[CLAIMS]

[Claim 1]

A pharmaceutical composition for the prevention or treatment of diabetes mellitus, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a variant selected from the group consisting of substitution, addition, deletion, modification and combinations thereof in one amino acid of a native insulin at a position selected from the group consisting of amino acids at positions 8, 12, 16, 24, and 25 of B chain and at positions 1, 2, and 16 of A chain.

[Claim 2]

A pharmaceutical composition for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in diabetic patients, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a variant selected from the group consisting of substitution, addition, deletion, modification and combinations thereof in one amino acid of a native insulin at a position selected from the group consisting of amino acids at positions 8, 12, 16, 24, and 25 of B chain and at positions 1, 2 and 16 of A chain.

[Claim 3]

A pharmaceutical composition for the prevention or treatment of diabetes mellitus, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a substitution in one amino acid of a native insulin at the position selected from the group consisting of positions 8 and 23 to 25 of the B chain of native insulin, and 1, 2, 14, and 19 of the A chain of native insulin is substituted with other amino acid,

wherein the amino acid at position 8 of the B chain is substituted with alanine; the amino acid at position 23 of the B chain is substituted with alanine; the amino acid at position 24 of the B chain is substituted with alanine; the amino acid at position 25 of the B chain is substituted with alanine; the amino acid at position 1 of the A chain is substituted with alanine; the amino acid at position 2 of the A chain is substituted with alanine; the amino acid at position 14 of the A chain is substituted with glutamic acid or asparagine; or the amino acid at position 19 of the A chain is substituted with alanine.

[Claim 4]

A pharmaceutical composition for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in diabetic patients, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a substitution in one amino acid of a native insulin at the position selected from the group consisting of positions 8 and 23 to 25 of the B chain of native insulin, and 1, 2, 14, and 19 of the A chain of native insulin is substituted with other amino acid,

wherein the amino acid at position 8 of the B chain is substituted with alanine; the

amino acid at position 23 of the B chain is substituted with alanine; the amino acid at position 24 of the B chain is substituted with alanine; the amino acid at position 25 of the B chain is substituted with alanine; the amino acid at position 1 of the A chain is substituted with alanine; the amino acid at position 2 of the A chain is substituted with alanine; the amino acid at position 14 of the A chain is substituted with glutamic acid or asparagine; or the amino acid at position 19 of the A chain is substituted with alanine.

[Claim 5]

The composition according to claim 1 or 2, wherein the insulin analogue comprises the amino acid sequence selected from the group consisting of SEQ ID Nos. 20, 22, 24, 26, 28, 30, 32, 34 and 36.

[Claim 6]

The composition according to claim 1 or 2, wherein the insulinotropic peptide is selected from the group consisting of GLP-1, exendin-3, exendin-4, agonists thereof, derivatives thereof, fragments thereof, variants thereof, and combinations thereof.

[Claim 7]

The composition according to claim 6, wherein the insulinotropic peptide is an insulinotropic peptide derivative in which the N-terminal histidine residue of insulinotropic peptide is substituted with a substance selected from the group consisting of des-amino-histidyl, dimethyl-histidyl, beta-hydroxy imidazopropionyl, 4-imidazoacetyl, and beta-carboxy imidazopropionyl.

[Claim 8]

The composition according to claim 7, wherein the insulinotropic peptide is selected from the group consisting of a native exendin-4, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is deleted, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is substituted with a hydroxyl group, an exendin-4 derivative in which the N-terminal amine group of exendin-4 is modified with a dimethyl group, an exendin-4 derivative in which α-carbon of the first amino acid (histidine) of exendin-4 is deleted, an exendin-4 variant in which the 12^{th} amino acid (lysine) of exendin-4 is substituted with serine, and an exendin-4 variant in which the 12^{th} amino acid (lysine) of exendin-4 is substituted with arginine.

[Claim 9]

The composition according to claim 1 or 2, wherein the long-acting insulin analogue conjugate is characterized that an insulin analogue in which an amino acid at position 14 of A

chain of insulin is substituted with glutamic acid, is linked to an immunoglobulin Fc region via a non-peptidyl polymer as a linker, and the long-acting insulinotropic peptide conjugate is characterized that an imidazo-acetyl exendin-4 as insulinotropic peptide is linked to an immunoglobulin Fc region via a non-peptidyl polymer as a linker.

[Claim 10]

The composition according to claim 1 or 2, wherein the biocompatible material is selected from the group consisting of polyethylene glycol, fatty acid, cholesterol, albumin and fragments thereof, albumin-binding materials, a polymer of repeating units of a particular amino acid sequence, antibodies, antibody fragments, FcRn binding material, in vivo connective tissues or derivatives thereof, nucleotides, fibronectin, transferrin, saccharides, and polymers.

[Claim 11]

The composition according to claim 10, wherein the insulin analogue or the insulinotropic peptide is linked to the biocompatible material via a linker selected from the group consisting of polyethylene glycol, fatty acids, saccharides, polymers, low-molecular weight compounds, nucleotides, and combinations thereof.

[Claim 12]

The composition according to claim 1 or 2, wherein the insulin analogue or the insulinotropic peptide is linked to the biocompatible material via a linker, and the biocompatible material is an FcRn binding material, wherein the linker is a peptide linker or a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and combinations thereof.

[Claim 13]

The composition according to claim 12, wherein the FcRn binding material includes an immunoglobulin Fc region.

[Claim 14]

The composition according to claim 12, wherein each end of the non-peptidyl linker respectively binds to the biocompatible material and an amine or thiol group of the insulin analogue or the insulinotropic peptide.

[Claim 15]

The composition according to claim 13, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 16]

The composition according to claim 13, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3, and CH4 domains.

[Claim 17]

The composition according to claim 13, wherein the immunoglobulin Fc region further includes a hinge region.

[Claim 18]

The composition according to claim 13, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

[Claim 19]

The composition according to claim 13, wherein the immunoglobulin Fc region is hybrid of domains of different origins selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 20]

The composition according to claim 13, wherein the immunoglobulin Fc region is a dimer or a multimer composed of single-chain immunoglobulins consisting of domains of the same origin.

[Claim 21]

The composition according to claim 1 or 2, further comprising a pharmaceutically acceptable carrier.

[Claim 22]

The composition according to claim 1 or 2, wherein the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate are to be administered simultaneously, sequentially, or reversely.

[Claim 23]

The composition according to claim 2, wherein the composition inhibits the progression of diabetes.

[Claim 24]

The composition according to claim 2, wherein the composition improves diabetic prognosis of subject suffering from diabetes mellitus.

[Claim 25]

Use of the composition of claim 1 in the manufacture of a medicament for the treatment of diabetes mellitus.

[Claim 26]

Use of the composition of claim 2 in the manufacture of a medicament for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in a diabetic subject suffering from diabetes mellitus.

[Claim 27]

Use of the composition of claim 3 in the manufacture of a medicament for treating diabetes mellitus.

[Claim 28]

Use of the composition of claim 4 in the manufacture of a medicament for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in a diabetic subject suffering from diabetes mellitus.