

What is claimed is:

1. A fusion protein comprising a Glucagon-like peptide 1 (GLP1) variant fused to a stabilizing domain, wherein the GLP1 variant comprises the amino acid sequence of SEQ ID NO: 7, and the stabilizing domain is an antibody or antigen-binding fragment thereof that specifically binds GLP1 receptor~~mature GLP1 (7-37) (SEQ ID NO: 4) having an addition of glutamine (Gln) to the N-terminus~~, and wherein the fusion protein has enhanced resistance to proteolytic cleavage and/or enhanced blood glucose lowering ability as compared to a fusion protein comprising mature GLP1.
- ~~2. The fusion protein of claim 1, wherein the GLP1 variant comprises an amino acid sequence of SEQ ID NO: 6.~~
- ~~3. The fusion protein of any one of claims 1—2 further comprising a stabilizing domain, wherein the stabilizing domain is an antigen-binding protein or antigen-binding fragment thereof that specifically binds GLP1 receptor and that comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR).~~
- ~~4. The fusion protein of claim 3, wherein the stabilizing domain is an antigen-binding protein comprising a heavy chain and a light chain, and the GLP1 variant is fused to the N-terminal or C-terminal of the heavy chain of the antigen-binding protein.~~
- ~~5. The fusion protein of claim 3, wherein the stabilizing domain is an antigen-binding protein comprising a heavy chain and a light chain, and the GLP1 variant is fused to the N-terminal or C-terminal of the light chain of the antigen-binding protein.~~
2. The fusion protein of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR), and the GLP1 variant is fused to the N-terminus or C-terminus of the HCVR of the antigen-binding protein or antigen-binding fragment thereof.
3. The fusion protein of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR), and the GLP1 variant is fused to the N-terminus or C-terminus of the LCVR of the antigen-binding protein or antigen-binding fragment thereof.

~~6.4.~~ The fusion protein of ~~claim 3~~any one of claims 1-3, wherein the stabilizing domain is an antibody ~~or fragment thereof~~.

~~7.~~ A fusion protein comprising a Glucagon-like peptide 1 (GLP1) variant fused to a stabilizing domain, wherein: (i) the GLP1 variant comprises mature GLP1 (7-37) (SEQ ID NO: 4) having an addition of glutamine (Gln) to the N-terminus; (ii) the stabilizing domain is an antigen-binding protein or antigen-binding fragment thereof that binds specifically to GLP1 receptor; and (iii) the fusion protein has enhanced resistance to proteolytic cleavage and/or enhanced blood glucose lowering ability as compared to a fusion protein comprising mature GLP1.

~~8.~~ The fusion protein of claim 7, wherein the stabilizing domain is an antibody or antigen-binding fragment thereof that comprises a HCVR and a LCVR.

~~9.5.~~ The fusion protein of claim ~~8~~3, wherein the stabilizing domain is an antibody that comprises a heavy chain and a light chain, and the GLP1 variant is fused to the N-terminus ~~terminal~~ of the light chain LCVR of the antibody or antigen-binding fragment thereof.

~~10.~~ The fusion protein of any one of claims ~~7-9~~, wherein the GLP1 variant comprises an amino acid sequence of SEQ ID NO: 6.

~~11.6.~~ A pharmaceutical composition comprising a fusion protein of any one of claims ~~1-5-1-10~~ and a pharmaceutically acceptable carrier or diluent.

~~12.7.~~ An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a fusion protein as set forth in any one of claims ~~1-5-1-10~~.

~~13.8.~~ A vector comprising the polynucleotide molecule ~~sequence~~ of claim ~~12~~7.

~~14.9.~~ A cell expressing the vector of claim ~~13~~8.

~~15.10.~~ Use of the pharmaceutical composition of claim ~~11-6~~ in the manufacture of a medicament for lowering high blood sugar level in a subject in need thereof.

~~16.11.~~ The use of claim ~~15~~10, wherein the subject has a disease or disorder selected from the group consisting of diabetes mellitus, obesity, insulin resistance, hypertension, dyslipidemia, Type 2 diabetes, Type 1 diabetes, pre-diabetes, cardiovascular disease, atherosclerosis, congestive heart failure, coronary heart disease, arteriosclerosis, peripheral artery disease,

stroke, respiratory dysfunction, renal disease, fatty liver disease, non-alcoholic steatohepatitis (NASH), and metabolic syndrome.

~~17.12.~~ Use of the pharmaceutical composition of claim ~~11.6~~ in the manufacture of a medicament for preventing, treating or ameliorating at least one symptom or indication of Type 2 diabetes in a subject in need thereof.

~~18.13.~~ The use of claim ~~17.12~~, wherein the at least one symptom or indication is selected from the group consisting of high blood sugar level, excessive thirst, increased urination, presence of ketones in urine, fatigue, weight fluctuations, blurred vision, slow healing sores, frequent infections, swollen or tender gums, obesity, heart disease, stroke, kidney disease, eye disease, nerve damage and high blood pressure.

~~19.14.~~ The use of any one of claims ~~15-18~~10-13, wherein the pharmaceutical composition is ~~for administration~~ to be administered in combination with a second therapeutic agent or therapy.

~~20.15.~~ The use of claim ~~19.14~~, wherein the second therapeutic agent or therapy is selected from the group consisting of an insulin or insulin analogue, metformin, a thiazolidinedione, a sulfonylurea, a biguanide, chlorpropamide, a glinide, an alpha glucosidase inhibitor, nateglinide, a DPP4 inhibitor, pramlintide, sitagliptin, bromocriptine, a SGLT2 inhibitor, canagliflozin, an anti-hypertensive drug, a statin, aspirin, dietary modification, exercise, and a dietary supplement.

~~21.16.~~ The use of any one of claims ~~15-20~~10-15, wherein the pharmaceutical composition is ~~for administration~~ to be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, or intramuscularly.