

CLAIMS

What is claimed is:

1. A complex comprising a first heterodimer and a second heterodimer, each of the first heterodimer and second heterodimer comprising:
 - a first polypeptide and a second polypeptide, wherein:
 - the first polypeptide comprising an IgG Fc sequence, the IgG Fc sequence comprising a CH3 sequence comprising at least one engineered protuberance; and
 - the second polypeptide comprising an IgG Fc sequence, the IgG Fc sequence comprising a CH3 sequence comprising at least one engineered cavity;
 - wherein the first polypeptide dimerizes with the second polypeptide via positioning of the protuberance of the first polypeptide into the cavity of the second polypeptide,
 - wherein either the C-terminus of the first polypeptide or the C-terminus of the second polypeptide is conjugated to the N-terminus of a GDF15 mutein comprising at least one N-linked glycosylation consensus site, and
 - wherein the GDF15 mutein in the first heterodimer dimerizes with the GDF15 mutein in the second heterodimer thereby forming the complex comprising the first heterodimer and second heterodimer.
2. The complex of claim 1, wherein the C-terminus of the first polypeptide is conjugated to the N-terminus of the GDF15 mutein.
3. The complex of any one of claims 1-2, wherein the GDF15 mutein comprises a contiguous amino acid sequence that is at least 90% identical to the amino acid sequence of wild type GDF15 (SEQ ID NO: 1).
4. The complex of any one of claims 1-3, wherein the GDF15 mutein comprises at least one substitution of the corresponding amino acid in SEQ ID NO: 1 that creates the N-linked glycosylation consensus site.

5. The complex of claim 4, wherein the substitution comprises D5T or D5S or R21N.
6. The complex of claim 4, wherein the GDF15 mutein comprises at least one of the following pairs of substitutions of the corresponding amino acids in SEQ ID NO: 1 that create the N-linked glycosylation consensus site:
- i) R16N and H18T or R16N and H18S;
 - ii) S23N and E25T or S23N and E25S;
 - iii) S50N and F52T or S50N and F52S;
 - iv) F52N and A54T or F52N and A54S;
 - v) R53N and A55T or R53N and A55S;
 - vi) S64N and H66T or S64N and H66S;
 - vii) K91N and D93T or K91N and D93S;
 - viii) D93N and G95T or D93N and G95S;
 - ix) T94N and V96T or T94N and V96S;
 - x) V96N and L98T or V96N and L98S;
 - xi) S97N and Q99T or S97N and Q99S; and
 - xii) A106N and D108T or A106N and D108S
7. The complex of any one of the preceding claims, wherein the contiguous amino acid sequence is at least 98 amino acids long and at least 95% identical to the amino acid sequence of SEQ ID NO: 1 and does not include the first amino acid, the first two amino acids, the first three amino acids, or the first six amino acids that correspond to the first amino acid, the first two amino acids, the first three amino acids, or the first six amino acids, respectively, present at the N-terminus of SEQ ID NO: 1, wherein the C-terminal amino acid corresponds to Isoleucine at position 112 in SEQ ID NO: 1.
8. The complex of claim 1, wherein the C-terminus of either the first polypeptide or the second polypeptide is conjugated to the N-terminus of the GDF15 mutein via a linker.

9. The complex of any one of the preceding claims wherein the Ig Fc sequence in the first polypeptide and the Ig Fc sequence in the second polypeptide each comprise a hinge region.

10. The complex of claim 2, wherein the first polypeptide comprises:

a hinge region; and wherein the engineered protuberance of the first polypeptide comprises at least one substitution of the corresponding amino acid in a human IgG 1 Fc sequence, wherein the substitution is selected from the group consisting of Q347W/Y, T366W/Y, and T394W/Y according to EU numbering; a linker; and wherein the GDF15 mutein comprises a contiguous amino acid sequence at least 98 amino acids long and at least 95% identical to the amino acid sequence of SEQ ID NO:1 wherein the C-terminal amino acid corresponds to Isoleucine at position 112 in SEQ ID NO:1, and the contiguous amino acid sequence does not comprise the first two amino acids present at the N-terminus of SEQ ID NO:1, and wherein the GDF15 mutein comprises a D5T substitution relative to the amino acid sequence of SEQ ID NO:1; and

the second polypeptide comprises:

a hinge region; and wherein the engineered cavity comprises at least one substitution of the corresponding amino acid in a human IgG 1 Fc sequence, wherein the substitution is selected from the group consisting of T366S, L368A, T394S, F405T/V/A, and Y407T/V/A, according to EU numbering.

11. The complex of claim 10, wherein the linker comprises the sequence Glycine-Glycine-Glycine-Ser (G₄S)_n, wherein n=2-5.

12. The complex of claim 10, wherein the linker comprises the sequence (G₄S)₃ or (G₄S)₅.

13. The complex of claim 10, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 3 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 4.

14. The complex of claim 10, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 5 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 6.

15. A nucleic acid encoding the first and second polypeptides of any one of the preceding claims, wherein the nucleic acid is optionally operably linked to an expression control element that confers expression of the first and second polypeptides from the nucleic acid; or

a first nucleic acid encoding the first polypeptide of any one of the preceding claims and a second nucleic acid encoding the second polypeptide of any one of the preceding claims, wherein each of the first and second nucleic acids is optionally operably linked to an expression control element that confers expression of the first and second polypeptides from the first and second nucleic acids, respectively.

16. A vector comprising the nucleic acid of claim 15, wherein the vector is optionally a viral vector; or

a first vector comprising the first nucleic acid and a second vector comprising the second nucleic acid of claim 15, wherein each of the first and second vectors is optionally a viral vector.

17. A host cell comprising:

- (a) the nucleic acid molecule of claim 15;
- (b) the first and the second nucleic acids of claim 15;
- (c) the vector of claim 16; or
- (d) the first and second vectors of claim 16.

18. A pharmaceutical composition comprising the complex of any one of claims 1-14 and a pharmaceutically acceptable diluent, carrier or excipient.
19. A composition comprising the complex of any one of claims 1-14 for treating or preventing a body weight disorder or a glucose metabolism disorder in a subject.
20. The composition of claim 19, wherein the subject is obese.
21. The composition of claim 19, wherein the subject has diabetes mellitus.