

## Claims

1. A ~~modified GDF15 dimer~~polypeptide comprising ~~two covalently joined polypeptides, wherein the two polypeptides each comprise a~~contiguous amino acid sequence that is at least ~~95~~90% identical to the amino acid sequence of SEQ ID NO: 1, ~~wherein the polypeptides each comprise at least~~polypeptide comprises one of the following pairs of substitutions of the corresponding amino acids in SEQ ID NO: 1:

K91N and D93T/S or D93N and G95T/S;

wherein the polypeptide is suitable for use in the treatment or prevention of a metabolic disease, a metabolic-associated disease, a body weight disorder or a glucose metabolism disorder.

2. The polypeptide of claim 1, wherein the contiguous amino acid sequence is at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

~~2.3.~~ The ~~modified GDF15 dimer~~polypeptide of claim 1, wherein the ~~two polypeptides each comprise an amino acid sequence~~contiguous amino acid sequence is at least 97% identical to the amino acid sequence of SEQ ID NO: 1.

~~3.4.~~ The ~~modified GDF15 dimer~~polypeptide of claim 1, wherein the ~~two polypeptides lack~~polypeptide lacks the first three amino acids present at the N-terminus of SEQ ID NO: 1.

~~4.5.~~ The polypeptide of any one of claims 1 to 4, comprising~~The modified GDF15 dimer of claim 1, wherein the two polypeptides comprise the amino acid sequence set forth in SEQ ID NO: 30.~~

~~5.~~ The modified GDF15 dimer of claim 1, wherein the two polypeptides comprise the amino acid sequence set forth in SEQ ID NO: 13.

6. The ~~modified GDF15 dimer~~polypeptide of claim 1, wherein the ~~two polypeptides comprise the amino acid sequence set forth in SEQ ID NO: 92.~~

~~7. The modified GDF15 dimer of any one of the preceding claims, wherein at least one of the polypeptides~~polypeptide is fused to a heterologous polypeptide.

~~7. , optionally~~The polypeptide of claim 6, wherein the heterologous polypeptide is serum albumin, maltose binding protein, or immunoglobulin Fc polypeptide, and optionally wherein the heterologous polypeptide is conjugated to the N-terminus of the polypeptide or the C-terminus of the polypeptide.

~~8. The modified GDF15 A dimer comprising the polypeptide of any one of the preceding claims, wherein the dimer is N-glycosylated~~ 1 to 7.

~~9. The dimer of claim 8, which is (a) a homodimer and/or (b) N-glycosylated.~~

~~10. The dimer of claim 8 or claim 9, which is a modified GDF15 N-glycosylated dimer, which is a homodimer having two polypeptides each comprising the same amino acid sequences, wherein the polypeptides contain at least one N-glycosylation site that is N-glycosylated.~~

~~9.11. The modified GDF15 of claim 1, wherein the~~The dimer of any one of claims 8 to 10, wherein said dimer comprises two polypeptides each consisting of the amino acid sequence set forth in SEQ ID NO: 30.

~~10.12. A nucleic acid molecule encoding the modified GDF15 polypeptide of any one of claims 1 to 7 or the dimer of any one of claims 1 to 9, optionally 8 to 11 operably linked to an expression control element that confers expression of the nucleic acid molecule in vitro or in vivo.~~

~~13. A vector comprising the nucleic acid molecule of claim 12, wherein the nucleic acid molecule is operably linked to an expression control element that confers expression of the nucleic acid molecule in vitro or in vivo.~~

~~11.14. A. The vector comprising the nucleic acid molecule of claim 10~~13, wherein the vector optionally comprises a viral vector.

~~12.15.~~ A ~~genetically modified mammalian~~ host cell that expresses the ~~modified GDF15~~ polypeptide of any one of claims 1 to 7 or the dimer of any one of claims ~~1 to 9~~ 8 to 11.

~~13.16.~~ A pharmaceutical composition, comprising the ~~modified GDF15 dimer~~ polypeptide of any one of claims 1 to 97 or the dimer of any one of claims 8 to 11, and a pharmaceutically acceptable diluent, carrier or excipient.

~~14.17.~~ A sterile container comprising the pharmaceutical composition of claim 13, optionally ~~16~~ wherein the sterile container is a syringe.

18. The sterile container of claim 17, wherein the sterile container is a syringe.

~~15.19.~~ A method of making the ~~modified GDF15 dimer~~ polypeptide of any one of claims 1 to 97 or the dimer of any one of claims 8 to 11, the method comprising:

culturing a ~~mammalian~~ host cell expressing the polypeptide or dimer; and  
purifying the expressed polypeptide or dimer.

~~16.20.~~ The ~~modified GDF15~~ polypeptide of any one of claims 1 to 7 the dimer of any one of claims 18 to 911, or the pharmaceutical composition of claim ~~13~~ 16, for use in a method of treating or preventing ~~obesity or hyperglycemia~~ a metabolic disease, a metabolic-associated disease, a body weight disorder or a glucose metabolism disorder in a subject.

~~17.21.~~ The ~~modified GDF15~~ polypeptide, dimer or pharmaceutical composition for use according to claim ~~16~~ 20, wherein the subject ~~has~~ glucose metabolism disorder is diabetes mellitus, hyperglycemia, hyperinsulinemia, glucose intolerance or metabolic syndrome.

~~18.22.~~ The ~~modified GDF15~~ polypeptide, dimer or pharmaceutical composition for use according to claim ~~16~~ 20 or claim ~~17~~ 21, wherein the subject is ~~obese~~ human.

~~19.23.~~ The ~~modified GDF15~~ polypeptide, dimer or pharmaceutical composition for use according to any one of claims ~~16 to 18~~ 20 to 21, wherein the subject is ~~human~~ obese.