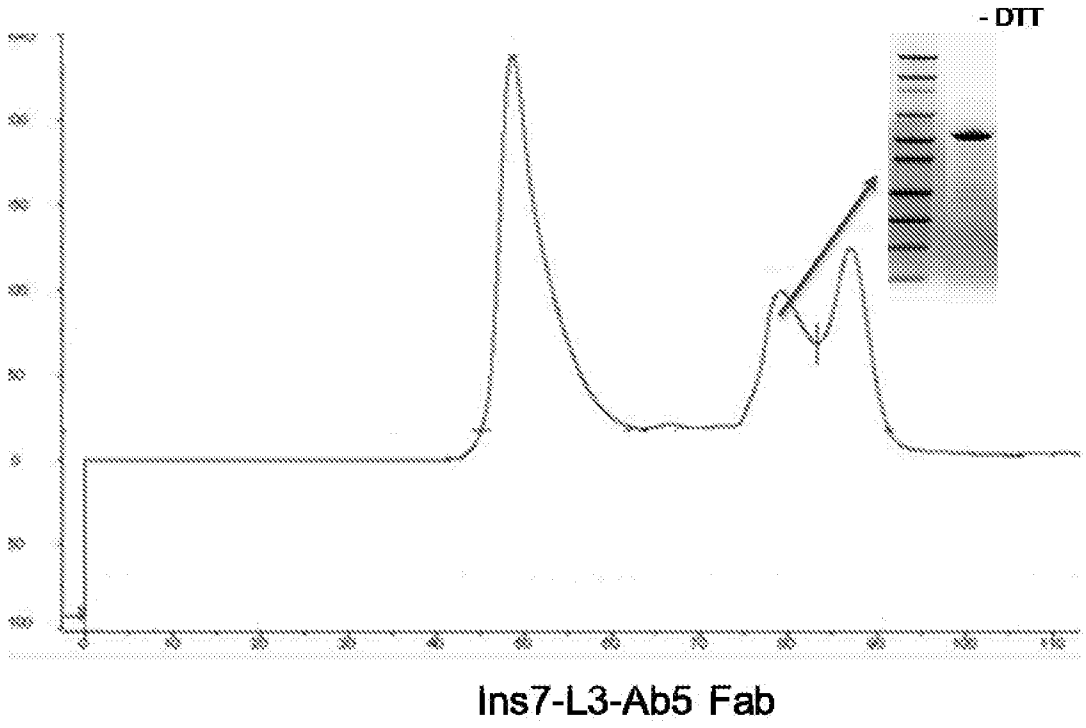
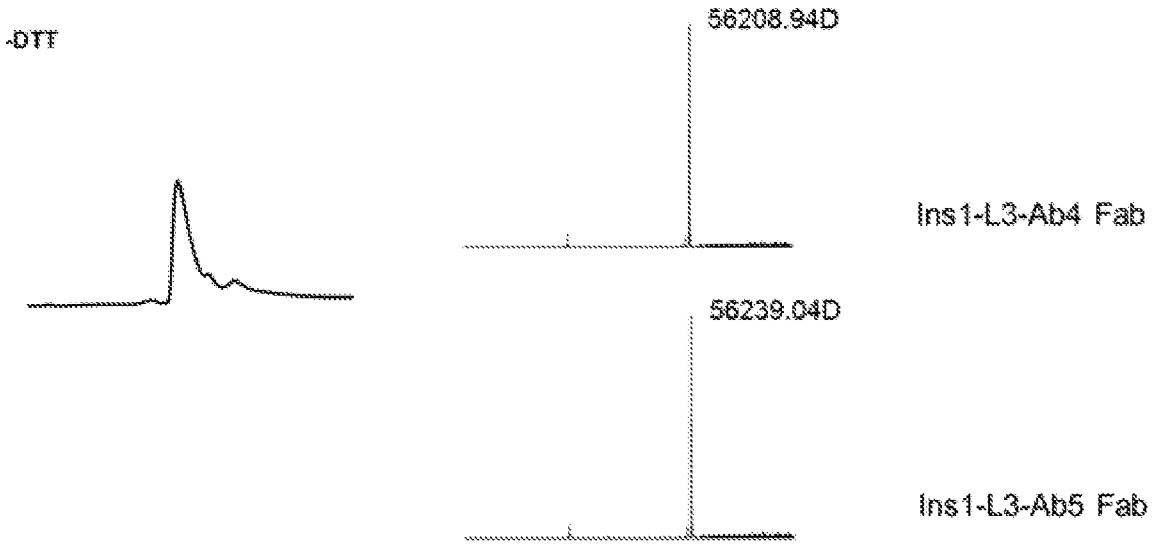
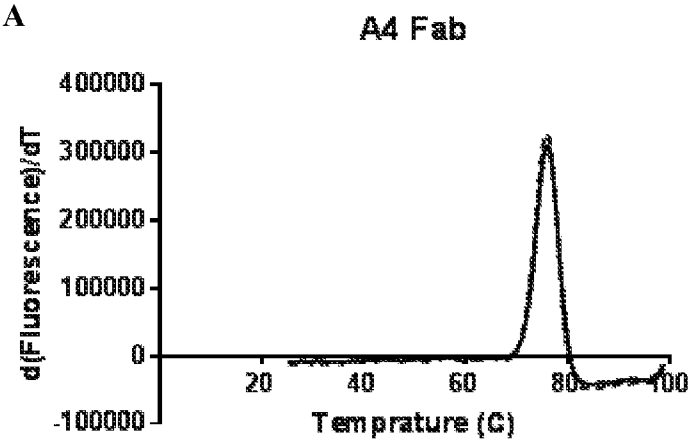

- DTT
Ins7-L3-Ab5 Fab

FIG. 30

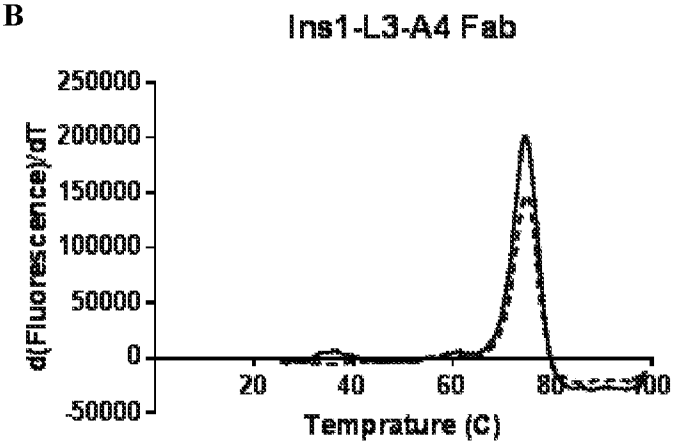

-DTT
56208.94D
Ins1-L3-Ab4 Fab
56239.04D
Ins1-L3-Ab5 Fab

FIGS. 31A-31C

A



B



C

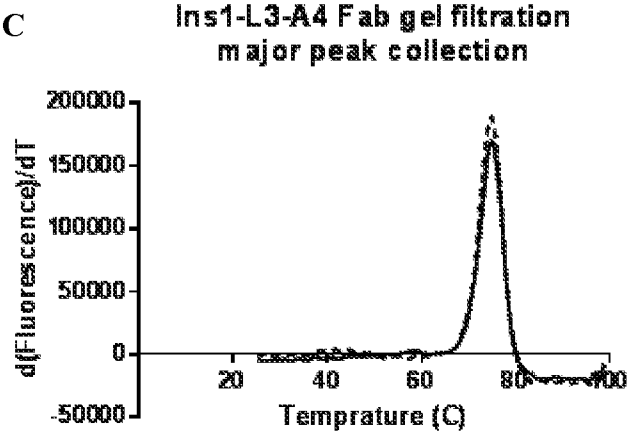


FIG. 32

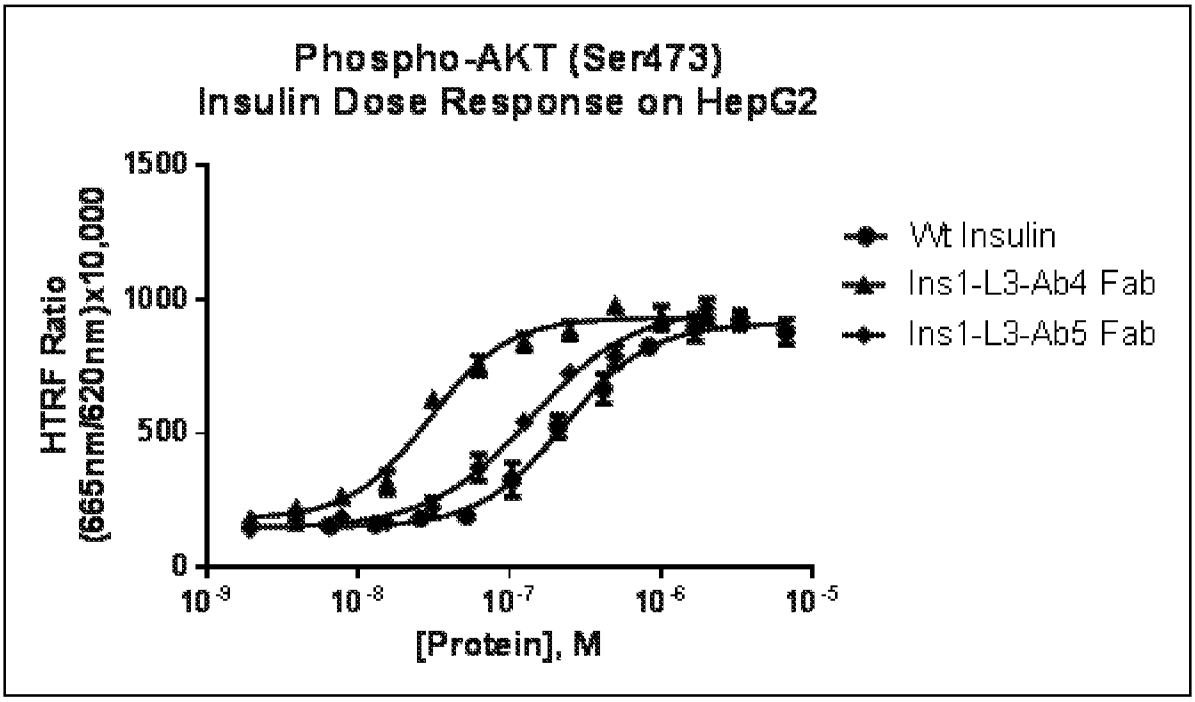

Phospho-AKT (Ser473)
Insulin Dose Response on HepG2
HTRF Ratio
(665nm/620nm)x10,000
1500
1000
500
0
10-9
10-8
10-7
10-6
10-5
[Protein], M
Wt Insulin
Ins1-L3-Ab4 Fab
Ins1-L3-Ab5 Fab

FIG. 33

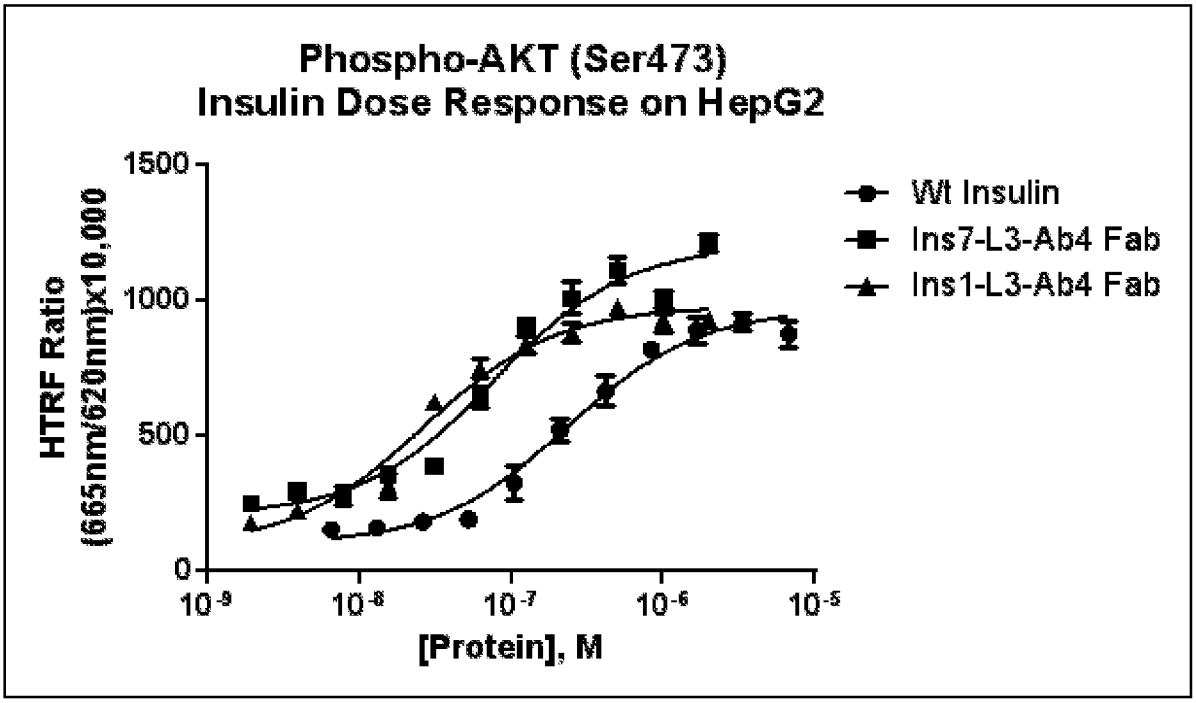

Phospho-AKT (Ser473)
Insulin Dose Response on HepG2
HTRF Ratio
(665nm/620nm)x10,000
1500
1000
500
0
10-9
10-8
10-7
10-6
10-5
[Protein], M
Wt Insulin
Ins7-L3-Ab4 Fab
Ins1-L3-Ab4 Fab

FIG. 34

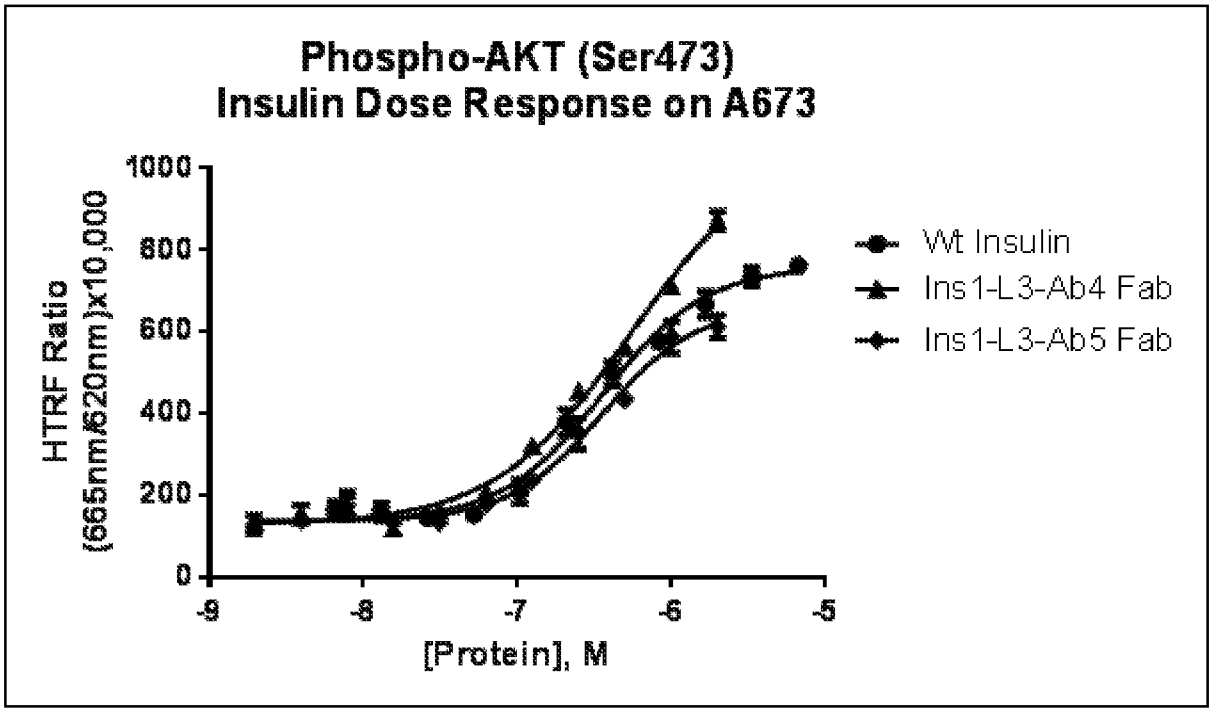

Phospho-AKT (Ser473)
Insulin Dose Response on A673
HTRF Ratio
(665nm/620nm)x10,000
1000
800
600
400
200
0
-9
-8
-7
-6
-5
[Protein], M
Wt Insulin
Ins1-L3-Ab4 Fab
Ins1-L3-Ab5 Fab

FIG. 35

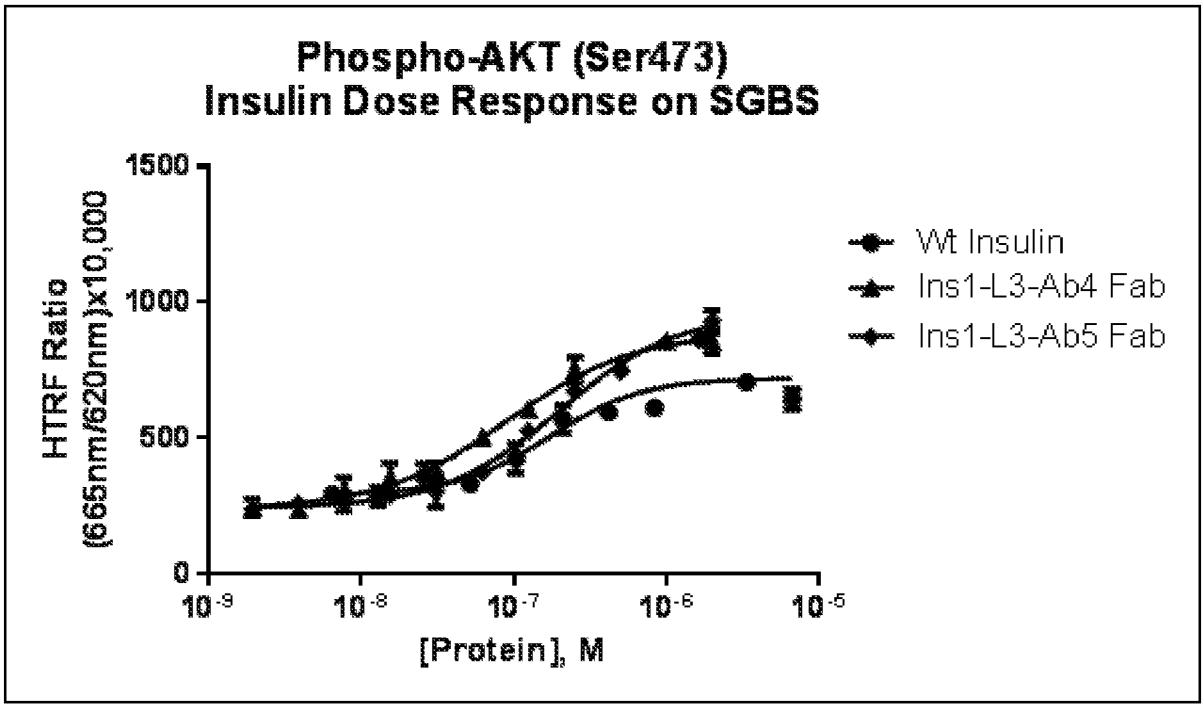

Phospho-AKT (Ser473)
Insulin Dose Response on SGBS
HTRF Ratio
(665nm/620nm)x10,000
1500
1000
500
0
10-9
10-8
10-7
10-6
10-5
[Protein], M
Wt Insulin
Ins1-L3-Ab4 Fab
Ins1-L3-Ab5 Fab

FIG. 36

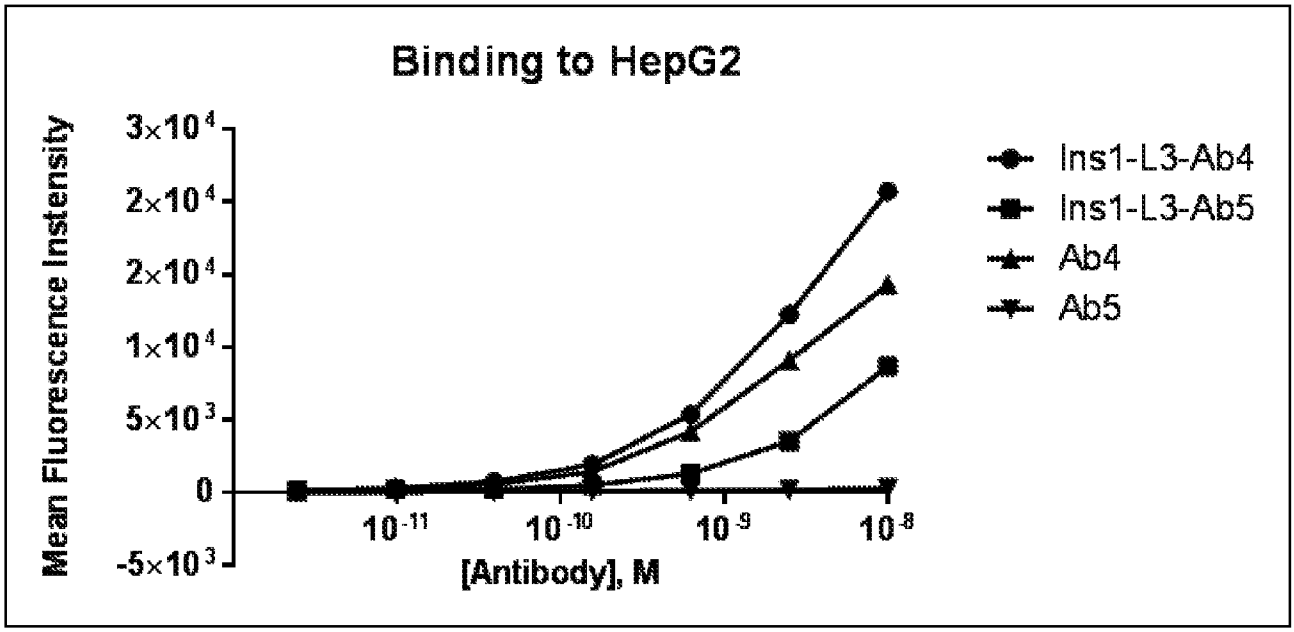

Binding to HepG2
Mean Fluorescence Instensity
3×10^4
2×10^4
2×10^4
1×10^4
5×10^3
0
-5×10^3
10^-11
10^-10
10^-9
10^-8
[Antibody], M
Ins1-L3-Ab4
Ins1-L3-Ab5
Ab4
Ab5

FIG. 37

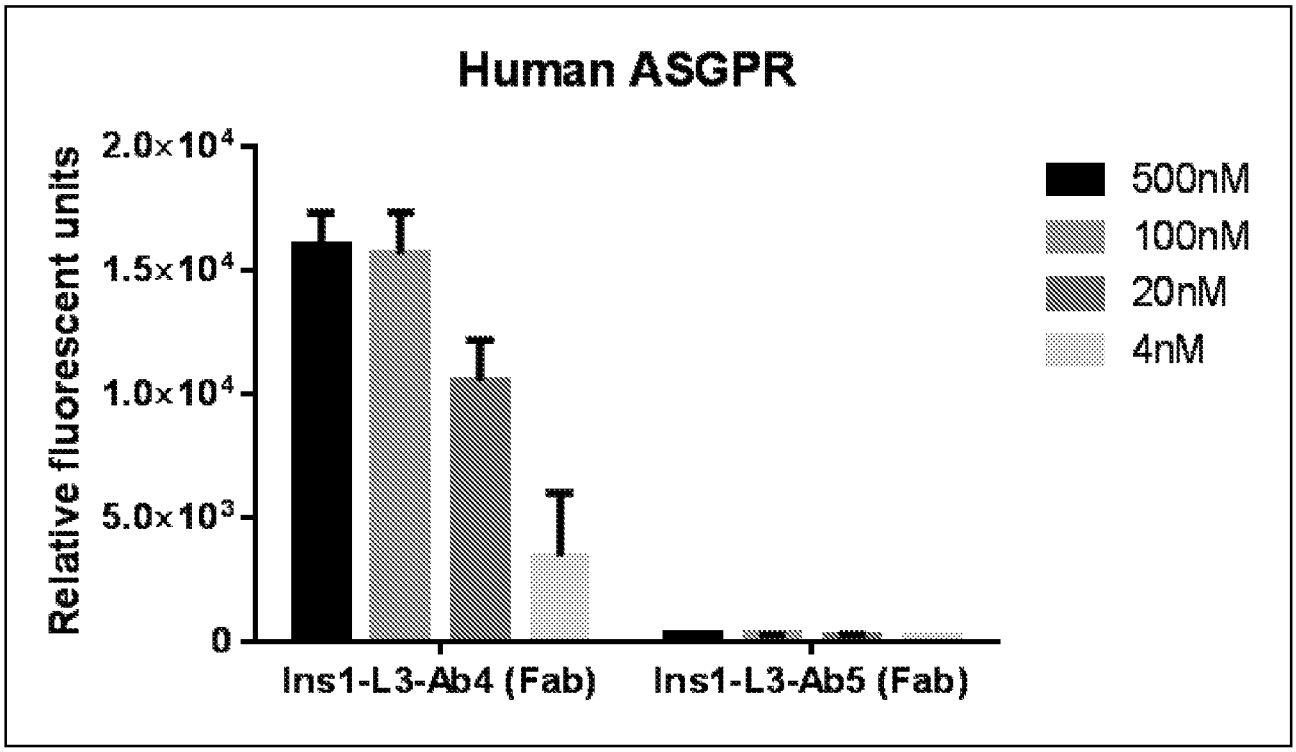

Human ASGPR
Relative fluorescent units
2.0×10^4
1.5×10^4
1.0×10^4
5.0×10^3
0
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)
500nM
100nM
20nM
4nM

FIG. 38

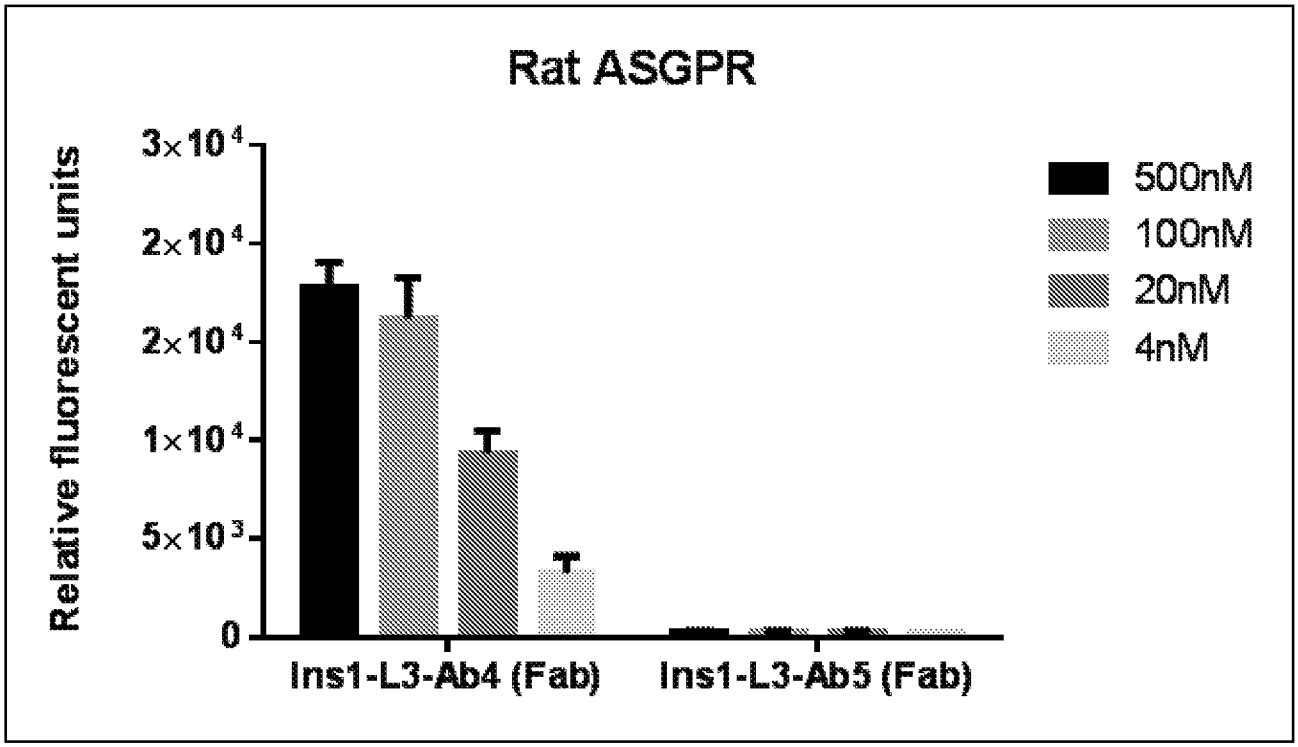

Rat ASGPR
Relative fluorescent units
3×10⁴
2×10⁴
2×10⁴
1×10⁴
5×10³
0
500nM
100nM
20nM
4nM
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)

FIG. 39

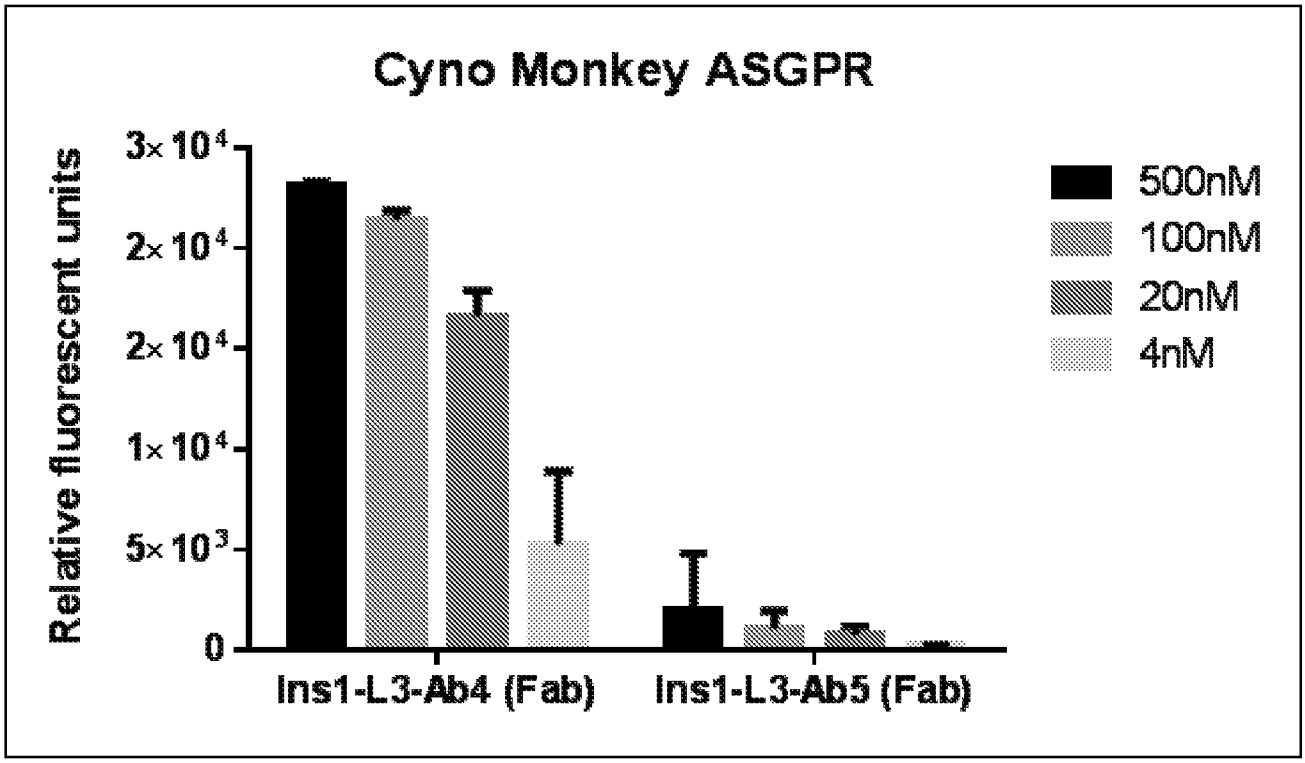

Cyno Monkey ASGPR
Relative fluorescent units
3×10⁴
2×10⁴
2×10⁴
1×10⁴
5×10³
0
500nM
100nM
20nM
4nM
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)

FIG. 40

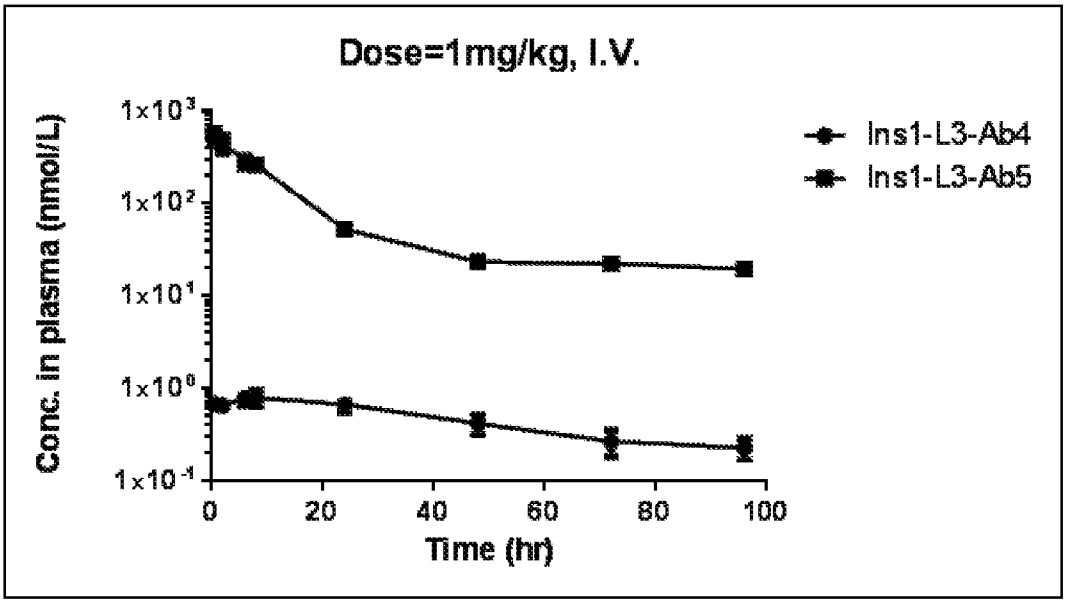

Dose=1mg/kg, I.V.
Conc. in plasma (nmol/L)
1x10³
1x10²
1x10¹
1x10⁰
1x10⁻¹
0
20
40
60
80
100
Time (hr)
Ins1-L3-Ab4
Ins1-L3-Ab5

FIG. 41

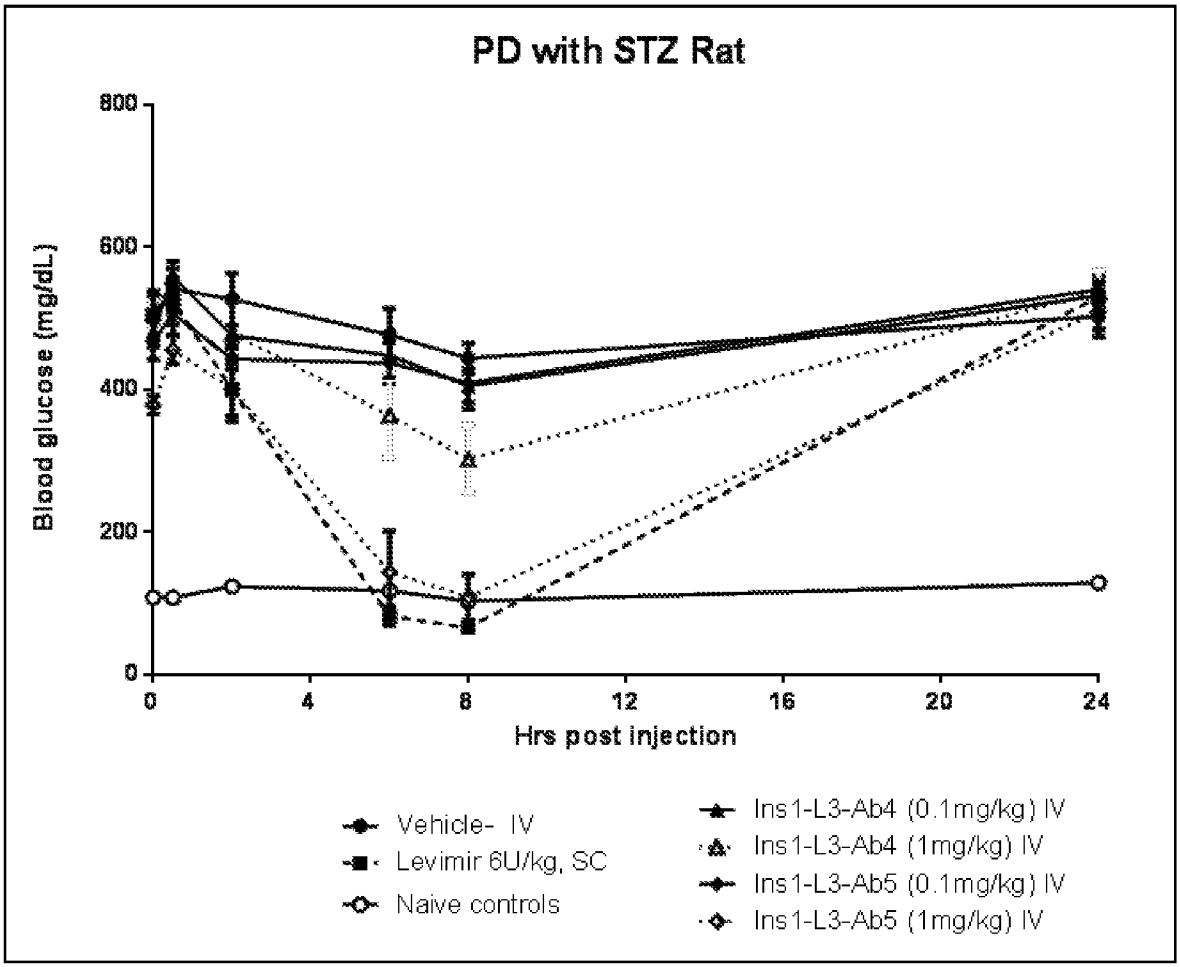

PD with STZ Rat
Blood glucose (mg/dL)
800
600
400
200
0
0
4
8
12
16
20
24
Hrs post injection
Vehicle- IV
Levimir 6U/kg, SC
Naive controls
Ins1-L3-Ab4 (0.1mg/kg) IV
Ins1-L3-Ab4 (1mg/kg) IV
Ins1-L3-Ab5 (0.1mg/kg) IV
Ins1-L3-Ab5 (1mg/kg) IV

FIG. 42

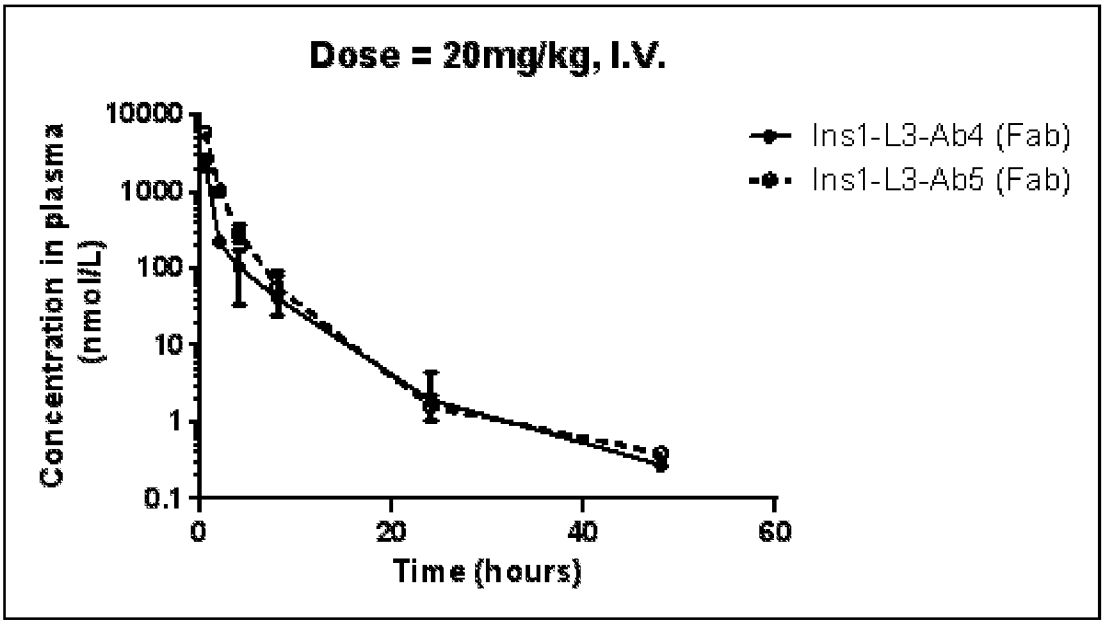

Dose = 20mg/kg, I.V.
Concentration in plasma (nmol/L)
10000
1000
100
10
1
0.1
0
20
40
60
Time (hours)
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)

FIG. 43

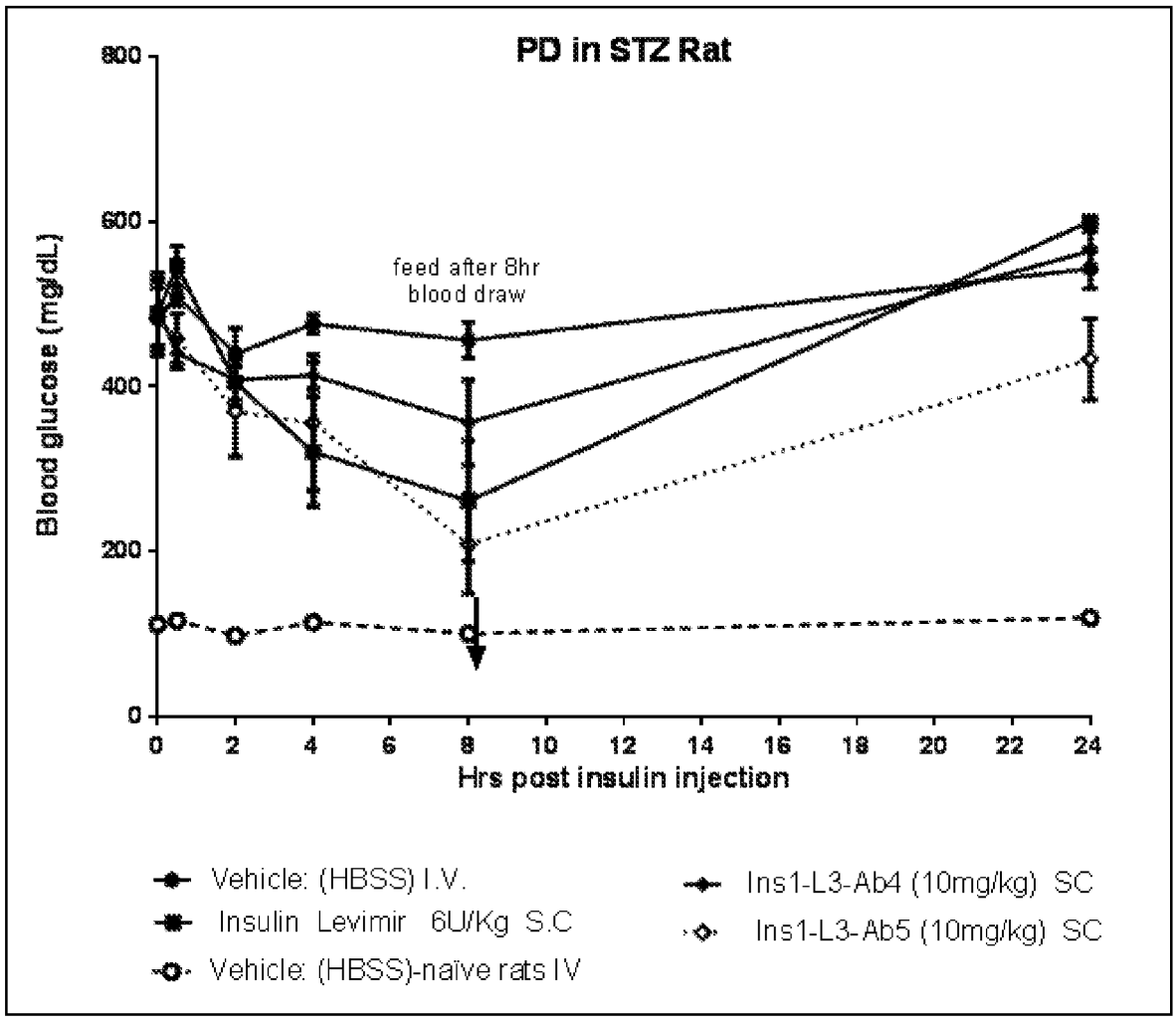

PD in STZ Rat
Blood glucose (mg/dL)
800
600
400
200
0
feed after 8hr
blood draw
0
2
4
6
8
10
12
14
16
18
20
22
24
Hrs post insulin injection
Vehicle: (HBSS) I.V.
Insulin Levimir 6U/Kg S.C
Vehicle: (HBSS)-naïve rats IV
Ins1-L3-Ab4 (10mg/kg) SC
Ins1-L3-Ab5 (10mg/kg) SC

FIG. 44

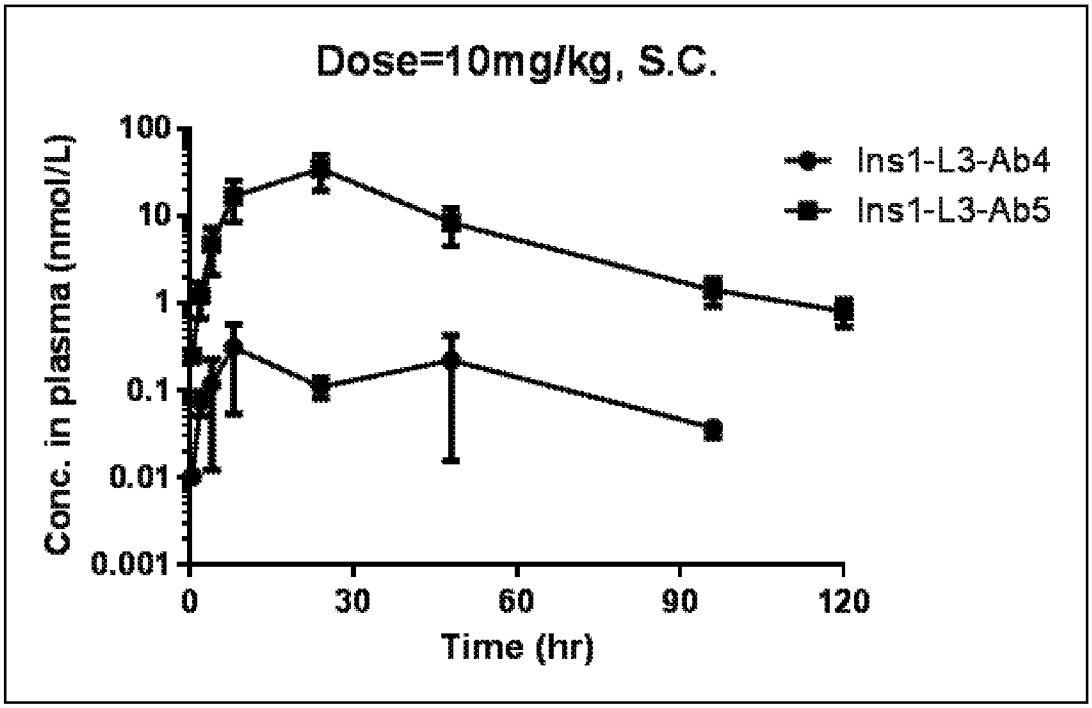

Dose=10mg/kg, S.C.
Conc. in plasma (nmol/L)
100
10
1
0.1
0.01
0.001
0
30
60
90
120
Time (hr)
Ins1-L3-Ab4
Ins1-L3-Ab5

FIG. 45

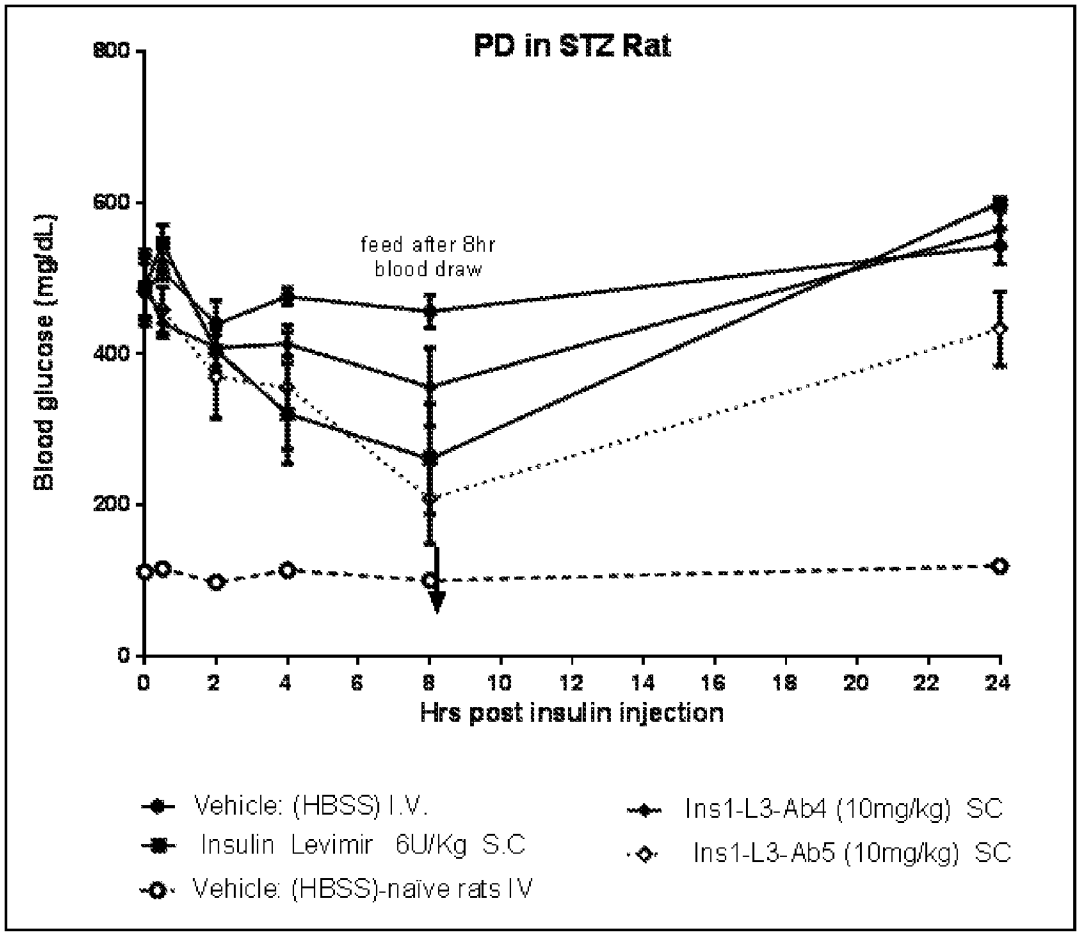

PD in STZ Rat
Blood glucose (mg/dL)
800
600
400
200
0
feed after 8hr
blood draw
0
2
4
6
8
10
12
14
16
18
20
22
24
Hrs post insulin injection
Vehicle: (HBSS) I.V.
Insulin Levimir 6U/Kg S.C
Vehicle: (HBSS)-naïve rats IV
Ins1-L3-Ab4 (10mg/kg) SC
Ins1-L3-Ab5 (10mg/kg) SC

FIG. 46

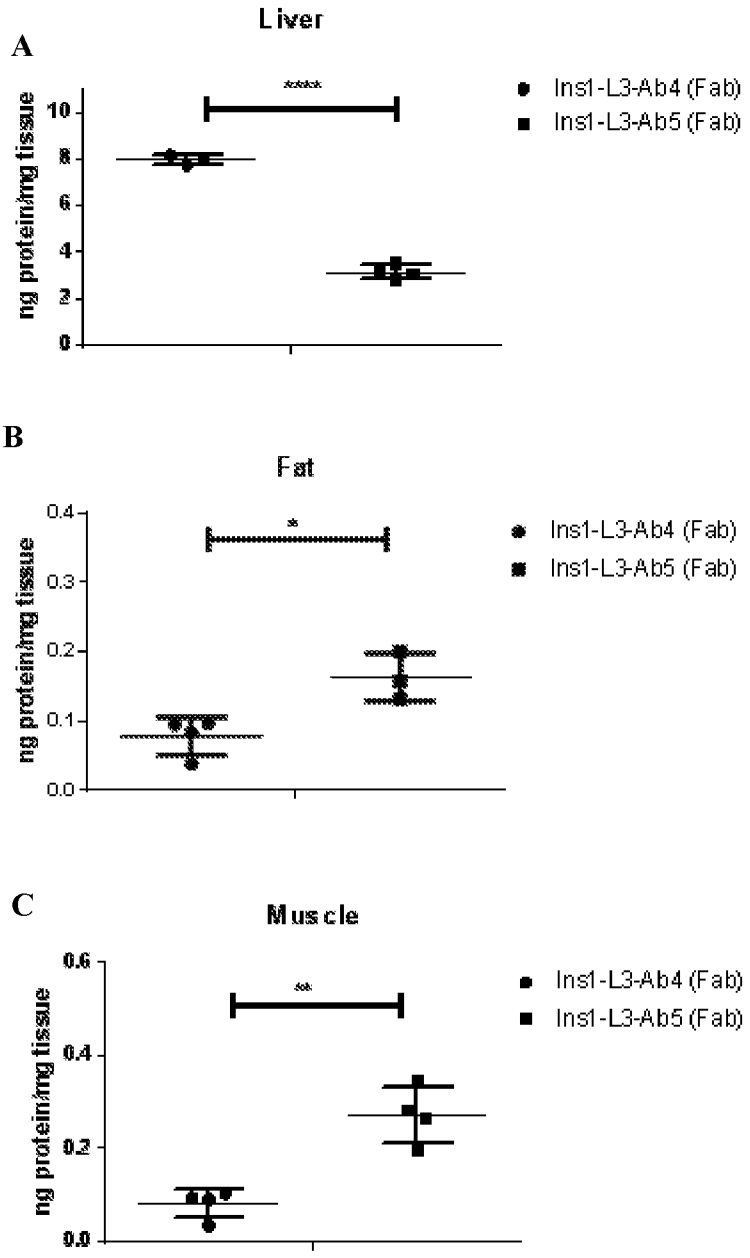

A
Liver
ng protein/mg tissue
10
8
6
4
2
0
****
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)
B
Fat
ng protein/mg tissue
0.4
0.3
0.2
0.1
0.0
*
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)
C
Muscle
ng protein/mg tissue
0.6
0.4
0.2
0.0
**
Ins1-L3-Ab4 (Fab)
Ins1-L3-Ab5 (Fab)

FIG. 47


Alignment
Human ASGPR QNSQLQEELRGLRETFSNFTASTEAQVKGLSTQGGNVGRKMKSLESQLEK
Cyno Monkey ASGPR QNAQLQEELRGLRETLSNFTASTEAQVKGLSTQGGNVGRKMKSLESQLEK
Rat ASGPR QNSQLEEDLRVLRQNFSNFTVSTETQVKALTTQGERVGRKMKLVESQLEK
Mouse ASGPR QNSQLEEDLLALRQNFSNLTVSTETQVKALSTQGSSVGRKMKLVESKLEK
Human ASGPR QQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERTCCPVNWVEH
Cyno Monkey ASGPR QQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERACCPVNWVEH
Rat ASGPR QQEDLAEDHSALLLHVKQLVSDVRSLSCQMAALEGNGSERICCPINWVEY
Mouse ASGPR QQKDLIEDHSSLLLHVEQLVSDVRSLSCQMAAIEGNGSERTCCPINWVEY
Human ASGPR ERSCYWFSRSGKAWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTW
Cyno Monkey ASGPR ERSCYWFSRSGKAWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGPVNTW
Rat ASGPR EQSCYWFSSSVKPWTEADSYCQLENAHLVVVTSWEEQRFVQQHMGPLNTW
Mouse ASGPR EQSCYWFSSSVRPWTEADKYCQLENAHLVVVTSPDEQNFLQRHMGPLNTW
Human ASGPR MGLHDQNGPWKWVDGTDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDD
Cyno Monkey ASGPR MGLHDQNGPWKWVDGTDYETGFKNWRPEQPDDWYGHGLGGGEDCAHFTDD
Rat ASGPR IGLTDQNGPWKWVDGTDYETGFKNWRPGQPDDWYGHGLGGGEDCAHFTTD
Mouse ASGPR IGLTDQNGFWKWVDGTDYETGFQNWRPEQPDNWYGHGLGGGEDCAHFTTD
Human ASGPR GRWNDDVCQRPYRWVCETELDKASQEPPLL
Cyno Monkey ASGPR GRWNDDVCQRPYRWVCETELRKASQEPPLL
Rat ASGPR GRWNDDVCRRPYRWVCETELGKAN----
Mouse ASGPR GRWNDDVCRRPYRWVCETELGKAN----

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A61K 38/28 (2006.01)

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(72) **Inventors**: **WANG, Feng**; 6151 Citracado Circle, Carlsbad, California 92009 (US). **TREMBLAY, Matthew S.**; 16777 Santanella Street, San Diego, California 92127 (US). **YOUNG, Travis**; 8012 Paseo Del Ocaso, La Jolla, California 92037 (US). **ALVAREZ, Nicole**; 1133 Adele Ln., San Marcos, California 92078 (US). **LIU, Yan**; 10717 Calle Mar De Mariposa, San Diego, California 92130 (US). **DU, Juanjuan**; 9120 Judicial Drive, Apt. 7127, San Diego, California 92122 (US). **SCHULTZ, Peter G.**; 1650 La Jolla Rancho Road, La Jolla, California 92037 (US).

(74) **Agent**: **HARDT, Ingo H.**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

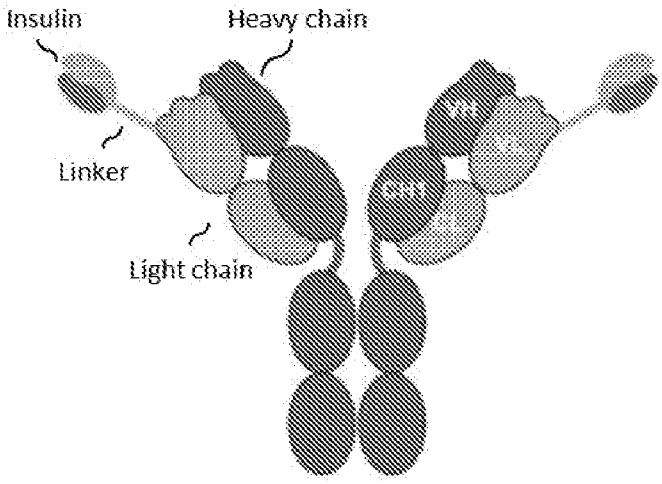
(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) **Title**: INSULIN IMMUNOGLOBULIN FUSION PROTEINS

(57) **Abstract**: Disclosed herein are immunoglobulin fusion proteins comprising an insulin therapeutic peptide and an immunoglobulin region that targets the insulin therapeutic peptide to the liver of an individual in need thereof. Further disclosed herein are compositions comprising the immunoglobulin fusion proteins and methods for using the immunoglobulin fusion proteins for the treatment or prevention of a disease or condition in a subject, for example, diabetes and diabetes related conditions.

FIG. 1A



WO 2017/041001 A3

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
4 May 2017

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/50213

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international searchwas carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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

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

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

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

3. ☒ Claims Nos.: 5-7, 10-13, 16, 19-44, 48-55, 62-93, 101-108, 114-136
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2, 3/1-2, 4/1-2, 8/1-2, 9/1-2, 14/1-2, 15/14/1-2, 45-47, 56-60, 61/59-60, 94-96, 97/94-96, 99-100, 109-113; SEQ ID NOs: 29,-30, 45-50, 78, 155

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/22, 38/28, 38/38 (2017.01)
CPC - A61K 38/22, 38/28, 38/38
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 38/00, 38/22, 38/28, 38/38 (2017.01)
CPC: A61K 38/00, 38/22, 38/28, 38/38

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO Discovery; PubMed; Google Scholar; The Lens; ENA; NCBI Blast; KEYWORDS: insulin, immunoglobulin, fusion protein therapeutic peptide, antigen binding domain, hepatocyte, liver, antigen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZHAO, X et al. 'Construction and Characterization of an Anti-Asialoglycoprotein Receptor Single-Chain Variable-Fragment-Targeted Melittin' Biotechnology and applied biochemistry, November 1, 2011, Vol. 58, No.6 pp. 405-411; abstract; page 404, first column, second paragraph; page 407, second column, fourth paragraph. DOI: 10.1002/bab.57	1-2, 3/1-2, 4/1-2 , 8/1-2, 9/1-2, 14/1-2, 15/14/1-2, 46-47, 109-113
Y	US 2013/0253172 A1 (ONCOMED PHARMACEUTICALS, INC.) September 26, 2013; paragraph [0025]	3/1-2
Y	US 2007/0136826 A1 (DUNN, R et al.) June 14, 2007; paragraph [0142]	4/1-2, 46-47
Y	US 2010/0273988 A1 (KIMURA, N) October 28, 2010; paragraph [0236]	8/1-2
Y	WO 2013/133450 A1 (BIO MATRIX RESEARCH, INC.,et al) September 12, 2013; page 16, lines 1-2	9/1-2
Y	US 2006/0258852 A1 (LUGOVSKOY, A et al.) November 16, 2006; paragraph [0054]	14/1-2, 15/14/1-2
Y	US 9,034,372 B2 (SDG, INC.) May 19, 2015; abstract; figure 12; column 2, lines 16-24; column 3, lines 25-26, 63 to column 4, line 6; column 5, lines 29-31; column 63, lines 3-15, 42-57	1-2, 3/1-2, 4/1-2 , 8/1-2, 9/12, 56-60, 61/59-60 109-113
Y	US 2013/0129723 A1 (BLANKENSHIP, J et al.) May 23, 2013; paragraph [0452]	59-60, 61/59-60

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2017 (24.02.2017)	16 MAR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/0028918 A1 (SONG, D et al.) January 31, 2013; abstract; paragraphs [0025], [0029]	56-58, 61/59-60
A	US 2013/0156786 A1 (CORVEY, C et al.) June 20, 2013; paragraph [0321]	45
A	US 2006/0292140 A1 (PONATH, P et al.) December 28, 2006; Table 4	94-96, 97/94-96, 99-100

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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-***-Continued from Box III Observations where unity of invention is lacking -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-4, 8-9, 14-15, 17-18, 45-47, 56-61, 94-100, 109-113; SEQ ID NO: 29 (HC), SEQ ID NO: 30 (LC), SEQ ID NO: 45 (HCDR1), SEQ ID NO: 46 (HCDR2), SEQ ID NO: 47 (HCDR3); SEQ ID NO: 48 (LCDR1), SEQ ID NO: 49 (LCDR2); SEQ ID NO: 50 (LCDR3); SEQ ID NO: 78 (fusion protein); SEQ ID NO: 155 (first immunoglobulin amino terminus) are directed toward immunoglobulin fusion proteins comprising an insulin therapeutic peptide and an immunoglobulin region that targets the insulin therapeutic peptide to the liver.

The fusion protein will be searched to the extent that it encompasses SEQ ID NO: 29 (first exemplary HC), SEQ ID NO: 30 (first exemplary LC), SEQ ID NO: 45 (first exemplary HCDR1), SEQ ID NO: 46 (first exemplary HCDR2), SEQ ID NO: 47 (first exemplary HCDR3); SEQ ID NO: 48 (first exemplary LCDR1), SEQ ID NO: 49 (first exemplary LCDR2); SEQ ID NO: 50 (first exemplary LCDR3) SEQ ID NO: 78 (first exemplary fusion protein), and SEQ ID NO: 155 (first exemplary first immunoglobulin amino terminus). Applicant is invited to elect additional fusion protein(s) comprising HC(s) and/or LC(s) with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO: and, where applicable CDR(s), represented by SEQ ID NO(s) or with specified substitution(s) at specified site(s) of a SEQ ID NO:, and/or associated immunoglobulin amino terminus sequence(s) to be searched. Additional sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-2, 3 (in-part), 4 (in-part), 8 (in-part), 9 (in-part), 14-15, 45 (in-part), 46 (in-part), 47 (in-part), 56-61, 94 (in-part), 95 (in-part), 96 (in-part), 97 (in-part), 99 (in-part), 100 (in-part), and 109-113 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 29 (HC), SEQ ID NO: 30 (LC), SEQ ID NO: 45 (HCDR1), SEQ ID NO: 46 (HCDR2), SEQ ID NO: 47 (HCDR3); SEQ ID NO: 48 (LCDR1), SEQ ID NO: 49 (LCDR2); SEQ ID NO: 50 (LCDR3) SEQ ID NO: 78 (fusion protein), and SEQ ID NO: 155 (first immunoglobulin amino terminus). Applicants must specify the claim(s) that encompass any additionally elected sequence(s). Applicants must further indicate, if applicable, the claim(s) which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a fusion protein encompassing SEQ ID NO: 79 (first exemplary fusion protein), and SEQ ID NO: 156 (first exemplary elected immunoglobulin amino terminus).

No technical features are shared between the fusion protein sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: an insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide and a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell; a composition comprising a molecule of Formula XVII: I-L-G (Formula XVII) wherein: I has the formula B-A, A-B, B-C-A, or A-C-B; wherein B comprises an insulin B chain; A comprises an insulin A chain; if present, C comprises a connecter connecting B and A; and B-A, A-B, or both B-A and A-B are linked by a moiety or disulfide bond; L comprises a linker; and G comprises an immunoglobulin, immunoglobulin fragment, peptide or other ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte; an immunoglobulin for specific binding to asialoglycoprotein receptor (ASGPR); and a method of treating a disease or condition associated with glucose metabolism in a subject in need thereof, the method comprising administering an effective amount of an insulin immunoglobulin fusion protein comprising an insulin therapeutic peptide and an immunoglobulin region comprising an antigen binding domain, wherein the antigen binding domain targets an antigen expressed or displayed by a hepatocyte.

However, these shared technical features are previously shared by US 9,034,372 B2 (SDG, INC.) (hereinafter 'SDG') in view of the publication entitled 'Construction and Characterization of an Anti-Asialoglycoprotein Receptor Single-Chain Variable-Fragment-Targeted Melittin' by Zhao, et al. (hereinafter 'Zhao').

SDG discloses an insulin therapeutic peptide (delivery of insulin for treatment of diabetes; abstract; column 5, lines 56-62) associated with a lipid construct that targets the construct to a hepatocyte receptor (abstract); a composition comprising a liver-targeted insulin therapeutic peptide associated with a lipid construct that targets the construct to a hepatocyte receptor (abstract), comprising an insulin B chain (figure 12; column 2, lines 16-24) and an insulin A chain (figure 12; column 2, lines 16-24), wherein the A chain and B chain are linked by a disulfide bond (figure 12); and a method of treating a disease or condition associated with glucose metabolism in a subject in need thereof (a method of treating diabetes (a disease or condition associated with glucose metabolism) in a subject in need thereof; abstract; column 63, lines 42-57), the method comprising administering an effective amount of an a liver-targeted insulin therapeutic peptide associated with a lipid construct that targets the construct to a hepatocyte receptor (column 5, lines 29-31; column 63, lines 3-15).

SDG does not disclose a first immunoglobulin region comprising one or more portions of an antigen binding domain, wherein the antigen binding domain has specificity for an antigen of a liver cell; a linker connecting an immunoglobulin, immunoglobulin fragment, peptide or other ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte; and an immunoglobulin for specific binding to asialoglycoprotein receptor (ASGPR).

Zhao discloses an immunoglobulin fusion protein (abstract) comprising a therapeutic peptide (abstract; page 407, second column, fourth paragraph) and a first immunoglobulin region (first immunoglobulin region; abstract) comprising one or more portions of an antigen binding domain (comprising an ASGRP antibody; paragraph [0044]), wherein the antigen binding domain has specificity for an antigen of a liver cell (the antigen binding domain has specificity for asialoglycoprotein receptor (an antigen of a liver cell); abstract); a linker connecting the therapeutic peptide and the ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte (a linker connecting the therapeutic peptide and the ligand that has specificity for binding to an antigen expressed or displayed by a hepatocyte; figure 1); and an immunoglobulin for specific binding to asialoglycoprotein receptor (ASGPR) (abstract).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of SDG to have provided an insulin-anti-ASPGR conjugate, based on the disclosure of Zhao, in order to more specifically target the insulin to ASPGR-expressing hepatocytes.

-***-Continued Within the Next Supplemental Box-***-

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-***-Continued from Previous Supplemental Box-***-

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the SDG and Zhao references, unity of invention is lacking.

摘要

本发明公开了免疫球蛋白融合蛋白，其包含胰岛素治疗肽和将胰岛素治疗肽靶向需要胰岛素治疗肽的个体肝脏的免疫球蛋白区域。本发明进一步公开了包含免疫球蛋白融合蛋白的组合物和使用免疫球蛋白融合蛋白治疗或预防受试者疾病或病症，例如糖尿病和糖尿病相关病症的方法。