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 GDF15 region and an Fc domain, wherein the Fc domain comprises an amino acid sequence of SEQ ID NO: 220. 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 for use in treating a metabolic disorder in a subject in need thereof. In another aspect, the present invention refers to a fusion protein of the present invention for use in reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject. In still another aspect, the present invention refers to a dimer of the present invention for use in treating a metabolic disorder in a subject in need thereof. In yet another aspect, the present invention refers to a dimer of the present invention for use in reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject. In another aspect, the present invention refers to a tetramer of the present invention for use in treating a metabolic disorder in a subject in need thereof. In another aspect, the present invention refers to a tetramer of the present invention for use in

reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject. ~~Provided~~ Also described herein are fusion proteins comprising a GDF15 polypeptide or a GDF15 mutant polypeptide and an Fc domain.

In ~~a~~ one ~~embodiment~~example, the Fc domain comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302. In another ~~embodiment~~example, the GDF15 polypeptide or a GDF15 mutant polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 52 and 55. In another ~~embodiment~~example, the fusion protein further comprises a polypeptide linker. In one ~~embodiment~~example, the polypeptide linker has a sequence selected from the group consisting of SEQ ID NOs:18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, 128. In one ~~embodiment~~example, the fusion protein comprises two or more Fc domains. In one ~~embodiment~~example, the fusion protein comprises two or more polypeptide linkers. In one ~~embodiment~~example, the fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 46, 24, 27, 32, 37, 20, 42, 50, 54, 57, 60, 63, 66, 68, 71, 74, 77, 82, 84, 88, 93, 96, 98, 100, 102, 104, 108, 134, 137, 139, 143, 146, 150, 153, 269, 272, 276, 279, 157, 160, 164, 167, 171, 174, 178, 181, 185, 188, 194, 197, 201, 204, 208, 211, 215, 218, 222, 225, 229, 232, 233, 238 and 240.

Also provided herein are dimers comprising (i) a first polypeptide chain comprising one of the foregoing fusion proteins, and (ii) a second polypeptide chain comprising an Fc domain. In yet a further ~~embodiment~~example, the construct further comprises a sequence selected from the group consisting of SEQ ID NOs: 16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

In one ~~embodiment~~example, the first and second polypeptide chains are non-covalently associated. In another ~~embodiment~~example, the first and second polypeptide chains are covalently associated. In one ~~embodiment~~example, the first and second polypeptide chains are covalently associated via disulfide bonds between their respective Fc domains. In another ~~embodiment~~example, the first and second polypeptide chains are associated by both covalent and non-covalent interactions.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) two fusion proteins comprising the sequence of SEQ ID NO:46; (b) two fusion proteins comprising the sequence of SEQ ID NO:24; or (c) two fusion proteins comprising the sequence of SEQ ID NO:27

In a particular ~~embodiment~~example, a dimer is provided comprising (a) two fusion proteins comprising the sequence of SEQ ID NO:32; or (b) two fusion proteins comprising the sequence of SEQ ID NO:37;

In a particular ~~embodiment~~example, a dimer is provided comprising a first polypeptide chain comprising the sequence of SEQ ID NO:20 and a second polypeptide chain comprising the sequence of SEQ ID NO:17.

In a particular ~~embodiment~~example, a dimer is provided comprising (a) a first polypeptide chain comprising the sequence of SEQ ID NO:42 and a second polypeptide chain comprising the sequence of SEQ ID NO:39; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:50 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:54 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (d) a first polypeptide chain comprising the sequence of SEQ ID NO:57 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (e) a first polypeptide chain comprising the sequence of SEQ ID NO:60 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (f) a first polypeptide chain comprising the sequence of SEQ ID NO:63 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (g) a first polypeptide chain comprising the sequence of SEQ ID NO:66 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (h) a first polypeptide chain comprising the sequence of SEQ ID NO:68 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (i) a first polypeptide chain comprising the sequence of SEQ ID NO:71 and a second polypeptide chain comprising the sequence of SEQ

ID NO:47; (j) a first polypeptide chain comprising the sequence of SEQ ID NO:74 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (k) a first polypeptide chain comprising the sequence of SEQ ID NO:77 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (l) a first polypeptide chain comprising the sequence of SEQ ID NO:80 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; (m) a first polypeptide chain comprising the sequence of SEQ ID NO:82 and a second polypeptide chain comprising the sequence of SEQ ID NO:47; or (n) a first polypeptide chain comprising the sequence of SEQ ID NO:84 and a second polypeptide chain comprising the sequence of SEQ ID NO:47.

In a particular ~~embodiment~~example, a dimer is provided comprising (a) a first polypeptide chain comprising the sequence of SEQ ID NO:88 and a second polypeptide chain comprising the sequence of SEQ ID NO:86; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:93 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:96 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; (d) a first polypeptide chain comprising the sequence of SEQ ID NO:98 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; (e) a first polypeptide chain comprising the sequence of SEQ ID NO:100 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; (f) a first polypeptide chain comprising the sequence of SEQ ID NO:102 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; (g) a first polypeptide chain comprising the sequence of SEQ ID NO:104 and a second polypeptide chain comprising the sequence of SEQ ID NO:90; or (h) a first polypeptide chain comprising the sequence of SEQ ID NO:108 and a second polypeptide chain comprising the sequence of SEQ ID NO:105.

In a particular ~~embodiment~~example, a dimer is provided comprising (a) a first polypeptide chain comprising the sequence of SEQ ID NO:112 and a second polypeptide chain comprising the sequence of SEQ ID NO:12; (b) two polypeptide chains, each comprising the sequence of SEQ ID NO:112; (c) two polypeptide chains, each comprising the sequence of SEQ ID NO:115; (d) two polypeptide chains, each comprising the sequence of SEQ ID NO:118; (e) two polypeptide chains, each comprising the sequence of SEQ ID NO:121; (f) two polypeptide chains, each comprising the sequence of SEQ ID NO:124; (g) two polypeptide chains, each comprising the sequence of SEQ ID NO:127; (h) two polypeptide chains, each comprising the sequence of SEQ ID NO:130; or (i) two polypeptide chains, each comprising the sequence of SEQ ID NO:242.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:134 and a second polypeptide chain comprising the sequence of SEQ ID NO:131; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:137 and a second polypeptide chain comprising the sequence of

SEQ ID NO:131; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:139 and a second polypeptide chain comprising the sequence of SEQ ID NO:131; (d) a first polypeptide chain comprising the sequence of SEQ ID NO:143 and a second polypeptide chain comprising the sequence of SEQ ID NO:140; (e) a first polypeptide chain comprising the sequence of SEQ ID NO:146 and a second polypeptide chain comprising the sequence of SEQ ID NO:140; (f) a first polypeptide chain comprising the sequence of SEQ ID NO:150 and a second polypeptide chain comprising the sequence of SEQ ID NO:147; (g) a first polypeptide chain comprising the sequence of SEQ ID NO:153 and a second polypeptide chain comprising the sequence of SEQ ID NO:147; (h) a first polypeptide chain comprising the sequence of SEQ ID NO:269 and a second polypeptide chain comprising the sequence of SEQ ID NO:267; (i) a first polypeptide chain comprising the sequence of SEQ ID NO:272 and a second polypeptide chain comprising the sequence of SEQ ID NO:267; (j) a first polypeptide chain comprising the sequence of SEQ ID NO:276 and a second polypeptide chain comprising the sequence of SEQ ID NO:274; or (k) a first polypeptide chain comprising the sequence of SEQ ID NO:279 and a second polypeptide chain comprising the sequence of SEQ ID NO:274.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:157 and a second polypeptide chain comprising the sequence of SEQ ID NO:154; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:160 and a second polypeptide chain comprising the sequence of SEQ ID NO:154; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:164 and a second polypeptide chain comprising the sequence of SEQ ID NO:161; (d) a first polypeptide chain comprising the sequence of SEQ ID NO:167 and a second polypeptide chain comprising the sequence of SEQ ID NO:161.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:171 and a second polypeptide chain comprising the sequence of SEQ ID NO:168; or (b) a first polypeptide chain comprising the sequence of SEQ ID NO:174 and a second polypeptide chain comprising the sequence of SEQ ID NO:168

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:178 and a second polypeptide chain comprising the sequence of SEQ ID NO:175; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:181 and a second polypeptide chain comprising the sequence of SEQ ID NO:175; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:185 and a second polypeptide chain comprising the sequence of SEQ ID NO:182; (d) a first polypeptide chain comprising the sequence of SEQ ID NO:188 and a second polypeptide chain comprising the sequence of SEQ ID NO:182; (e) a first polypeptide chain comprising

the sequence of SEQ ID NO:194 and a second polypeptide chain comprising the sequence of SEQ ID NO:191; (f) a first polypeptide chain comprising the sequence of SEQ ID NO:197 and a second polypeptide chain comprising the sequence of SEQ ID NO:191; (g) a first polypeptide chain comprising the sequence of SEQ ID NO:201 and a second polypeptide chain comprising the sequence of SEQ ID NO:198; or (h) a first polypeptide chain comprising the sequence of SEQ ID NO:204 and a second polypeptide chain comprising the sequence of SEQ ID NO:198.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:208 and a second polypeptide chain comprising the sequence of SEQ ID NO:205; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:211 and a second polypeptide chain comprising the sequence of SEQ ID NO:205; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:215 and a second polypeptide chain comprising the sequence of SEQ ID NO:212; or (d) a first polypeptide chain comprising the sequence of SEQ ID NO:218 and a second polypeptide chain comprising the sequence of SEQ ID NO:212.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) a first polypeptide chain comprising the sequence of SEQ ID NO:222 and a second polypeptide chain comprising the sequence of SEQ ID NO:219; (b) a first polypeptide chain comprising the sequence of SEQ ID NO:225 and a second polypeptide chain comprising the sequence of SEQ ID NO:219; (c) a first polypeptide chain comprising the sequence of SEQ ID NO:229 and a second polypeptide chain comprising the sequence of SEQ ID NO:226; or (d) a first polypeptide chain comprising the sequence of SEQ ID NO:232 and a second polypeptide chain comprising the sequence of SEQ ID NO:226.

In a particular ~~embodiment~~example, a dimer is provided comprising: (a) two polypeptide chains, each comprising the sequence of SEQ ID NO:235; (b) two polypeptide chains, each comprising the sequence of SEQ ID NO:238; or (c) two polypeptide chains, each comprising the sequence of SEQ ID NO:240.

In certain ~~embodiment~~examples, a tetramer is provided, comprising (i) a first dimer comprising one of the foregoing dimers and (ii) a second dimer comprising one of the foregoing dimers. In certain ~~embodiment~~examples, the first polypeptide chain of the first dimer is linked to the first polypeptide chain of the second dimer via an interchain disulfide bond between their respective GDF15 regions.

In some ~~embodiment~~examples, the dimer is not selected from the group comprising DhCpmFc(-)-$(G_4S)_4$-GDF15:DhCpmFc(+)., DhCpmFc(+)-$(G_4S)_4$-GDF15:DhCpmFc(-), DhCpmFc(-)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(-), DhCpmFc(+)-$(G_4S)_4$-GDF15(N3Q):DhCpmFc(-), DhCpmFc(+)-GDF15:DhCpmFc(-), DhCpmFc(+)-G_4-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4S)_2$-

GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4Q)_4$-GDF15:DhCpmFc(-), DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C), DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C), CpmFc(-)-$(G_4S)_4$-GDF15:CpmFc(+), Fc-$(G_4S)_8$-Fc-GS$(G_4S)_4$-GDF15, Fc-$(G_4S)_3$-Fc-GS$(G_4S)_4$-GDF15 and Fc-$(G_4S)_5$-Fc-GS$(G_4S)_4$-GDF15.

In some ~~embodiment~~examples, the dimer is not selected from the group consisting of DhCpmFc(-)-$(G_4S)_4$-GDF15:DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15:DhCpmFc(-), DhCpmFc(-)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(-), DhCpmFc(+)-$(G_4S)_4$-GDF15(N3Q):DhCpmFc(-), DhCpmFc(+)-GDF15:DhCpmFc(-), DhCpmFc(+)-G_4-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4S)_2$-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4Q)_4$-GDF15:DhCpmFc(-), DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C) and DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C).

In some ~~embodiment~~examples, the fusion protein is not a selected from the group consisting of Fc-$(G_4S)_8$-Fc-GS$(G_4S)_4$-GDF15, Fc-$(G_4S)_3$-Fc-GS$(G_4S)_4$-GDF15 and Fc-$(G_4S)_5$-Fc-GS$(G_4S)_4$-GDF15.

In some ~~embodiment~~examples, the dimer is not selected from the group consisting of DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C) and DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C).

In some ~~embodiment~~examples, the dimer is not DhCpmFc(-)-$(G_4S)_4$-GDF15:DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15:DhCpmFc(-), DhCpmFc(-)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(-), DhCpmFc(+)-$(G_4S)_4$-GDF15(N3Q):DhCpmFc(-), DhCpmFc(+)-GDF15:DhCpmFc(-), DhCpmFc(+)-G_4-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4S)_2$-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4Q)_4$-GDF15:DhCpmFc(-), DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C), DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C), CpmFc(-)-$(G_4S)_4$-GDF15:CpmFc(+), Fc-$(G_4S)_8$-Fc-GS$(G_4S)_4$-GDF15, Fc-$(G_4S)_3$-Fc-GS$(G_4S)_4$-GDF15 or Fc-$(G_4S)_5$-Fc-GS$(G_4S)_4$-GDF15.

In some ~~embodiment~~examples, the dimer is not DhCpmFc(-)-$(G_4S)_4$-GDF15:DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15:DhCpmFc(-), DhCpmFc(-)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(+), DhCpmFc(+)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(-), DhCpmFc(+)-$(G_4S)_4$-GDF15(N3Q):DhCpmFc(-), DhCpmFc(+)-GDF15:DhCpmFc(-), DhCpmFc(+)-G_4-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4S)_2$-GDF15:DhCpmFc(-), DhCpmFc(+)-$(G_4Q)_4$-GDF15:DhCpmFc(-), DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C) or DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C).

In some ~~embodiment~~examples, the fusion protein is not selected from the group consisting of Fc-$(G_4S)_8$-Fc-GS$(G_4S)_4$-GDF15, Fc-$(G_4S)_3$-Fc-GS$(G_4S)_4$-GDF15 and Fc-$(G_4S)_5$-Fc-GS$(G_4S)_4$-GDF15.

In some ~~embodiment~~examples, the fusion protein is not selected from the group consisting of DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C) and DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C).

In some ~~embodiment~~examples, the dimer is not DhCpmFc(-)-$(G_4S)_4$-GDF15:DhCpmFc(+). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-$(G_4S)_4$-GDF15:DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(-)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(+). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-$(G_4S)_4$-GDF15(H6D):DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-$(G_4S)_4$-GDF15(N3Q):DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-GDF15:DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-G_4-GDF15:DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-$(G_4S)_2$-GDF15:DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)-$(G_4Q)_4$-GDF15:DhCpmFc(-). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)(L351C)-G_4-GDF15:DhCpmFc(-)(L351C). In some ~~embodiment~~examples, the dimer is not DhCpmFc(+)(S354C)-G_4-GDF15:DhCpmFc(-)(Y349C). In some ~~embodiment~~examples, the dimer is not CpmFc(-)-$(G_4S)_4$-GDF15:CpmFc(+). In some ~~embodiment~~examples, the dimer is not Fc-$(G_4S)_8$-Fc-GS$(G_4S)_4$-GDF15. In some ~~embodiment~~examples, the dimer is not Fc-$(G_4S)_3$-Fc-GS$(G_4S)_4$-GDF15. In some ~~embodiment~~examples, the dimer is not Fc-$(G_4S)_5$-Fc-GS$(G_4S)_4$-GDF15.

Also provided herein are fusion proteins comprising a GDF15 polypeptide or a GDF15 mutant polypeptide and a human serum albumin (HSA) polypeptide. In a further ~~embodiment~~example, the HSA polypeptide the sequence of SEQ ID NO:110. In another ~~embodiment~~example, the GDF15 polypeptide or a GDF15 mutant polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 52 and 55. In another ~~embodiment~~example, the fusion protein further comprises a polypeptide linker, joining the GDF15 polypeptide or GDF15 mutant polypeptide to the HSA polypeptide. In one ~~embodiment~~example, the polypeptide linker has a sequence selected from the group consisting of SEQ ID NOs:18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, 128. In one ~~embodiment~~example, the fusion protein comprises two or more HSA polypeptides. In one ~~embodiment~~example, the fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 115, 118, 121, 124, 127 and 130.

Also provided herein are dimers comprising (i) a first polypeptide chain comprising a fusion protein comprising a first GDF15 region and a first HSA polypeptide, and (ii) a second polypeptide chain comprising a second HSA polypeptide. In some ~~embodiment~~examples, the second polypeptide chain further comprises a second GDF15 region. In some ~~embodiment~~examples, the dimer is a heterodimer (i.e., the first and second polypeptide chain have different sequences). In some ~~embodiment~~examples, the dimer is a homodimer (i.e., the first and second polypeptide chain have the same sequence). In some ~~embodiment~~examples, the first polypeptide chain comprises a sequence selected from the group consisting of SEQ ID NOs: 115, 118, 121, 124, 127 and

130. In some ~~embodiment~~examples, the second polypeptide chain comprises a sequence selected from the group consisting of SEQ ID NOs: 115, 118, 121, 124, 127 and 130. In one ~~embodiment~~example, the first and second polypeptide chains are non-covalently associated. In another ~~embodiment~~example, the first and second polypeptide chains are covalently associated. In one ~~embodiment~~example, the second polypeptide chain comprises a second GDF15 region and first and second polypeptide chains are covalently associated via disulfide bonds between their respective GDF15 regions. In another ~~embodiment~~example, the first and second polypeptide chains are associated by both covalent and non-covalent interactions.

Also provided herein are dimers comprising (i) a first polypeptide chain comprising a fusion protein comprising a first GDF15 region and an HSA polypeptide, and (ii) a second polypeptide chain comprising a second GDF15 region. In some ~~embodiment~~examples, the first polypeptide chain comprises a sequence selected from the group consisting of SEQ ID NOs: 115, 118, 121, 124, 127 and 130. In some ~~embodiment~~examples, the second polypeptide chain comprises a sequence selected from the group consisting of SEQ ID NOs: 4, 8, 12, 25, 52 and 55. In one ~~embodiment~~example, the first and second polypeptide chains are non-covalently associated. In another ~~embodiment~~example, the first and second polypeptide chains are covalently associated. In another ~~embodiment~~example, the first and second polypeptide chains are associated by both covalent and non-covalent interactions.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphic depicting of a knob-hole construct comprising a dimer of two DhknobFc-$(G_4S)_4$-GDF15:DhholeFc heterodimers.

Figure 2 is a graphic depicting a DhMonoFc construct comprising a dimer of two DhMonoFc-$(G_4S)_4$-GDF15 fusion proteins.

Figure 3 is a graphic depicting a HemiFc construct comprising a dimer of two GGGFc-$(G_4S)_4$-Fc-S$(G_4S)_4$-GDF15 fusion proteins.

Figure 4 is a graphic depicting a charged pair (delHinge) construct comprising a dimer of two DhCpmFc(-)-$(G_4S)_2$-GDF15:DhCpmFc(+) heterodimers.

Figure 5 is a graphic depicting a charged pair (delHinge) cysteine clamp construct comprising a dimer of two DhCpmFc(-)(L351C)-$(G_4S)_2$-GDF15:DhCpmFc(-)(L351C) heterodimers.

Figure 6 is a graphic depicting an HSA construct comprising a dimer of two HSA-$(G_4S)_4$-GDF15 fusion proteins.

Figure 7 is a plot showing the effect on food intake (g food/g body weight (BW) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhknobFc-G_4-GDF15:DhholeFc heterodimer.

CLAIMS

What is claimed is:

1. A fusion protein comprising a GDF15 region and an Fc domain, wherein the Fc domain comprises an amino acid sequence of SEQ ID NO: 220.

2. The fusion protein of claim 1, wherein the Fc domain comprises a tyrosine to cysteine mutation at position 113.

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

4. The fusion protein of any one of the preceding claims, wherein the GDF15 region comprises an amino acid sequence of SEQ ID NO: 4, 8, 12, 25, 52 or 55.

5. The fusion protein of claim 4, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO: 222, 225, 229, or 232.

6. The fusion protein of any one of the preceding claims, wherein the GDF15 region and the Fc domain are joined by a polypeptide linker.

7. The fusion protein of claim 4, 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.

8. A dimer comprising (i) a first protein comprising a fusion protein of any one of claims 1-7, and (ii) a second protein comprising an Fc domain.

9. The dimer of claim 8, wherein the second protein comprises an amino acid sequence of SEQ ID NO: 219, 226, 301, or 302.

10. The dimer of claim 8 or 9, wherein the first protein and the second protein are non-covalently associated.

11. The dimer of claim 8 or 9, wherein the first protein and the second protein are covalently associated.

12. The dimer of claim 8 or 9, wherein the first protein and the second protein are associated via a disulfide bond.

13. A tetramer comprising (a) a first dimer of any one of claims 8-12 and (b) a second dimer of of any one of claims 8-12.

14. The tetramer of claim 13, wherein the first dimer and the second dimer are non-covalently associated.

15. The tetramer of claim 13, wherein the first dimer and the second dimer are covalently associated.

16. The tetramer of claim 13, wherein the first dimer and the second dimer are associated via a disulfide bond.

17. The tetramer of claim 16, wherein the first dimer and the second dimer are associated via an interchain disulfide bond a GDF15 region of the first dimer and a GDF15 region of the second dimer.

18. A fusion protein of any one of claims 1-7 for use in treating a metabolic disorder in a subject in need thereof.

19. The fusion protein of claim 18, wherein the metabolic disorder is diabetes, obesity, dyslipidemia or diabetic nephropathy.

20. A fusion protein of any one of claims 1-7 for use in reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject.

21. A dimer of any one of claims 8-12 for use in treating a metabolic disorder in a subject in need thereof.

22. The dimer of claim 21, wherein the metabolic disorder is diabetes, obesity, dyslipidemia or diabetic nephropathy.

23. A dimer of any one of claims 8-12 for use in reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject.

24. A tetramer of any one of claims 13-17 for use in treating a metabolic disorder in a subject in need thereof.

25. The tetramer of claim 24, wherein the metabolic disorder is diabetes, obesity, dyslipidemia or diabetic nephropathy.

26. A tetramer of any one of claims 13-17 for use in reducing food intake, body weight, insulin levels, triglyceride levels, cholesterol levels or glucose levels in a subject.

CLAIMS

What is claimed is:

1. A fusion protein comprising a GDF15 region and an Fc domain.

2. The fusion protein of claim 1, wherein the Fc domain comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

3. The fusion protein of claim 2, wherein the GDF15 region comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 52 and 55.

4. The fusion protein of claim 2, wherein the GDF15 region and the Fc domain are joined by a polypeptide linker.

5. The fusion protein of claim 4, wherein the polypeptide linker is selected from the group consisting of SEQ ID NOs:18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, 128.

6. The fusion protein of claim 1, wherein the fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 46, 24, 27, 32, 37, 20, 42, 50, 54, 57, 60, 63, 66, 68, 71, 74, 77, 82, 84, 88, 93, 96, 98, 100, 102, 104, 108, 134, 137, 139, 143, 146, 150, 153, 269, 272, 276, 279, 157, 160, 164, 167, 171, 174, 178, 181, 185, 188, 194, 197, 201, 204, 208, 211, 215, 218, 222, 225, 229, 232, 233, 238 and 240.

7. The fusion protein of claim 1, wherein the fusion protein comprises two or more Fc domains.

8. A dimer comprising (i) a first polypeptide chain comprising a GDF15 region and a first Fc domain, and (ii) a second polypeptide chain comprising a second Fc domain.

9. The dimer of claim 8, wherein first Fc domain comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

10. The dimer of claim 9, wherein second Fc domain comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106,

132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

11. The dimer of claim 9, wherein the GDF15 region comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 52 and 55.

12. The dimer of claim 9, wherein the GDF15 region and the Fc domain are joined by a polypeptide linker.

13. The dimer of 12, wherein the polypeptide linker is selected from the group consisting of SEQ ID NOs:18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, 128.

14. The dimer of claim 8, wherein the fusion protein comprises a sequence selected from the group consisting of SEQ ID NOs: 46, 24, 27, 32, 37, 20, 42, 50, 54, 57, 60, 63, 66, 68, 71, 74, 77, 82, 84, 88, 93, 96, 98, 100, 102, 104, 108, 134, 137, 139, 143, 146, 150, 153, 269, 272, 276, 279, 157, 160, 164, 167, 171, 174, 178, 181, 185, 188, 194, 197, 201, 204, 208, 211, 215, 218, 222, 225, 229, 232, 233, 238 and 240.

15. The dimer of claim 8, wherein the first and second polypeptide chains are non-covalently associated.

16. The dimer of claim 8, wherein the first and second polypeptide chains are covalently associated.

17. The dimer of claim 16, wherein the first and second polypeptide chains are covalently associated via disulfide bonds between their respective Fc domains.

18. A tetramer comprising (i) a first dimer and (ii) a second dimer, wherein the first and second dimer independently comprise a dimer of claim 1 and wherein the first polypeptide chain of the first dimer is linked to the first polypeptide chain of the second dimer via an interchain disulfide bond between their respective GDF15 regions.

19. The tetramer of claim 18, wherein the Fc domain of the first polypeptide of the first dimer comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

20. The tetramer of claim 19, wherein the GDF15 region of the first polypeptide chain of the first dimer comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 52 and 55.

21. The tetramer of claim 20, wherein the GDF15 region and the Fc domain are joined by a polypeptide linker.

22. The tetramer of claim 21, wherein the polypeptide linker is selected from the group consisting of SEQ ID NOs:18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125, 128.

23. The tetramer of claim 18, wherein the Fc domain of the first polypeptide of the first dimer comprises a sequence selected from the group consisting of SEQ ID NOs: 46, 24, 27, 32, 37, 20, 42, 50, 54, 57, 60, 63, 66, 68, 71, 74, 77, 82, 84, 88, 93, 96, 98, 100, 102, 104, 108, 134, 137, 139, 143, 146, 150, 153, 269, 272, 276, 279, 157, 160, 164, 167, 171, 174, 178, 181, 185, 188, 194, 197, 201, 204, 208, 211, 215, 218, 222, 225, 229, 232, 233, 238 and 240.

24. The tetramer of claim 19, wherein the Fc domain of the first polypeptide of the second dimer comprises a sequence selected from the group consisting of SEQ ID NOs:16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 220, 227, 233, 236, 268, 275, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301 and 302.

25. The tetramer of claim 24,, wherein the Fc domain of the first polypeptide of the second dimer comprises a sequence selected from the group consisting of SEQ ID NOs: 46, 24, 27, 32, 37, 20, 42, 50, 54, 57, 60, 63, 66, 68, 71, 74, 77, 82, 84, 88, 93, 96, 98, 100, 102, 104, 108, 134, 137, 139, 143, 146, 150, 153, 269, 272, 276, 279, 157, 160, 164, 167, 171, 174, 178, 181, 185, 188, 194, 197, 201, 204, 208, 211, 215, 218, 222, 225, 229, 232, 233, 238 and 240.