GDF15 peptide further contains two additional cysteine residues that form a fourth intrachain disulfide bond. Biologically active GDF15 is a 25KD homodimer of the mature peptide covalently linked by one interchain disulfide bond.

GDF15 circulating levels have been reported to be elevated in multiple pathological and physiological conditions, most notably pregnancy (Moore AG 2000. *J Clin Endocrinol Metab* 85: 4781-4788), β-thalassemia (Tanno T 2007, *Nat Med* 13:1096-101; Zimmermann MB, 2008 *Am J Clin Nutr* 88:1026-31), and congenital dyserythropoietic anemia (Tamary H 2008, *Blood.* 112:5241-4). GDF15 has also been linked to multiple biological activities in literature reports. Studies of GDF15 knockout and transgenic mice suggested that GDF15 may be protective against ischemic/reperfusion- or overload-induced heart injury (Kempf T, 2006, *Circ Res.*98:351-60; Xu J, 2006, *Circ Res.* 98:342-50), protective against aging-associated motor neuron and sensory neuron loss (Strelau J, 2009, *J Neurosci.* 29 :13640-8), mildly protective against metabolic acidosis in kidney, and may cause cachexia in cancer patients (Johnen H 2007 *Nat Med.* 11:1333-40). Many groups also have studied the role of GDF15 in cell apoptosis and proliferation and reported controversial results using different cell culture and xenograft models. Studies on transgenic mice showed that GDF15 is protective against carcinogen or Apc mutation induced neoplasia in intestine and lung (Baek SJ 2006, *Gastroenterology.* 131:1553-60; Cekanova M 2009, *Cancer Prev Res* 2:450-8).

SUMMARY OF THE INVENTION

In a first aspect, the present invention refers to a fusion protein comprising a biological active growth differentiation factor 15 (GDF15) region which is joined via a polypeptide linker to an Fc domain of SEQ ID NO: 220 or a Fc domain of SEQ ID NO:220 comprising a tyrosine to cysteine mutation at position 113. In another aspect, the present invention refers to a dimer comprising (i) a first protein comprising a fusion protein of the present invention, and (ii) a second protein comprising an Fc domain. In yet another aspect, the present invention refers to a tetramer comprising (a) a first dimer of the present invention and (b) a second dimer of the present invention. In another aspect, the present invention refers to a fusion protein of the present invention, or a dimer of the present invention, or a tetramer of the present invention for use in therapy. In another aspect, the present invention refers to a fusion protein of the present invention, or a dimer of the present invention, or a tetramer of the present invention in the manufacture of a medicament for treating diabetes, obesity, dyslipidemia or diabetic nephropathy. Also described

CLAIMS

What is claimed is:

1. A fusion protein comprising a biological active growth differentiation factor 15 (GDF15) region which is joined via a polypeptide linker to an Fc domain of SEQ ID NO: 220 or a Fc domain of SEQ ID NO: 220 comprising a tyrosine to cysteine mutation at position 113.

2. The fusion protein of claim 1, wherein the Fc domain has the amino acid sequence of SEQ ID NO: 227.

3. The fusion protein of claim 1 or 2, wherein the GDF15 region comprises an amino acid sequence that is at least about 85 percent identical to SEQ ID NO: 4, 8, or 12.

4. The fusion protein of claim 1, wherein the GDF15 region comprises an amino acid sequence that is at least about 85 percent identical to SEQ ID NO: 12 and comprises a mutation at position 3.

5. The fusion protein of claim 4, wherein the mutation at position 3 is a N3Q mutation.

6. The fusion protein of claim 1 or 2, wherein the GDF15 region comprises an amino acid sequence of SEQ ID NO: 4, 8, 12, 25, 52 or 55.

7. The fusion protein of claim 6, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO: 222, 225, 229, or 232.

8. The fusion protein of claim 6, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO: 18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, or 128.

9. A dimer comprising (i) a first protein comprising a fusion protein of any one of claims 1-8, and (ii) a second protein comprising an Fc domain.

10. The dimer of claim 9, wherein the second protein comprises an amino acid sequence of SEQ ID NO: 219, 226, 301, or 302.

11. The dimer of claim 9 or 10, wherein the first protein and the second protein are non-covalently associated.

12. The dimer of claim 9 or 10, wherein the first protein and the second protein are covalently associated.

13. The dimer of claim 9 or 10, wherein the first protein and the second protein are associated via a disulfide bond.

14. A tetramer comprising (a) a first dimer of any one of claims 6-10 and (b) a second dimer of any one of claims 9-13.

15. The tetramer of claim 14, wherein the first dimer and the second dimer are non-covalently associated.

16. The tetramer of claim 14, wherein the first dimer and the second dimer are covalently associated.

17. The tetramer of claim 14, wherein the first dimer and the second dimer are associated via a disulfide bond.

18. The tetramer of claim 17, wherein the first dimer and the second dimer are associated via an interchain disulfide bond between a GDF15 region of the first dimer and a GDF15 region of the second dimer.

19. A fusion protein of any one of claims 1-8, or a dimer of any one of claims 6 to 10, or a tetramer of any one of claims 11 to 15 for use in therapy.

20. Use of a fusion protein of any one of claims 1 to 8, or a dimer of any one of claims 9 to 13, or a tetramer of any one of claims 14 to 18 in the manufacture of a medicament for treating diabetes, obesity, dyslipidemia or diabetic nephropathy.