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(54) Benævnelse: **VÆKSTDIFFERENTIERINGSFAKTOR 15 (GDF-15)-KONSTRUKTIONER**

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Fortsættes ...

DESCRIPTION

FIELD OF THE INVENTION

[0001] The instant disclosure relates to monomers and multimers comprising a polypeptide comprising a GDF15 region.

BACKGROUND OF THE INVENTION

[0002] Growth differentiation factor 15 (GDF.15) is a divergent member of the TGFβ superfamily. It is also called macrophage inhibitory cytokine 1 (MIC1) (Bootcov MR, 1997, Proc Natl Acad Sci 94:11514-9), placental bone morphogenetic factor (PLAB) (Hromas R 1997, Biochim Biophys Acta. 1354:40-4), placental transforming growth factor beta (PTGFB) (Lawton LN 1997, Gene. 203:17-26), prostate derived factor (PDF) (Paralkar VM 1998, J Biol Chem. 273:13760-7), and nonsteroidal anti-inflammatory drug-activated gene (NAG-1) (Baek SJ 2001, J Biol Chem. 276: 33384-92).

[0003] Human GDF15 gene is located on chromosome 19p13.2-13.1; rat GDF15 gene is located on chromosome 16; and mouse GDF15 gene is located on chromosome 8. The GDF15 open reading frames span two exons (Bottner M 1999, Gene. 237:105-11 and NCBI). The mature GDF15 peptide shares low homology with other family members (Katoh M 2006, Int J Mol Med. 17:951-5.).

[0004] GDF15 is synthesized as a large precursor protein that is cleaved at the dibasic cleavage site to release the carboxyterminal mature peptide. The mouse and rat GDF15 prepro-peptides both contain 303 amino acids. Human full-length precursor contains 308 amino acids. The rodent mature peptides contain 115 amino acids after processing at the RGRR (SEQ ID NO:1) cleavage site. The human mature peptide contains 112 amino acids after processing at the RGRRRAR (SEQ ID NO:2) cleavage site. Human mature GDF15 peptide shares 66.1% and 68.1% sequence similarity with rat and mouse mature GDF15 peptides (Bottner M 1999, Gene. 237:105-11; Bauskin AR 2000, EMBO J. 19:2212-20; NCBI). There is no glycosylation site in the mature GDF15 peptide.

[0005] The mature GDF15 peptide contains the seven conserved cysteine residues required for the formation of the cysteine knot motif (having three intrachain disulfide bonds) and the single interchain disulfide bond that are typical for TGFβ superfamily members. The mature 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.

[0006] 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-mduced 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 Neurasci. 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).

[0007] WO 99/06445 and WO 2010/048670 provide an overview of GDF 15. Fusion proteins involving an Fc domain are derivable from WO 2006/000448 and WO 2011/064758

SUMMARY OF THE INVENTION

[0008] Provided herein are fusion proteins comprising a GDF15 polypeptide or a GDF15 mutant polypeptide and an Fc domain.

[0009] Embodiments of the present invention are:

1. 1. A fusion protein comprising a GDF15 region and an Fc domain, wherein
    1. a) the Fc domain comprises the sequence of SEQ ID NO: 220 and wherein the Fc domain is a Dh3CpmFc(-) domain, wherein the Dh3CpmFc(-) domain is a sequence with an N-terminal sequence which is the sequence of SEQ ID NO: 220; or
    2. b) the Fc domain comprises the sequence of SEQ ID NO: 227 and wherein the Fc domain is a Dh3CpmFc(-)(Y349C) domain, wherein the Dh3CpmFc(-)(Y349C) domain is a sequence with an N-terminal sequence which is the sequence of SEQ ID NO: 227.
2. 2. The fusion protein of embodiment 1, wherein the fusion protein comprises a the sequence of any of SEQ ID NO: 222, 225, 229 or 232.
3. 3. The fusion protein of embodiment 1 wherein the Fc domain of the fusion protein has the sequence of SEQ ID NO: 220.
4. 4. The fusion protein of embodiment 1 wherein the Fc domain of the fusion protein has the sequence of SEQ ID NO: 227.
5. 5. The fusion protein of embodiment 1, wherein the fusion protein comprises two or more Fc domains.
6. 6. A dimer comprising (i) a first polypeptide chain comprising a GDF15 region and a first

Fc domain, wherein

1. a) the Fc domain comprises the sequence of SEQ ID NO: 220 and wherein the Fc domain is a Dh3CpmFc(-) domain, wherein the Dh3CpmFc(-) domain is a sequence with an N-terminal sequence which is the sequence of SEQ ID NO: 220; or
2. b) wherein the Fc domain comprises the sequence of SEQ ID NO: 227 and wherein the Fc domain is a Dh3CpmFc(-)(Y349C) domain, wherein the Dh3CpmFc(-)(Y349C) domain is a sequence with an N-terminal sequence which is the sequence of SEQ ID NO: 227,

and (ii) a second polypeptide chain comprising a second Fc domain.

7. 7. The dimer of embodiment 6, wherein the first polypeptide chain comprises the sequence of any of SEQ ID NO: 222, 225, 229 or 232.
8. 8. The dimer of embodiment 6, wherein the Fc domain of the first polypeptide chain has the sequence of SEQ ID NO: 220.
9. 9. The dimer of embodiment 6, wherein the Fc domain of the first polypeptide chain has the sequence of SEQ ID NO: 227.
10. 10. The dimer of embodiment 6, wherein the first polypeptide chain comprises two or more Fc domains.
11. 11. The dimer of any one of embodiments 6-10, 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, 219, 220, 226, 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.
12. 12. The dimer of any one of embodiments 6-10, wherein the first and second polypeptide chains are non-covalently associated.
13. 13. The dimer of any one of embodiments 6-10, wherein the first and second polypeptide chains are covalently associated.
14. 14. The dimer of embodiment 13, wherein the first and second polypeptide chains are covalently associated via disulfide bonds between their respective Fc domains.
15. 15. A tetramer comprising (i) a first dimer and (ii) a second dimer, wherein the first and second dimer independently comprise a dimer of any one of embodiments 6-14.
16. 16. The tetramer of embodiment 15, 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.
17. 17. The fusion protein of any of embodiments 1-5, the dimer of any of embodiments 6-14 or the tetramer of any of embodiments 15-16, wherein the GDF15 region or the GDF15 region of the first polypeptide, respectively, comprises an amino acid sequence that is at least about 85% identical to SEQ ID NO:4, 8 or 12.
18. 18. The fusion protein of any one of embodiments 1-5, the dimer of any one of embodiments 6-14 or the tetramer of any one of embodiments 15-16, wherein the GDF15 region or the GDF15 region of the first polypeptide, respectively, comprises a sequence selected from the group consisting of SEQ ID NOs:4, 8, 12, 25, 62 and 55.
19. 19. The fusion protein of any one of embodiments 1-5, the dimer of any one of embodiments 6-14 or the tetramer of any one of embodiments 15-16, wherein the

GDF15 region and the Fc domain are joined by a polypeptide linker.

20. 20. The fusion protein, the dimer or the tetramer of embodiment 19, 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, and 128.
21. 21. The fusion protein of any one of embodiments 1-5, the dimer of any one of embodiments 6-14 or the tetramer of any one of embodiments 15-16, for use in treating a metabolic disorder in a subject in need thereof.
22. 22. The fusion protein, the dimer or the tetramer of embodiment 21, wherein the metabolic disorder is diabetes, obesity, dyslipidemia or diabetic nephropathy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010]

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-GDF 15:DhholeFc heterodimer.

Figure 8 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Fc-$(G_4S)_4$-GDF15 fusion protein.

Figure 9 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Fc-$(G_4S)_4$-GDF15(H6D) fusion protein.

Figure 10 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Fc-$(G_4S)_4$-Fc-$(G_4S)_4$-(GDF15 fusion protein.

Figure 11 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhFc-$(G_4S)_5$-DhFc-$(G_4S)_4$-GDF15 fusion protein.

Figure 12 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-) heterodimer.

Figure 13 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-GDF 15 :DhCpmFc(+) heterodimer.

Figure 14 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-GDF15(N3D):DhCpmFc(+) heterodimer.

Figure 15 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-GDF15(Nde13):DhCpmFc(+) heterodimer.

Figure 16 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-G_4-GDF15(N3D):DhCpmFc(+) heterodimer.

Figure 17 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-G_4S-GDF15:DhCpmFc(+) heterodimer.

Figure 18 is a plot showing the effect on food intake (g food/g body weight) of ob/ob:

mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-$(G_4S)_2$-GDF15:DhCpmFc(+) heterodimer.

Figure 19 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-$(G_4S)_2$-GDF15(N3D):DhCpmFc(+) heterodimer.

Figure 20 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-$(G_4Q)_2$-GDF15(N3D):DhCpmFc(+) heterodimer.

Figure 21 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a

function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-G_4P-GDF15:DhCpmFc(+) heterodimer.

Figure 22 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-(G_4P)2-GDF 15:DhCpmFc(+)heterodimer.

Figure 23 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-G_4Q-GDF15:DhCpmFc(+) heterodimer.

Figure 24 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-(G_4Q)$_2$-GDF15(N3D):DhCpmFc(+) heterodimer.

Figure 25 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)-(G_4Q)$_2$-GDF15(Nde13):DhCpmFc(+) heterodimer.

Figure 26 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(+)(Y349C)-GDF15(N3D):DhCpmFc(-)(S354C) heterodimer.

Figure 27 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C) heterodimer.

Figure 28 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C) heterodimer.

Figure 29 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(Y349C)-GDF15(Nde13):DhCpmFc(+)(S354C) heterodimer.

Figure 30 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(Y349C)-G_4-GDF15(N3D):DhCpmFc(+)(S354G) heterodimer.

Figure 31 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(Y349C)-(G_4S)$_2$-GDF15(N3D):DhCpmPc(+)(S354C) heterodimer.

Figure 32 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg- BW]) using a dimer of the DhCpmFc(-)(Y349C)-(G_4Q)$_2$-GDF15(N3D):DhCpmFc(+)(S354C) heterodimer.

Figure 33 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(L351C)-$(G_4S)_2$-GDF15:DhCpmFc(+)(L351C) heterodimer.

Figure 34 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GSAAQAAQQGS-GDF15 fusion protein.

Figure 35 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GSPAPAPGS-GDF15 fusion protein.

Figure 36 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GS$(AAQAAQQ)_2$GS-GDF15 fusion protein.

Figure 37 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GS$(PAPAP)_2$GS-GDF15 fusion protein.

Figure 38 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GDF15 fusion protein.

Figure 39 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-GGNAEAAAKEAAAKEAAAKAGG-GDF15 fusion protein.

Figure 40 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the HSA-$(G_4S)_6$-GDF15 fusion protein.

Figure 41 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)-GDF15(Nde13) :DhCpmFc(+)(N297G) heterodimer.

Figure 42 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G) heterodimer.

Figure 43 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)(Y349C)-GDF15(Nde13):DhCpmFc(+)(N297G)(S354C) heterodimer.

Figure 44 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)(Y349C)-GDF15(N3D):DhCpinFc(+)(N297G)(S354C) heterodimer.

Figure 45 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)(L351C)-GDF15(Nde13):DhCpmFc(+)(N297G)(L351C) heterodimer.

Figure 46 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)(L351C)-GDF15(N3D):DhCpmFc(+)(N297G)(L351C) heterodimer.

Figure 47 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhCpmFc(-)(N297G)(A287C)-GDF15(Nde13):DhCpmFc(+)(N297G)(L306C) heterodimer.

Figure 48 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the CpmFc(-)(N297G)-GDF15(Nde13):CpmFc(+)(N297G) heterodimer.

Figure 49 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(N297G) heterodimer.

Figure 50 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)(N297G) heterodimer.

Figure 51 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Dh3CpmFc(-)(Y349C)-GDF15(Nde13):Dh3CpmFc(+)(N297G)(S354C) heterodimer.

Figure 52 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the Dh3CpmFc(-)(Y349Q-GDF15(N3D):Dh3CpmFc(-)(N297G)(S354C) heterodimer.

Figure 53 is a plot showing the effect on food intake (g food/g body weight) of ob/ob mice as a function of dose (log [g construct/kg BW]) using a dimer of the DhMonoFc(N297G)-GDF15 fusion protein.

Figure 54 is a plot of body weight (g) as a function of time (days post 1st injection) for vehicle, 0.1 nmol, 1 nmol and 10 nmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, and 0.1 nmol, 1 nmol and 10 nmol of a dimer of the Dh3ComFc(-)-GDF15(Nde13) heterodimer.

Figure 55 is a bar graph of area under the curve (AUC) for a glucose tolerance test at week 2 of treatment with (a) vehicle (b) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer (c) 1 mmol: of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (d) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (e) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+) heterodimer (g) 1 mmol of a dimer of the Dh3CpmFc(-)-

GDF15(Nde13):Dh3CpmFc(+) heterodimer, or (g) 0.1: mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde1):Dh3CpmFc(+) heterodimer.

Figure 56 is a bar graph of insulin (ng/mL) (fed) at week 3 of treatment with (a) vehicle (b) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer (c) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (d) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (e) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+) heterodimer (g) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+) heterodimer, or (g) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde1):Dh3CpmEc(+) heterodimer.

Figure 57 is a bar graph of triglycerides (mg/mL) (fed) at week 3 of treatment with (a) vehicle (b) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer (c) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (d) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (e) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+) heterodimer (g) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+) heterodimer, or (g) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde1):Dh3CpmFc(+) heterodimer.

Figure 58 is a bar graph of cholesterol (mg/mL) (fed) at week 3 of treatment with (a) vehicle (b) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer (c) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (d) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (e) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFe(+) heterodimer (g) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+) heterodimer, or (g) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde1):Dh3CpmFc(+) heterodimer.

Figure 59 is a bar graph of area under the curve (AUC) for a glucose tolerance test at week 5 of treatment with (a) vehicle (b) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer (c) 1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (d) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimer, (e) 10 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+) heterodimer (g) 31 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+) heterodimer. or (g) 0.1 mmol of a dimer of the Dh3CpmFc(-)-GDF15(Nde1):Dh3CpmFc(+) heterodimer.

Figure 60 is a bar graph showing SPR Binding (RU) with respect to FcγRI, FcγRIIIA and FcγRIIA for (a) a dimer of DhCpmFc(-)-GDF15(Nde13):DhCpmFc(+), (b) a dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3): DhCpmFc(+)(S354C); (c) a dimer of Dh3CpmFc(-)-GDF15(Ndel3); (d) a dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3)-Dh3CpmFc(+)(S354C); (e) a dimer of Dh3CpmFc(-)-GDF15(N3D) ; and (f) a dimer of Dh3CpmFc(-)(Y349C)-GDF15(N3D):Dh3CpmFc(+)(S354C) (from left to right with respect to each receptor).

Figure 61 is a bar graph showing DSC first Tm (°C) with respect to (a) (for pair of bars captioned "N3D"), a dimer of DhCpmFc(-)-GDF15(N3D):DhCpmFc(+) and a dimer of Dh3CpmFc(-)-GDF15(N3D):DhCpmFc(+); (b) (for the pair of bars captioned. "Nde13"), a dimer

of DhCpmFc(-)-GDF15(Ndel3):DhCpmFc(+) and a dimer of Dh3CpmFc(-)-GDF15(Ndel3):DhCpmFc(+); (c) (for the pair of bars captioned "N3D+CC"), a dimer of DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C) and a dimer of Dh3CpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C);and (d) (for the pair of bars captioned "Ndel3+CC"), a dimer of DhCpmFc(-)(Y349C)-GDF15(Nde13):DhCpmFc(+)(S354C) and a dimer of Dh3CpmFc(-)(Y349C)-GDF15(Nde13):DhCpmFc(+)(S354C).

DETAILED DESCRIPTION OF THE INVENTION

[0011] The instant disclosure provides fusion proteins comprising a GDF 15 polypeptide or a GDF15 mutant polypeptides and constructs comprising such fusion proteins. GDF15 polypeptides, GDF15 mutant polypeptides, and certain polypeptide constructs comprising GDF15 polypeptides and GDF15 mutant polypeptides, are described in co-owned PCT/US2012/032415, filed 04/05/2012, and PCT/2013/023465, filed 01/28/2013.

[0012] Recombinant polypeptide and nucleic acid methods used herein, including in the Examples, are generally those set forth in Sambrook et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1989) or Current Protocols in Molecular Biology (Ausubel et al.,eds.,Green Publishers Inc. and Wiley and Sons 1994).

I. General Definitions

[0013] Following convention, as used herein "a" and "an" mean "one or more" unless specifically indicated otherwise.

[0014] As used herein, the terms "amino acid" and "residue" are interchangeable and, when used in the context of a peptide or polypeptide, refer to both naturally-occurring and synthetic amino acids, as well as amino acid analogs, amino acid mimetics and non-naturally-occurring amino acids that are chemically similar to the naturally-occurring amino acids.

[0015] The terms "naturally-occurring amino acid" and "naturally encoded amino acid" are used interchangeably and refer to an amino acid that is encoded by the genetic code, as well as those amino acids that are encoded by the genetic code that are modified after synthesis, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine.

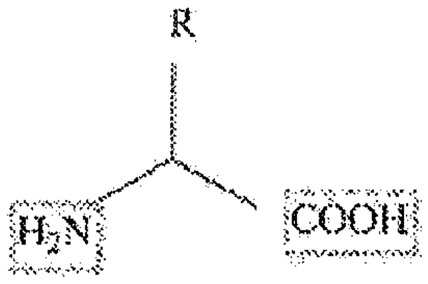
[0016] An "amino acid analog" is a compound that has the same basic chemical structure as a naturally-occurring amino acid, *i.e.,* an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs can have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but will retain the same basic chemical structure as a naturally-

occurring amino acid.

[0017] An "amino acid mimetic" is a chemical compound that has a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally-occurring amino acid. Examples include a methacryloyl or acryloyl derivative of an amide, β-, γ-, δ-imino acids (such as piperidine-4-carboxylic acid) and the like.

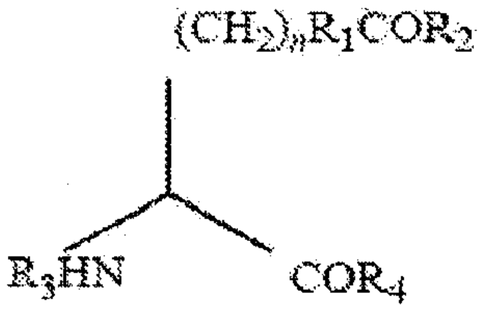
[0018] The terms "non-naturally-occurring amino acid" and "non-naturally encoded amino acid" are used interchangeably and refer to a compound that has the same basic chemical structure as a naturally-occurring amino acid, but is not incorporated into a growing polypeptide chain by the translation complex. "Non-naturally-occurring amino acid" also includes, but is not limited to, amino acids that occur by modification (*e.g.*, posttranslational modifications) of a naturally encoded amino acid (including but not limited to, the 20 common amino acids) but are not themselves naturally incorporated into a growing polypeptide chain by the translation complex. A non-limiting lists of examples of non-naturally-occurring amino acids that can be inserted into a polypeptide sequence or substituted for a wild-type residue in polypeptide sequence include β-amino acids, homoamino acids, cyclic amino acids and amino acids with derivatized side chains. Examples include (in the L-form or D-form; abbreviated as in parentheses): citrulline (Cit), homocitrulline (hCit), Nα-methylcitrulline (NMeCit), Nα-methylhomocitrulline (Nα-MeHoCit), ornithine (Orn), Nα-Methylornithine (Nα-MeOrn or NMeOrn), sarcosine (Sar), homolysine (hLys or hK), homoarginine (hArg or hR), homoglutamine (hQ), Nα-methylarginine (NMeR), Nα-methylleucine (Nα-MeL or NMeL), N-methylhomolysine (NMeHoK), Nα-methylglutamine (NMeQ), norleucine (Nle), norvaline (Nva), 1,2,3,4-tetrahydroisoquinoline (Tic), Octahydroindole-2-carboxylic acid (Oic), 3-(1-naphthyl)alanine (1-Nal), 3-(2-naphthyl)alanine (2-Nal), 1,2,3,4-tetrahydroisoquinoline (Tic), 2-indanylglycine (Igl), para-iodophenylalanine (pI-Phe), para-aminophenylalanine (4AmP or 4-Amino-Phe), 4-guanidino phenylalanine (Guf), glycyllysine (abbreviated "K(Nε-glycyl)" or "K(glycyl)" or "K(gly)"), nitrophenylalanine (nitrophe), aminophenylalanine (aminophe or Amino-Phe), benzylphenylalanine (benzylphe), γ-carboxyglutamic acid (γ-carboxyglu), hydroxyproline (hydroxypro), p-carboxyl-phenylalanine (Cpa), α-aminoadipic acid (Aad), Nα-methyl valine (NMeVal), N-α-methyl leucine (NMeLeu), Nα-methylnorleucine (NMeNle), cyclopentylglycine (Cpg), cyclohexylglycine (Chg), acetylarginine (acetylarg), α, β-diaminopropionoic acid (Dpr), α, y-diaminobutyric acid (Dab), diaminopropionic acid (Dap), cyclohexylalanine (Cha), 4-methyl-phenylalanine (MePhe), β, β-dlphenyl-alanine (BiPhA), aminobutyric acid (Abu), 4-phenyl-phenylalanine (or biphenylalanine; 4Bip), α-amino-isobutyric acid (Aib), beta-alanine, beta-aminopropionic acid, piperidinic acid, aminocaprioic acid, aminoheptanoic acid, aminopimelic acid, desmosine, diaminopimelic acid, N-ethylglycine, N-ethylaspargine, hydroxylysine, allo-hydroxylysine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, N-methylvaline, 4-hydroxyproline (Hyp), γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, ω-methylarginine, 4-Amino-O-Phthalic Acid (4APA), N-acetylglucosaminyl-L-serine, N-acetylglucosylaminyl-L-threonine, O-phosphotyrosine and other similar amino acids, and derivatized forms of any of those specifically listed.

[0019] Also included in the definition of "non-naturally-occurring amino acid" is any amino acid comprising the structure



wherein the R group is any substituent other than the one used in the twenty natural amino acids.

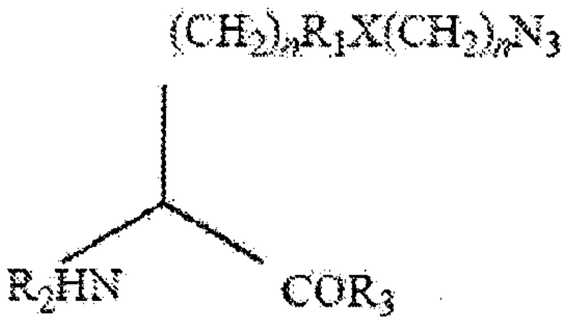
[0020] In some embodiments, the non-naturally encoded amino acid comprises a carbonyl group. In some embodiments, the non-naturally encoded amino acid has the structure:



wherein n is 0-10; R_1 is an alkyl, aryl, substituted alkyl, or substituted aryl; R_2 is H, an alkyl, aryl, substituted alkyl, and substituted aryl; and R_3 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R_4 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

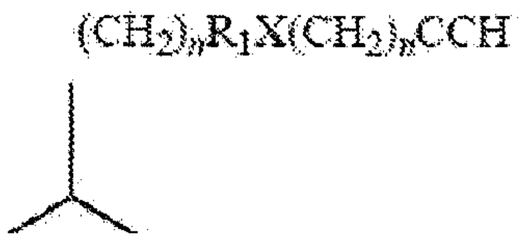
[0021] In some embodiments, the non-naturally encoded amino acid comprises an aminooxy group. In some embodiments, the non-naturally encoded amino acid comprises a hydrazide group. In some embodiments, the non-naturally encoded amino acid comprises a hydrazine group. In some embodiments, the non-naturally encoded amino acid residue comprises a semicarbazide group.

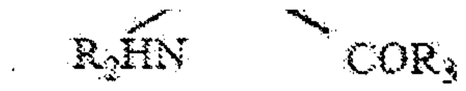
[0022] In some embodiments, the non-naturally encoded amino acid residue comprises an azide group. In some embodiments, the non-naturally encoded amino acid has the structure:



wherein n is 0-10; R_1 is an alkyl, aryl, substituted alkyl, substituted aryl or not present; X is O, N, S or not present; m is 0-10; R_2 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R_3 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

[0023] In some embodiments, the non-naturally encoded amino acid comprises an alkyne group. In some embodiments, the non-naturally encoded amino acid has the structure:





wherein n is 0-10; R_1 is an alkyl, aryl, substituted alkyl, or substituted aryl; X is O, N, S or not present; m is 0-10, R_2 is H, an amino acid, a polypeptide, or an amino terminus modification group, and R_3 is H, an amino acid, a polypeptide, or a carboxy terminus modification group.

[0024] The term "substituted" means that a hydrogen atom on a molecule or group is replaced with a group or atom, which is referred to as a substituent. Typical substituents include: halogen, C_{1-8}alkyl, hydroxyl, C_{1-8}alkoxy, $-NR^xR^x$, nitro, cyano, halo or perhaloC_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, $-SR^x$, $-S(=O)2R^x$, $-C(=O)OR^x$, $-C(=O)R^x$, wherein each R^x is independently hydrogen or C_1-C_8 alkyl. It is noted that when the substituent is $-NR^xR^x$, the R^x groups may be joined together with the nitrogen atom to form a ring.

[0025] The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms, which groups are commonly represented as C_{1-8}alkyl.

[0026] The term "alkoxy" means an alkyl group bonded to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy and isobutoxy. Common alkoxy groups are C_{1-8}alkoxy.

[0027] The term "halogen" or "halo" means chlorine, fluorine, bromine or iodine.

[0028] The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bonds. Representative examples alkenyl groups include ethenyl, propenyl, allyl, butenyl and 4-methylbutenyl. Common alkenyl groups are C_{2-8}alkenyl.

[0029] The term "alkynyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon triple bonds. Representative examples of alkynyl groups include ethynyl, propynyl (propargyl) and butynyl. Common alkynyl groups are C_{2-8} alkynyl.

[0030] The term "cycloalkyl" means a cyclic, nonaromatic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl group can contain one or more double bond. Examples of cycloalkyl groups that contain double bonds include cyclopentenyl, cyclohexenyl, cyclohexadienyl and cyclobutadienyl. Common cycloalkyl groups are C_{3-8} cycloalkyl groups.

[0031] The term "perfluoroalkyl" means an alkyl group in which all of the hydrogen atoms have been replaced with fluorine atoms. Common perfluoroalkyl groups are C_{1-8}perfluoroalkyl. An example of a common perfluoroalkyl group is CF_3.

[0032] The term "acyl" means a group derived from an organic acid by removal of the hydroxy group (-OH). For example, the acyl group $CH_3C(=O)$- is formed by the removal of the hydroxy group from $CH_3C(=O)OH$.

[0033] The term "aryl" means a cyclic, aromatic hydrocarbon. Examples of aryl groups include phenyl and naphthyl. Common aryl groups are six to thirteen membered rings.

[0034] The term "heteroatom" as used herein means an oxygen, nitrogen or sulfur atom.

[0035] The term "heteroaryl" means a cyclic, aromatic hydrocarbon in which one or more carbon atoms of an aryl group have been replaced with a heteroatom. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heteroaryl groups include pyridyl, pyrimidinyl, imidazolyl, thienyl, furyl, pyrazinyl, pyrrolyl, indolyl, triazolyl, pyridazinyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, naphthyridinyl, quinoxalinyl, isothiazolyl and benzo[b]thienyl. Common heteroaryl groups are five to thirteen membered rings that contain from 1 to 4 heteroatoms. Heteroaryl groups that are five and six membered rings that contain 1 to 3 heterotaoms are particularly common.

[0036] The term "heterocycloalkyl" means a cycloalkyl group in which one or more of the carbon atoms has been replaced with a heteroatom. If the heterocycloalkyl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heterocycloalkyl groups include tetrahydrofuryl, morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl. It is also possible for the heterocycloalkyl group to have one or more double bonds, but is not aromatic. Examples of heterocycloalkyl groups containing double bonds include dihydrofuran. Common heterocycloalkyl groups are three to ten membered rings containing from 1 to 4 heteroatoms. Heterocycloalkyl groups that are five and six membered rings that contain 1 to 2 heterotaoms are particularly common.

[0037] It is also noted that the cyclic ring groups, i.e., aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, can comprise more than one ring. For example, the naphthyl group is a fused bicyclic ring system. It is also intended that the present invention include ring groups that have bridging atoms, or ring groups that have a spiro orientation.

[0038] Representative examples of five to six membered aromatic rings, optionally having one or two heteroatoms, are phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl, and pyrazinyl.

[0039] Representative examples of partially saturated, fully saturated or fully unsaturated five to eight membered rings, optionally having one to three heteroatoms, are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and phenyl. Further exemplary five membered rings are furyl, thienyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl), pyrazolidiny1, isoxazolyl, isothiazolyl. 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl,1,2,5-oxadiazolyl, 1,3,4oxadiazolyl, 1,2,3-triazolyl, 1,2,4-trizaolyl, 1,3,4-thiadiazolyl,

3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl, and 1,3-oxathiolyl.

[0040] Further exemplary six membered rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyndazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazitiyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-(3 oxathiazinyl, and 1,4,2-oxadiazinyl.

[0041] Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-triazepinyl.

[0042] Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

[0043] Exemplary bicyclic rings consisting of two fused partially saturated, fully saturated or fully unsaturated five and/or six membered rings, optionally having one to four heteroatoms, are indolizinyl, indolyl, isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)pyridinyl, pyrido(3,2-b)pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyland 4H-1,4-benzoxazinyl.

[0044] A cyclic ring group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3-, or 4-pyridyl, and the term "thienyl" includes 2-, or 3-thienyl.

[0045] The term "isolated nucleic acid molecule" refers to a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end (*e.g.,* a GDF15 nucleic acid sequence provided herein), or an analog thereof, that has been separated from at least about 50 percent of polypeptides, peptides, lipids, carbohydrates, polynucleotides or other materials with which the nucleic acid is naturally found when total nucleic acid is isolated from the source cells. Preferably, an isolated nucleic acid molecule is substantially free from any other contaminating nucleic acid molecules or other molecules that are found in the natural environment of the nucleic acid that would interfere with its use in polypeptide production or its therapeutic, diagnostic, prophylactic or research use.

[0046] The term "isolated polypeptide" refers to a polypeptide (*e.g.*, a GDF15 polypeptide or GDF15 mutant polypeptide provided herein) that has been separated from at least about 50 percent of polypeptides, peptides, lipids, carbohydrates, polynucleotides, or other materials

with which the polypeptide is naturally found when isolated from a source cell. Preferably, the isolated polypeptide is substantially free from any other contaminating polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic or research use.

[0047] The term "encoding" refers to a polynucleotide sequence encoding one or more amino acids. The term does not require a start or stop codon. An amino acid sequence can be encoded in any one of the different reading frames provided by a polynucleotide sequence.

[0048] The terms "identical" and percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) can be addressed by a particular mathematical model or computer program (*i.e.,* an "algorithm"). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in Computational Molecular Biology, (Lesk, A. M., ed.), (1988) New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., (1987) Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., (1988) SIAM J. Applied Math. 48:1073.

[0049] In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., (1984) Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, WI). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (*see,* Dayhoff et al., (1978) Atlas of Protein Sequence, and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., (1992) Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0050] Recommended parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

Algorithm: Needleman et al., 1970, J. Mol, Biol 48:443-13:

Comparison matrix: BLOSUM 62 from Henikoff *et al.*, 1992, *supra*;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

[0051] Certain alignment; schemes for aligning two amino acid sequences can result in matching of only a short region of the two sequences, and this small aligned region can have very high sequence identity even though there is no Significant relationship between the two full-length sequences. Accordingly, the selected alignment method (*e.g.,* the GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

[0052] The term "GDF15 polypeptide" means a naturally-occurring or "wild-type" GDF15 expressed in a mammal, including without limitation, a human, rabbit, monkey (e.g. cynomolgous monkey), dog, rat mouse or pig. In one aspect, GDF15polypeptide refers to any full-length GDF15, *e.g.,* SEQ ID NO:4, which consists of 308 amino acid residues and which is encoded by the nucleotide sequence SEQ ID NO:3; any form comprising the active and prodomains of the polypeptide, *e.g.*, SEQ ID NO:8, which consists of 279 amino acid residues and which is encoded by the nucleotide sequence SEQ ID NO:7, and in which the 29 amino acid residues at the amino-terminal end of the full-length GDF1 5 (*i.e.,* which constitute the signal peptide) have been removed; and any form of GDF 15 comprising the active domain from which the prodomain and signal sequence have been removed, *e.g.*, SEQ ID NO:12, which consists of 112 amino acid residues and which is encoded by the nucleotide sequence SEQ ID NO:11, in which the signal sequence and the prodomain have been removed. GDF15 polypeptides can but need not comprise an amino-terminal methionine, which may be introduced by engineering or as a result of a bacterial expression process.

[0053] The term "GDF15 mutant polypeptide" refers to a GDF15 polypeptide (*e.g.,* SEQ ID NOs:4, 8 or 12) that has been modified. Such modifications include, but are not limited to, one or more amino acid substitutions, including substitutions with non-naturally-occurring amino acids non-naturally-occurring amino acid analogs and amino acid mimetics, additions or deletions. In one aspect, the term "GDF15 mutant polypeptide" refers to a GDF15 polypeptide in which at least one residue normally found at a given position of the naturally-occurring GDF15 polypeptide is deleted or is replaced by a residue not normally found at that position in the naturally-occurring GDF15 polypeptide. In some cases it will be desirable to replace a single residue normally found at a given position in the sequence of a naturally-occurring GDF15 polypeptide with more than one residue that is not normally found at the position; in still other cases it may be desirable to maintain the sequence of the naturally-occurring GDF15 polypeptide and insert one or more residues at a given position in the protein; in still other

cases it may be desirable to delete a given residue entirely; all of these constructs are encompassed by the term "GDF15 mutant polypeptide."

[0054] In various embodiments, a GDF15 mutant polypeptide comprises an amino acid sequence that is at least about 85 percent identical to a naturally ^occurring GDF15 polypeptide (*e.g.*, SEQ ID NOs:4, 8 or 12). In other embodiments, a GDF15 mutant polypeptide comprises an amino acid sequence that is at least about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to a naturally-occurring GDF15 polypeptide amino acid sequence (*e.g.,* SEQ ID NOs:4, 8 or 12). Such GDF15 mutant polypeptides preferably, but need not, possess at least one activity of a naturally-occurring GDF15 polypeptide, such as the ability to lower blood glucose, insulin, triglyceride, or cholesterol levels; the ability to reduce body weight; the ability to improve glucose tolerance, lipid tolerance, or insulin sensitivity; or the ability to lower urine glucose and protein excretion.

[0055] The term "GDF15 region" encompasses GDF15 polypeptides and GDF15 mutant polypeptides and sequences as defined above.

[0056] A GDF15 polypeptide or a GDF15 mutant polypeptide is preferably biologically active. In some instances, a GDF15 polypeptide or a GDF15 mutant polypeptide used to treat or ameliorate a metabolic disorder in a subject from or derived from a different species as the subject. In some instances, a GDF15 polypeptide or a GDF15 mutant polypeptide used to treat or ameliorate a metabolic disorder in a subject from or derived from the same species as the subject.

[0057] The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. The original immunoglobulin source of the native Fc is preferably of human origin and may be any of the immunoglobulins, although IgGI and IgG2 are preferred. Native Fc's are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (*e.g.,* IgG, IgA, IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgAl, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al. (1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomelic, dimeric, and multimeric forms.

[0058] The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc. Such modifications include, but are not limited to, one or more amino acid substitutions, including substitutions with non-naturally-occurring amino acids, non-naturally-occurring amino acid analogs and amino acid mimetics, deletions or additions. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks

one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter, In various embodiments, an Fc variant comprises an amino acid sequence that is at least about 85 percent identical to a native Fc. In other embodiments, an Fc variant comprises an amino acid sequence that is at least about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to a native Fc.

[0059] The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fcs, the term "Fc domain" includes molecules in monomeric or multimeric form.

[0060] The term "multimer" as applied to Fc domains or molecules Comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers, trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting: activity of the native Ig source of the Fc or by derivatizing such a native Fc.

[0061] The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently, non-covalently or by both covalent and non-covalent interactions.

[0062] The term "hinge" or "hinge region" herein includes the flexible polypeptide comprising the amino acids between the first and second constant domains of an antibody. The "hinge region" as referred to herein is a sequence region of 6-62 amino acids in length, only present in IgA, IgD and IgG, which encompasses the cysteine residues that bridge the two heavy chains.

[0063] The "polypeptide linker" refers to a short polypeptide, generally from 1 to 30 amino acid residues in length, that covalently links together two polypeptides, typically via peptide bonds.

[0064] As used herein, the term HSA polypeptide encompasses a naturally-occurring "wild type" human serum albumin. The term also includes various bioactive fragments and variants, fusion proteins, and modified forms of the wild type HSA protein. Such bioactive fragments or variants, fusion proteins, and modified forms of wild type HSA protein have at least a portion of the amino acid sequence of substantial sequence identity to the wild type HAS protein. In certain embodiments, such bioactive fragments or variants, fusion proteins, and modified forms of wild type HSA protein have an amino acid sequence that is at least about 85 percent identical to the wild type HSA. In other embodiments, such bioactive fragments or variants, fusion proteins, and modified forms of wild type HSA protein have an amino acid sequence that is at least about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to the wild type

HAS.

II. Fc Fusions Comprising GDF15 Polypeptides or GDF15 Mutant Polypeptides, and Polynucleotides

[0065] A range of Fc fusion proteins comprising a GDF15 polypeptide or a GDF15 mutant polypeptide are provided herein (see claims). Illustrated fusion proteins comprise a native Fc. In some examples, the fusion proteins comprise an Fc domain that has been engineered.

[0066] In some embodiments, the GDF15 polypeptide- (or GDF15 mutant polypeptide-) containing Fc fusion proteins associate with another polypeptide chain consisting of or comprising an Fc domain to form a heterodimer. In some embodiments, two such heterodimers associate to form a heterotetramer. Some of these polypeptide constructs (i.e., GDF15 polypeptide- (or GDF15 mutant polypeptide-) containing Fc fusion proteins and multimers comprising one or more such GDF15 polypeptide- (or GDF15 mutant polypeptide-) containing Fc fusion proteins) were studied empirically, as described in the Examples presented herein below.

[0067] Antibodies belong to the immunoglobulin class of proteins which includes IgG, IgA, IgE, IgM, and IgD. The most abundant immunoglobulin class in human serum is IgG (Deisenhofer J 1981 Biochem 20:2361-2370; Huber R 1984 Behring Inst Mitt 76:1-14; Roux KH 1999 Int Arch Allergy Immunol 120:85-99). The IgG structure has four chains, two light and two heavy chains; each light chain has two domains and each heavy chain has four domains. The antigen binding site is located in the Fab domain (Fragment antigen binding) which contains a variable light (VL) and a variable heavy (VH) chain domain as well as constant light (LC) and constant heavy (CH1) chain domains. The CH2 and CH3 domain region of the heavy chain is called Fc (Fragment crystallizable). The IgG molecule can be considered as a heterotetramer having two heavy chains that are held together by disulfide bonds (-S-S-) at the hinge region and two light chains. The number of hinge disulfide bonds varies among the immunoglobulin subclasses (Papadea C 1989 Crit Rev Clin Lab Sci 27:27-58). The FcRn binding site is located in the Fc domain of the antibody (Martin WL 2001 Mol Cell 7:867-877), and thus the extended serum half-life property of the antibody is retained in the Fc fragment. The Fc domain alone can be thought of as a homodimer of heavy chains comprising CH2 and CH3 domains.

[0068] In certain preferred embodiments, the fusion proteins described herein comprise an IgG Fc domain, derived from a wild-type human IgG Fc domain. By "wild-type" human IgG Fc, it is meant a sequence of amino acids that occurs naturally within the human population. Of course, just as the Fc sequences may vary slightly between individuals, one or more alterations may be made to a wild-type sequence and still remain within the scope of the invention. For example, the Fc domain may contain additional alterations that are not related to the present invention, such as a mutation in a glycosylation site or the inclusion of an unnatural amino acid. In certain embodiments, the polypeptide containing the CH3 region is an IgG molecule and further contains a CH1 and CH2 domain. Exemplary human IgG sequences

comprise the constant regions of IgG1, IgG2, IgG3 and IgG4. The Fc domain also may be comprised within the constant region of an IgA, IgD, IgE, and IgM heavy chain.

[0069] Some Fc fusion proteins containing GDF15 polypeptide or GDF15 mutant polypeptide, and multimers comprising such Fc fusion proteins include those described below.

II.E. Charged pair (delHinge)

[0070] The designation "CpmFc(+) domain" in the instant disclosure refers to an Fc domain comprising a "positive" charged pair mutation. The designation "CpmFc(-) domain" in the instant disclosure refers to an Fc domain comprising a "negative" charged pair mutation. Note that use of the terms "positive" and "negative" is for ease of reference (i.e., to describe the nature of the charged pair mutations in the Fc domains) and not to indicate that the overall sequence or construct necessarily has a positive or negative charge.

[0071] A "positive" charged pair mutation is provided by introducing a glutamic acid to lysine mutation (E356K) and an aspartic acid to lysine mutation (D399K) in the sequence of an Fc domain. A "negative" charged pair mutation is provided by introducing two lysine to aspartic acid mutations (K392D, K409D) in the sequence of an Fc domain.

[0072] When incubated together, the aspartate residues associate with the lysine residues through electrostatic force, facilitating formation of heterodimers between the CpmFc(+) domains and CpmFc(-) domains, and reducing or preventing formation of homodimers between the CpmFc(+) sequences or between CpmFc(-) sequences.

[0073] The C-terminal lysine (K447) optionally may be deleted in the CpmFc(+) domain, the CpmFc(-) domain, or both. This may be advantageous, for example, when a peptide is fused at the C-terminus to reduce proteolysis of the fusion protein.

[0074] A "DhCpmFc(+)" domain is illustrated by introducing a glutamic acid to lysine mutation (E356K) and an aspartic acid to lysine mutation (D399K) in the sequence of an Fc domain from which all or part of the hinge region has been removed. A "DhCpmFc(-)" domain is illustrated introducing two lysine to aspartic acid mutations (K392D, K409D) in the sequence of an Fc domain from which all or part of the hinge region has been removed.

[0075] When incubated together, the aspartate residues associate with the lysine residues through electrostatic force, facilitating formation of heterodimers between the DhCpmFc(+) domains and DhCpmFc(-) domains, and reducing or preventing formation of homodimers between the DhCpmFc(+) sequences or between DhCpmFc(-) sequences.

[0076] The C-terminal lysine (K447) optionally may be deleted in the DhCpmFc(+), the DhCpmFc(-), or both. This may be advantageous, for example, when a peptide is fused at the C-terminus to reduce proteolysis of the fusion protein.

[0077] A heterodimer is illustrated comprising (i) a first polypeptide chain comprising a GDF15 region linked to a CpmFc(+) domain, and (ii) a second polypeptide chain comprising a CpmFc(-) domain. The N-terminus of the GDF15 region may be linked to the C-terminus of the CpmFc(+) domain, directly or via a polypeptide linker. The N-terminus of the CpmFc(+) domain may be linked to the C-tenninus of the GDF15 region, directly or via a polypeptide linker.

[0078] A heterodimer is illustrated comprising (i) a first polypeptide chain comprising a GDF15 region linked to a CpmFc(-) domain, and (ii) a second polypeptide chain comprising a CpmFc(+) domain. The N-terminus of the GDF15 region may be linked to the C-terminus of the CpmFc(-) domain, directly or via a polypeptide linker. The N-terminus of the CpmFc(-) domain may be linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0079] A heterodimer is illustrated comprising (i) a first polypeptide chain comprising a GDF15 region linked to a DhCpmFc(+) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(-) domain. The N-terminus of the GDF15 region may be linked to the C-terminus of the DhCpmFc(+) domain, directly or via a polypeptide linker. The N-terminus of the DhCpmFc(+) domain is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0080] A heterodimer is illustrated Comprising (i) a first polypeptide chain comprising a GDFI.5 region linked to a DhCpmFc(-) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain. In some embodiments, the N-tenninus of the GDF15 region is linked to the C-terminus of the DhCpmFc(-) domain, directly or via a polypeptide linker. In other embodiments, the N-terminus of the DhCpmFc(-) domain is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0081] In some embodiments, a tetramer is provided comprising a dimer of two such heterodimers in which the two first polypeptide chains of the heterodimers are linked via an interchain disulfide bond between their respective GDF15 regions. *See* Figure 4 for a graphic depiction of an embodiment of a tetramer comprising two heterodimers, where each heterodimer comprises (i) a first polypeptide chain comprising a GDF15 polypeptide linked via a polypeptide linker to a DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

II.E.1 DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)

[0082] The designation "DhCpmFc(+)-(1K)-GDF15:DhCpmFe(-)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(+) domain via a linker comprising the sequence of SEQ ID NO:40 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(+) domain and (ii) a second polypeptide chain comprising a DhCpmFc(-) domain.

[0083] A tetramer is illustrated comprising a dimer of two DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0084] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:38),
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:282),
3. (c) two GDF 15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence:
   GSGSATGGSGSVASSGSGSATHL (SEQ ID NO:40)

each linking the N-terminus of a GDF15 polypeptide to the C-termmus of a DhCpmFc(+) domain via a peptide bond.

II.E.2 DhCpmFc(-)-GDF15:DhCpmFc(+)

[0085] The designation "DhCpmFc(-)-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0086] A tetramer may be provided comprising a dimer of two DhCpmFc(-)-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0087] More particularly, the tetramer may comprise:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the amino acid sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG(SEQ ID NO:283),

2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the amino acid sequence:
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG(SEQ ID NO:48),

and,

3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12.

[0088] The first polypeptide chain comprises the amino acid sequence:
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVL
SPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYN
PMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:50),
which is encoded by the nucleic acid sequence:
gcacctgaactcctgggggaccgtcagtcttcctcttcccccaaaacc
caaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtgg
tggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggac
ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaa
cagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggc
tgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcc
cccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccaca
ggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtca
gcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggag
tgggagagcaatgggcagccggagaacaactacgacaccacgcctcccgt
gctggactccgacggctccttcttcctctatagcgacctcaccgtggaca
agagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag
gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtgc
gcgcaacggagaccactgtccgctcgggcccgggcgttgctgccgtctgc
acacggtccgcgcgtcgctggaagacctgggctgggccgattgggtgctg
tcgccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagcca
gttccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccgcc
tgaagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaat
cccatggtgctcattcaaaagaccgacaccggggtgtcgctccagaccta
tgatgacttgttagccaaagactgccactgcata (SEQ ID NO:49).

[0089] The second polypeptide chain may comprise the amino acid sequence:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD

GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA

PIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE

WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE

ALHNHYTQKSLSLSPGK(SEQ ID NO:47),

which is encoded by the nucleic acid sequence:

gcacctgaactcctgggggaccgtcagtcttcctcttccccccaaaacc

caaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtgg

tggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggac

ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaa

cagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggc

tgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcc

cccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccaca

ggtgtacaccctgcccccatcccggaaggagatgaccaagaaccaggtca

gcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggag

tgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgt

gctgaagtccgacggctccttcttcctctatagcaagctcaccgtggaca

agagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgag

gctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaa

atga (SEQ ID NO:51).

[0090] As discussed above, a tetramer is illustrated comprising two polypeptide chains having the sequence of SEQ ID NO:50 and two polypeptide chains having the sequence of SEQ ID NO:47.

II.E.3 DhCpmFc(-)-GDF15(N3D):DhCpmFc(+)

[0091] The designation "DhCpmFc(-)-GDF15(N3D):DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a naturally-occurring variant of a GDF15 having an asparagine to aspartic acid mutation (N3D) ("GDF15(N3D)"), the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain. The N3D mutation may reduce deamidation induced heterogeneity.

[0092] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)-GDF15(N3D):DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0093] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) having the sequence of SEQ ID NO:283,

2. (b) two DhCpmFc(-) domains (one each heterodimer) having the sequence of SEQ ID N0:48, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence:
   ARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPS
   QFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQT
   YDDLLAKDCHCI (SEQ ID NO:52).

II.E.4 DhCpmFc(-)-GDF15(Ndel3):DhCpmFc(+)

[0094] The designation "DhCpmFc(-)-GDF15(Nde13):DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising(i) a first polypeptide chain comprising a variant of GDF15 in which the first three amino acids are deleted ("GDF15(Ndel3"), the N-terminus of which is linked directly to the C-tenninus of a DhCpmFc(-) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain. The Nde13 variant may reduce N3 deamidation and subsequent D3 isomerization induced heterogeneity.

[0095] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)-GDF15(Nde13):DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0096] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) having the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) having the sequence of SEQ ID N0:48, and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) having the sequence:
   GDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR
   AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDD
   LLAKDCHCI (SEQ ID NO:55).

II.E.6 DhCpmFc(-)-G_4S-GDF15:DhCpmFc(+)

[0097] The designation "DhCpmFc(-)-G_4S-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-) domain via a polypeptide linker comprising the sequence of SEQ ID NO:61 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of

the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0098] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)-G_4S-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0099] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGS (SEQ ID NO:61)

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) domain via peptide bonds.

II.E.7 DhCpmFc(-)-$(G_4S)_2$GDF15:DhCpmFc(+)

[0100] The designation "DhCpmFc(-)-$(G_4S)_2$-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-) domain via a polypeptide linker comprising the sequence of SEQ ID NO:64 that connects N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0101] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)-$(G_4S)_2$-GDF15:DhCpmFc(+) heterodimerS in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0102] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and

4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGSGGGGS (SEQ ID NO:64),

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) sequence via a peptide bond.

II.E.8 DhCpmFc(-)-$(G_4S)_2$-GDF15(N3D):DhCpmFc(+)

[0103] The designation "DhCpmFc(-)-$(G_4S)_2$-GDF15(N3D):DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:64 that connects the N-terminus of the GDF15(N3D) polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0104] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)-$(G_4S)_2$-GDF15(N3D):DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0105] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:64, each linking the N-tenninus of a GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E.9 DhCpmFc(-)-G_4P-GDF15:DhCpmFc(+)

[0106] The designation "DhCpmFc(-)-(G_4P)-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDFI5 polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:69 that connects the N-terminus
of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0107] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)-(G_4P)-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0108] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGP (SEQ ID NO:69),

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E. 10 DhCpmFc(-)-G_4P)$_2$-GDF15:DhCpmFc(+)

[0109] The designation "DhCpmFc(-)-(G_4P)$_2$-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:72 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second v comprising a DhCpmFc(+) sequence.

[0110] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)-(G_4P)$_2$-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF 15 regions.

[0111] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:1 2, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGPGGGGP(SEQ ID NO:72),

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E. 11 DhCpmFc(-)-G_4Q-GDF15:DhCpmFc(+)

[0112] The designation "DhCpmFc(-)-G_4Q-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:75 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain. tetramer is, comprising a dimer of two DhCpmFc(-)-G_4Q-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0113] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) chains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) chains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGQ (SEQ ID NO:75)

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E.12 DhCpmFc(-)-$(G_4Q)_2$-GDF15:DhCpmFc(+)

[0114] The designation "DhCpmFc(-)-$(G_4Q)_2$-GDF15:DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:78 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain. tetramer is comprising a dimer of two DhCpmFc(-)-$(G_4Q)_2$-GDF15:DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions,

[0115] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence: GGGGQGGGGQ (SEQ ID NO:78)

each linking the N-terminus of a GDF15 polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E.13 DhCpmFc(-)-$(G_4Q)_2$-GDF15(N3D):DhCpmFc(+)

[0116] The designation "DhCpmFc(-)-$(G_4Q)_2$-GDF15(N3D):DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:78 that connects the N-terminus of the GDF15(N3D) polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0117] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)-$(G_4Q)_2$-GDF15(N3D):DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0118] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:78 each linking the N-terminus of a GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.E.14 DhCpmFc(-)-$(G_4Q)_2$-GDF15(NdeI3):DhCpmFc(+)

[0119] The designation "DhCpmFc(-)-$(G_4Q)_2$-GDF15(Ndel3):DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide linked to a DhCpmFc(-) domain via a linker comprising the sequence of SEQ ID NO:78 that connects the N-terminus of the GDF15(Ndel3) polypeptide to the C-terminus of the DhCpmFc(-) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain.

[0120] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)-$(G_4Q)_2$-GDF15(Ndel3):DhGpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0121] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:283,
2. (b) two DhCpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:48,
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:78 each linking the N-terminus of a GDF15(Ndel3) polypeptide to the C-terminus of a DhCpmFc(-) domain via a peptide bond.

II.F. Charged pair (delHinge) Cysteine Clamp

[0122] A "cysteine clamp" mutation may be introduced into a Fc domain, such as a CpmFc(+) domain, a CpmFc(-) domain, a DhCpmFc(+) domain, or a DhCpmFc(-) domain. A "cysteine clamp" mutation typically involves the introduction of a cysteine into the CH3 domain of an Fc domain at a specific location through mutation so that when incubated with another Fc domain, also having a cysteine introduced into the CH3 domain at a specific location through mutation, a disulfide bond (cysteine clamp) may be formed between the two Fc domains (e.g., between a CpmFc(+) domain having a "cysteine clamp" mutation and a CpmFc(-) domain having a "cysteine clamp" mutation or between a DhCpmFc(+) domain having a "cysteine clamp" mutation and a DhCpmFc(-) domain having a "cysteine clamp" mutation). An Fc domain may contain one or more such cysteine clamp mutations.

[0123] A cysteine clamp is illustrated by introducing a serine to cysteine mutation (S354C) into a first Fc domain and a tyrosine to cysteine mutation (Y349C) into a second Fc domain.

[0124] The designation "DhCpmFc(-)(S354C)" domain in the instant disclosure refers to an

DhCpmFc(-) domain comprising a serine to cysteine mutation (S354C). The designation "DhCpmFc(+)(S354C)" domain in the instant disclosure refers to an DhCpmFc(+) domain comprising a serine to cysteine mutation (S354C). The designation "DhCpmFc(-)(Y349C)" domain in the instant disclosure refers to an DhCpmFc(-) domain comprising a serine to cysteine mutation (Y349C). The designation "DhCpmFc(+)(Y349C)" domain in the instant disclosure refers to an DhCpmFc(+) domain comprising a serine to cysteine mutation (Y349C).

[0125] The designation "CpmFc(-)(S354C)" domain in the instant disclosure refers to an CpmFc(-) domain comprising a serine to cysteine mutation (S354C). The designation "CpmFc(+)(S354C)" domain in the instant disclosure refers to an CpmFc(+) domain comprising a serine to cysteine mutation (S354C). The designation "CpmFc(-)(Y349C)" domain in the instant disclosure refers to an CpmFc(-) domain comprising a serine to cysteine mutation (Y349C). The designation "CpmFc(+)(Y349C)" domain in the instant disclosure refers to an CpmFc(+) domain comprising a serine to cysteine mutation (Y349C).

[0126] A cysteine clamp is illustrated by introducing a leucine to cysteine mutation (L351C) into both a first and Fc domain.

[0127] The designation "DhCpmFe(-)(L35 1C)" domain in the instant disclosure refers to an DhCpmFc(-) domain comprising a serine to cysteine mutation (L351C). The designation "DhCpmFc(+)(L351C)" domain in the instant disclosure refers to an DhCpmFc(+) domain comprising a serine to cysteine mutation (L351C).

[0128] The designation "CpmFc(-)(L351C)" domain in the instant disclosure refers to an CpmFc(-) domain comprising a serine to cysteine mutation (L351C). The designation "CpmFc(+)(L351C)" domain in the instant disclosure refers to an CpmFc(+) domain comprising a serine to cysteine mutation (L351C).

[0129] The C-terminal lysine (K447) optionally may be deleted in the CpmFc(+) domain, the CpmFc(-) domain, or both. This may be advantageous, for example, when a peptide is fused at the C-terminus to reduce proteolysis of the fusion protein.

[0130] A heterodimer is illustrated comprises (i) a first polypeptide chain comprising a GDF15 region linked to a CpmFc(+) domain comprising a cysteine clamp mutation and (ii) a second polypeptide chain comprising a CpmFc(-) domain comprising a cysteine clamp mutation. The N-terminus of the GDF15 region is linked to the C-terminus of the CpmFc(+) domain comprising a cysteine clamp mutation, directly or via a polypeptide linker. Alternatively the N-terminus of the CpmFc(+) domain comprising a cysteine clamp mutation is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0131] A heterodimer is illustrated comprises (i) a first polypeptide chain comprising a GDF15 region linked to a CpmFc(-) domain comprising a cysteine clamp mutation and (ii) a second polypeptide chain comprising a CpmFc(+) domain comprising a cysteine clamp mutation. The N-terminus of the GDF15 region may be linked to the C-terminus of the CpmFc(-) domain

comprising a cysteine clamp mutation, directly or via a polypeptide linker. Alternatively, the N-terminus of the CpmFc(-) domain comprising a cysteine clamp mutation is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0132] A heterodimer is illustrated comprises (i) a first polypeptide chain comprising a GDF15 region linked to a DhCpmFc(+) domain comprising a cysteine clamp mutation and (ii) a second polypeptide chain comprising a DhCpmFc(-) domain comprising a cysteine clamp mutation. The N-terminus of the GDF15 region may be linked to the C-terminus of the DhCpmFc(+) domain comprising a cysteine clamp mutation, directly or via a polypeptide linker. Alternatively, the N-terminus of the DhCpmFc(+) domain comprising a cysteine clamp mutation is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0133] A heterodimer is illustrtated comprises (i) a first polypeptide chain comprising a GDF15 region linked to a DhCpmFc(-) domain comprising a cysteine clamp mutation and (ii) a second polypeptide chain comprising a DhCpmFc(+) domain comprising a cysteine clamp mutation. The N-terminus of the GDF15 region may be linked to the C-terminus of the DhCpmFc(-) domain comprising a cysteine clamp mutation, directly or via a polypeptide linker. Alternatively the N-terminus of the DhCpmFc(-) domain comprising a cysteine clamp mutation is linked to the C-terminus of the GDF15 region, directly or via a polypeptide linker.

[0134] A tetramer is illustrated comprising a dimer of two such heterodimers in which the two first polypeptide chains of the heterodimers are linked via an interchain disulfide bond between their respective GDF15 regions. *See* Figure .5 for a graphic depiction of an embodiment of a tetramer comprising two heterodimers, where each heterodimer comprises (i) a first polypeptide chain comprising a GDF15 polypeptide linked via a polypeptide linker to a DhCpmFc(+)(L351C) domain and (ii) a second polypeptide chain comprising a DhCpmFc(-)(L351C) domain.

II.F. 1 DhCpmFc(+)(S354C-GDF15(N3D):DhCpmFc(-)(Y349C)

[0135] The designation "DhCpmFc(+)(S354C)-GDF15(N3D):DhCpmFc(-)(Y349C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(+)(S354C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(-)(Y349C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C354 of the first polypeptide chain and C349 of the second polypeptide chain.

[0136] A tetramer is illustrated, comprising a dimer of two DhCpmFc(+)(S354C)-GDF15(N3D):DhCpmFc(-)(Y349C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0137] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:85),
2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:284),

   and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.F.2 DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C)

[0138] The designation "DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0139] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0140] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:285),

2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:91),

   and
3. (c) two GDF15 polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:12.

II.F.3 DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C)

[0141] The designation "DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C)" in the instant disclosure refers to heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(Y349C) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide and C354 of the second polypeptide.

[0142] A tetramer is comprising a dimer of two DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions. An N3D mutation in GDF15 sequence may be introduced, e.g., to eliminate heterogeneity caused by N deamidation.

[0143] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:285,
2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:91, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.F.4 DhCpmFc(-)(Y349C)-GDF15(NdeI3):DhCpmFc(+)(S354C)

[0144] The designation "DhCpmFc(-)(Y349C)-GDF15(NdeI3):DhCpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a

GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0145] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions. Deletion of the N-tenninal 3 amino acids (Ndel3) in GDF15 sequence may be introduced, e.g., to eliminate heterogeneity caused by deamidation of asparagines or isomerization of aspartic acid.

[0146] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) of comprising the sequence of SEQ ID NO:285,
2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:91, and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.F.5 DhCpmFc(-)(Y349C)-G_4-GDF15(N3D):DhCpmFc(+)(S354C)

[0147] The designation "DhCpmFc(-)(Y349C)-G_4-GDF15(N3D):DhCpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide linked to a DhCpmFc(-)(Y349C) domain via a linker comprising the sequence of SEQ ID NO:58 that connects the N-terminus of the GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-)(Y349C) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0148] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)(Y349C)-G_4-GDF15(N3D):DhCpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0149] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) of comprising the

sequence of SEQ ID NO:285,

2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:91,
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:58 each linking the N -terminus of a GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-)(Y349C) domain via a peptide bond.

II.F.7 DhCpmFc(-)(Y349C)-$(G_4Q)_2$GDF15(N3D):DhCpmPc(+)(S354C)

[0150] The designation "DhCpmFc(-)(Y349C)-$(G_4Q)_2$GDF15(N3D):DhCpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide linked to a DhCpmFc(-)(Y349C) domain via a linker comprising the sequence of SEQ ID NO:78 that connects the N-terminus of the GDF15(N3D) polypeptide to the C-terminus of the DhCpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0151] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(Y349C)-$(G_4Q)_2$GDF15(N3D):DhCpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15regions.

[0152] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(S354C) domains (one each heterodimer) of comprising the sequence of SEQ ID NO:285,
2. (b) two DhCpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:91,
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:78 each linking the N-terminus of a GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-)(Y349C) domain via a peptide bond.

II.F.8: DhCpmFc(-)(L351C)-$(G_4S)_2$-GDF15:DhCpmFc(+)(L351C)

[0153] The designation "DhCpmFc(-)(L351C)-($(G_4S)_2$-(GDF15:DhCpmFc(+)(L351C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15 polypeptide linked to a DhCpmFc(-)(L351C) domain via a linker comprising the sequence of SEQ ID NO:64 that connects the N-terminus of the GDF15 polypeptide to the C-terminus of the DhCpmFc(-)(L351C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(L351C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C351 of the first polypeptide chain and C351 of the second polypeptide chain.

[0154] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(L351C)-($(G_4S)_2$-GDF15:DhCpmFc(+)(L351C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0155] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(L351C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTCPPSRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:286),
2. (b) two DhCpmFc(-)(L351C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTCPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:106),
3. (c) two GDF15 polypeptide chains (one each heterodimer) comprising the sequence of SEQ ID NO: 12, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:64 each linking the N-terminus of, a GDF15 polypeptide to the C-terminus of a DhCpmFc(-)(L351C) domain via a peptide bond.

II.H. Constructs with Mutations to Address Affinity for FcγR Binding

[0156] It was found that certain charged pair (delHinge) multimers exhibited Fcγ receptor (FcγR) binding, particularly to FcγRI and FcγRIII. See, e.g., Example 7. In some cases, the FcyR binding affinity was comparable to that of observed in multimers comprising a hinge region. This was unexpected, because the Fcγ receptor interacts with the hinge region and these multimers were delHinge, as described above, lacking all or part of the hinge region.

Mutational analyses of the Fc residues involved in binding to FcγR suggest that the main interaction site is localized in the hinge region and CH2 domain (Tamm A, 1997, Int. Rev. Immunol. 16:57-85). *See also,* Radaev S, et al., J. Biol. Chem. 276:16469-16477; Sondermann, P, et al., 2000, Nature 406:267-273.

[0157] Antibody-dependent cellular cytotoxicity (ADCC), an immune response mediated primarily by natural killer (NK) cells in humans, depends on the interaction of FcγRs, especially FcγRIIIA in humans, with the Fc domain of an antibody or Fc-containing protein. In ADCC, Fc binding to FcγRIII on the surface of an NK cell activates the NK cell, which releases perforins and granzymes.

[0158] Accordingly, constructs are provided having additional modifications to modulate the interaction of the construct with the FcyR. In one series of embodiments, an asparagine to glycine mutation (N297G) is introduced to a native Fc or Fc variant, including the various Fc domains described above. The N297G mutation removes a conserved N-glycosylation site at in the CH2 domain.

[0159] In another series of embodiments, additional N-terminal amino acid residues are deleted from an Fc domain from which all or a portion of the hinge region has been removed. For example, the amino acid sequence:

GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:303)

is provided by deletion of amino acid residues N-terminal to G236 of the Fc domain of wild-type IgG1. In some embodiments, the C-terminal lysine (K447) optionally may be deleted from this Fc variant. The amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:304)

is provided by deletion of amino acid residues N-terminal to G237 from the Fc domain of wild-type IgG1. In some embodiments, the C-terminat lysine (K447) optionally may be deleted from this Fc variant. The amino acid sequence:

PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO:305)

is provided by deletion of amino acid residues N-terminal to P238 of the Fc domain of wild-type IgG1. The C-terminal lysine (K447) optionally may be deleted from this Fc variant.

[0160] A DhCpmFc(-) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(N297G)" domain).In another

embodiment, a DhCpmFc(+) domain into which an asparagine to glycine mutation (N297G) has been introduced is provided (referred to herein as a "DhCpmFc(+)(N297G)" domain).

[0161] A DhCpmFc(-)(Y349C) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(N297G)(Y349C)" domain). In another embodiment, a DhCpmFc(+)(S354C) domain into which an asparagine to glycine mutation (N297G) has been introduced is provided (referred to herein as a "DhCpmFc(+)(N297G)(S354C)" domain).

[0162] A DhCpmFc(+)(Y349C) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(N297G)(Y349C)"domain). A DhCpmFc(-)(S354C) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as "DhCpmFc(-)(N297G)(S354C)" domain).

[0163] A DhCpmFc(+)(L351C) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(N297G)(L351C)" domain). A DhCpmFc(-)(L351C) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(N297G)(L351C)" domain).

[0164] A DhCpmFc(-) domain into which an alanine to cysteine mutation (A287C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(A287C)" domain). A DhCpmFc(+) domain into which an alanine to cysteine mutation (A287C) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(A287C)" domain).

[0165] A DhCpmFc(-) domain into which a leucine to cysteine mutation (L306C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(L306C)" domain). A DhCpmFc(+) domain into which a leucine to cysteine mutation (L306C) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(L306C)" domain).

[0166] A DhCpmFc(-)(A287C) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(A287C)(Y349C)" domain). A DhCpmFc(+)(A287C) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(A287C)(Y349C)" domain).

[0167] A DhCpmFc(-)(A287C) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(A287C)(S354C)" domain). A DhCpmFc(+)(A287C) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(A287C)(S354C)" domain).

[0168] A DhCpmFc(-)(L306C) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(L306C)(Y349C)" domain). A DhCpmFc(+)(L306C) domain into which a tyrosine to cysteine mutation (Y349C) has been

introduced is illustrated (referred to herein as a "DhCpmFc(+)(L306C)(Y349C)" domain).

[0169] A DhCpmFc(-)(L306C) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "DhCpmFc(-)(L306C)(S354C)" domain). A DhCpmFc(+)(L306C) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "DhCpmFc(+)(A287C)(L306C)" domain).

[0170] A DhCpmFc(-) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(-)" domain).

[0171] A DhCpmFc(+) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(+)" domain).

[0172] A DhCpmFc(-)(Y349C) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(-)(Y349C)" domain). A DhCpmFc(+)(S354C) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(+)(S354C)" domain).

[0173] A DhCpmFc(+)(Y349C) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(+)(Y349C)" domain). A DhCpmFc(-)(S354C) domain from which the N-terminal 7 amino acids have been removed is illustrated (referred to herein as a "Dh2CpmFc(-)(S354C)" domain).

[0174] A CpmFc(+) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "CpmFc(+)(N297G)"domain). A CpmFc(-) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "CpmFc(-)(N297G)" domain).

[0175] A Dh2CpmFc(+) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(+)(N297G)"domain). A Dh2CpmFc(-) domain into which an asparagine to glycine mutation (N297G) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(-)(N297G)"domain).

[0176] A Dh2CpmFc(-)(N297G) domain into which an alanine to cysteine mutation (A287C) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(-)(N297G)(A287C)" domain). A Dh2CpmFc(+)(N297G) domain into which a leucine to cysteine mutation (L306C) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(+)(N297G)(L306C)" domain).

[0177] A Dh2CpmFc(-)(N297G)(A287C) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(-)(N297G)(A287C)(Y349C)" domain). A Dh2CpmFc(+)(N297G)(L306C) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "Dh2CpmFc(+)(N297G)(L306C)(S354C)" domain).

[0178] A Dh2CpmFc(-) domain onto which two glycines have been added to the N-terminus is illustrated (referred to herein as a "GG-Dh2CpmFc(-)(N297G)" domain). A Dh2CpmFc(+) domain onto which two glycines have been added to the N-terminus is illustrated (referred to herein as a "GG-Dh2CpmFc(+)(N297G)" domain).

[0179] A GG-Dh2CpmFc(-) domain into which a tyrosine to cysteine mutation (Y349C) have been introduced is illustrated (referred to herein as a "GG-Dh2CpmFc(-)(Y349C)" domain). A GG-Dh2CpmFc(+) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "GG-Dh2CpmFc(+)(S354C)" domain).

[0180] A GG-Dh2CpmFc(+) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "GG-Dh2CpmFc(+)(Y349C)" domain). A GG-Dh2CpmFc(-) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "GG-Dh2CpmFc(-)(S354C)" domain).

[0181] A Dh2CpinFc(-) domain onto which a glycine has been added to the N-terminus is illustrated (referred to herein as a "Dh3CpmFc(-)(N297G)" domain). A Dh2CpmFc(+) domain onto which a glycine has been added to the N-terminus is illustrated (referred to herein as a "Dh3CpmFc(+)" domain).

[0182] A Dh3CpmFc(-) domain into which a tyrosine to cysteine mutation (Y349C) has been introduced is illustrated (referred to herein as a "Dh3CpmFc(-)(Y349C)" domain). A Dh3CpmFc(+) domain into which a serine to cysteine mutation (S354C) has been introduced is illustrated (referred to herein as a "Dh3CpmFc(+)(S354C)" domain).

[0183] An asparagine to glycine mutation (N297G) is introduced into a DhMonoFc domain (referred to herein as "DhMonoFc(N297G)").

H.H.1 DhCpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G)

[0184] The designation "DhCpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G) domain.

[0185] A tetramer is illustrated comrising a dimer of two DhCpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0186] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG(SEQ ID NO:287),
2. (b) two DhCpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG(SEQ ID NO:132),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.2 DhCpmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G)

[0187] The designation "DhCpmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) sequence, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G) domain.

[0188] A tetramer is illustrated comprising a dimer of two DhepmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0189] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:287,
2. (b) two DhCpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO: 132, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.3 DhCpmFc(-)(N297G)-G_4-GDF15(N3D):DhCpmFc(+)(N297G)

[0190] The designation "DhGpmFc(-)(N297G)-G_4-GDF15(N3D):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide linked to a DhCpmFc(-)(N297G) domain via a linker comprising the sequence of SEQ ID NO:58 that connects the N-terminus of the GDF15(N3D) polypeptide to the C-terminus of the DhCpmFc(-)(N297G) domain and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G) domain.

[0191] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)-G_4-GDF15(N3D):DhCpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0192] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:287,
2. (b) two DhCpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:132,
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52, and
4. (d) two polypeptide linkers (one each heterodimer) comprising the sequence of SEQ ID NO:58 each linking the N-termmus of a GDF15(N3D) polypeptide to the C-terminus of a DhCpmFc(-)(N297G) domain via a peptide bond.

II.H.4 DhCpmFc(-)(N297G)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(N297G)(S354C)

[0193] The designation "DhCpmFc(-)(N297G)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(N297G)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0194] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(N297G)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0195] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(S354C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:288),
2. (b) two DhCpmFc(-)(N297G)(Y349C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:141),
   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

11.H.5 DhCpmFc(-)(N297G)(Y349C)-GDF15(N3D):DhCpmFc(+)(N297G)(S354C)

[0196] The designation "DhCpmFc(-)(N297G)(Y349C)-GDF15(N3D):DhCpmFc(+)(N297G)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(S345C) domain, The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0197] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(Y349C)-GDF15(N3D):DhCpmFc(+)(N297G)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF 15 regions.

[0198] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:288,
2. (b) two DhCpmFc(-)(N297G)(Y349C) domains comprising the sequence of SEQ ID NO:141, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of

SEQ ID NO:52.

II.H.6 DhCpmFc(-)(N297G)(L351C)-GDF15(NdeI3):DhCpmFc(+)(N297G)(L351C)

[0199] The designation "DhCpmFc(-)(N297G)(L351C)-GDF15(Nde13):DhCpmFc(+)(N297G)(L351C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(NdeI3) polypeptide, the N-terminus of which is linked directly to the C-terminusof a DhCpmFc(-)(N297G)(L351C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L351C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C351 of the first polypeptide chain and C351 of the second polypeptide chain.

[0200] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(L351C)-GDF15(Nde13):DhCpmFc(+)(N297G)(L351C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0201] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L351C) domains (one each heterodimer) comprising the sequence:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTCPPSREEMTKNQVSLTCLVKGFYPSDIAVE

WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO:289),

2. (b) two DhCpmFc(-)(N297G)(L351C) domains (one each heterodimer) comprising the sequence:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTCPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO:148),

and

3. (c) two GDF15(Nde13) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.7 DhCpmFc(-)(N297G)(L351C)-GDF15(N3D):DhCpmFc(+)(N297G)(L351C)

[0202] The designation "DhCpmFc(-)(N297G)(L351C)-GDF15(N3D):DhCpmFc(+)(N297G)(L351C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(L351C) domain by a peptide bond and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L351C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C351 of the first polypeptide chain and C351 of the second polypeptide chain.

[0203] A tetramer is comprising a dimer of two DhCpmFc(-)(N297G)(L351C)-GDF15(N3D):DhCpmFc(+)(N297G)(L351C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15regions.

[0204] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L351C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:289,
2. (b) two DhCpmFc(-)(N297G)(L351C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:148, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.8 DhCpmFc(-)(N297G)(A287C)-GDF15(NdeI3):DhCpmFc(+)(N297G)(L306C)

[0205] The designation "DhCpmFc(-)(N297G)(A287C)-GDF15(NdeI3):DhCpmFc(+)(N297G)(L306C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF 15(NdeI3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(A287C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L306C) domain.

[0206] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(A287C)-GDF15(NdeI3):DhCpmFc(+)(N297G)(L306C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0207] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L306C) domains (one each heterodimer) comprising the sequence:

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNCKTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE

WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO:290),

2. (b) two DhCpmFc(-)(N297G)(A287C) domains (one each heterodimer) comprising the sequence:
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNCKTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO:268),
and
3. (c) two GDF15(Ndc13) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.9 DhCpmFc(-)(N297G)(A287C)-GDF15(N3D):DhCpmFc(+)(N297G)(L306C)

[0208] The designation "DhCpmFc(-)(N297G)(A287C)-GDF15(N3D):DhCpmFc(+)(N297G)(L306C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(A287C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L306C) domain.

[0209] A tetramer is illustrated, comprising a dimer of two DhCpmFc(-)(N297G)(A287C)-GDF15(N3D):DhCpmFc(+)(N297G)(L306C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0210] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L306C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:290,
2. (b) two DhCpmFc(-)(N297G)(A287C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:268,
and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.10 DhCpmFc(-)(N297G)(A287C)(Y349C)-GDF15(Ndel3): DhCpmFc(+)(N297G)(L306C)(S354C)

[0211] The designation "DhCpmFc(-)(N297G)(A287C)(Y349G)-GDF15(Ndel3):DhCpmFc(+)(N297G)(L306C)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(A287C)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L306C)(S354C) domain.

[0212] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(A287C)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(N297G)(L306C)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0213] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L306C)(Y349C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNCKTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:291),
2. (b) two DhCpmFc(-)(N297G)(A287C)(S354C) domains (one each heterodimer) comprising the sequence:
   APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
   GVEVHNCKTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPA
   PIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
   WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHE
   ALHNHYTQKSLSLSPG (SEQ ID NO:275),

   and
3. (c) two GDF15(Nde13) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.11 DhCpmFc(-)(N297G)(A287C)(Y349C)-GDF15(N3D): DhCpmFc(+)(N297G)(L306C)(S354C)

[0214] The designation "DhCpmFc(-)(N297G)(A287C)(Y349C)-GDF15(N3D):DhCpmFc(+)(N297G)(L306C)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terrninus of which is linked directly to the C-terminus of a DhCpmFc(-)(N297G)(A287C)(Y349C) domain, and (ii) a second polypeptide chain comprising a DhCpmFc(+)(N297G)(L306C)(S354C) domain.

[0215] A tetramer is illustrated comprising a dimer of two DhCpmFc(-)(N297G)(A287C)(Y349C)-GDF15(N3D):DhCpmFc(+)(N297G)(L306C)(S354C) heterodimers in which the two

first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0216] More particularly, the tetramer comprises:

1. (a) two DhCpmFc(+)(N297G)(L3Q6C)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:291,
2. (b) two DhCpmFc(-)(N297G)(A287C)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:275, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.12 Dh2CpmFc(-)-GDF15(Ndel3):Dh2CpmFc(+)

[0217] The designation "Dh2CpmFc(-)-GDF15(Ndel3):Dh2CpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+) domain.

[0218] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)-GDF15(Ndel3):Dh2CpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions,

[0219] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG(SEQ ID NO:292),
2. (b) two Dh2CpmFc(-) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG(SEQ ID NO:155),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.13 Dh2CpmFc(-)-GDF15(N3D):Dh2CpmFc(+)

[0220] The designation "Dh2CpmFc(-)-GDF15(N3D):Dh2CpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-) domain by a peptide bond, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+) domain.

[0221] A tetramer is illustrated comprising a dimer of two Dh2CpmFc(-)-GDF15(N3D):DhCpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0222] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:292,
2. (b) two Dh2CpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:155, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.14 Dh2CpmFc(-)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(S354C)

[0223] The designation "Dh2CpmFc(-)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Nde13) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0224] A tetramer is comprising a dimer of two Dh2CpmFc(-)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0225] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:293),
2. (b) two Dh2CpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:162),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.15 Dh2CpmFc(-)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(S354C)

[0226] The designation "Dh2CpmFc(-)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0227] A tetramer is illustrated comprising a dimer of two Dh2CpmFc(-)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(S354C) heterodimers in which two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0228] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:293,
2. (b) two Dh2CpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:162, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.16 CpmFc(-)(N297G)-GDF15(Ndel3):CpmFc(+)(N297G)

[0229] The designation "CpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a CpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a CpmFc(+)(N297G) domain.

[0230] A tetramer is illustrated comprising a dimer of two CpmFc(-)(N297G)-GDF15(Ndel3):CpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0231] More particularly, the tetramer comprises:

1. (a) two CpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence (part of the hinge region in parentheses):
   (DKTHTCPPCP)APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
   EDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
   YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCL
   VKGFYPSDIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQ
   QGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:294),
2. (b) two CpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence (part of the hinge region in parentheses):
   (DKTHTCPPCP)APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
   EDPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKE
   YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL
   VKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQ
   QGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:169),

   and
3. (c) two GDF15(Nde13) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.17 CpmFc(-)(N297G)-GDF15(N3D):CpmFc(+)(N297G)

[0232] The designation "CpmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a CpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a CpmFc(+)

(N297G) domain.

[0233] A tetramer is illustrated comprising a dimer of two CpmFc(-)(N297G)-GDF15(N3D):CpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF 15 regions.

[0234] More particularly, the tetramer comprises:

1. (a) two CpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:294,
2. (b) two CpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:169, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.18 Dh2CpmFc(-)(N297G)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)

[0235] The designation "Dh2CpmFc(-)(N297G)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G) domain.

[0236] A tetramer is comprising a dimer of two Dh2CpmFc(-)(N297G)-GDF15(Ndel3):Dh2CpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0237] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence:

PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG(SEQ ID NO:295),

2. (b) two Dh2CpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence:

PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP

ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG(SEQ ID NO:176),

and

3. (c) two GDF15(Nde13) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.19 Dh2CpmFc(-)(N297G)-GDF15(N3D):Dh2CpmFc(+)(N297G)

[0238] The designation "Dh2CpmFc(-)(N297G)-GDF15(N3D):DhCpmFc(+)(N297G)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G) domain.

[0239] A tetramer is comprising a dimer of two Dh2CpmFc(-)(N297G)-GDF15(N3D):Dh2CpmFc(+)(N297G) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0240] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:295,
2. (b) two Dh2CpmFc(-)(N297G) domains (one each heterodimer) comprising the sequence of SEQ ID NO:176, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.20 Dh2CpmFc(-)(N297G)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(S354C)

[0241] The designation "Dh2CpmFc(-)(N297G)(Y349C)-GDF15(Nde13):Dh2CpmFc(+)(N297G)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G)(Y349C) polypeptide, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain,

[0242] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)(N297G)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0243] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(N297G)(S354C) domains (one each heterodimer) comprising the sequence:

   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:296),

2. (b) two Dh2CpmFc(-)(N297G)(Y349C) domains (one each heterodimer) comprising the sequence:

   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
   KTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:183),

   and

3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.21 Dh2CpmFc(-)(N297G)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(S354C)

[0244] The designation "Dh2CpmFc(-)(N297G)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(S354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(S345C) domain The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide and C354 of the second polypeptide.

[0245] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)(N297G)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0246] More particularly, the tetramer comprises:

1. (a) two Dh2CpmFc(+)(N297G)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:296,
2. (b) two Dh2CpmFc(-)(N297G)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO: 183, and
3. (c) two GDF15(N3D) polypeptide (one each heterodimer) comprising the sequence of SEQ ID NO:52.

11.H.22 Dh2CpmFc(-)(N297G)(A287C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(L306C)

[0247] The designation "Dh2CpmFc(-)(N297G)(A287C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(L306C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G)(A287C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(L306C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C287 of the first monomer and C306 of the second monomer.

[0248] A tetramer is illustrated comprising a dimer of two Dh2CpmFc(-)(N297G)(A287C)-GDF15(Ndel3):Dh2CpmFc(+)(N297C)(L306C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0249] More particularly a tetramer is illustrated which comprises:

1. (a) two Dh2CpmFc(+)(N297G)(L306C) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNC
   KTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:297),
2. (b) two Dh2CpmFc(-)(N297G)(A287C) (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNC
   KTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:192),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.23 Dh2CpmFc(-)(N297G)(A287C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(L306C)

[0250] The designation "Dh2CpmFc(-)(N297G)(A287C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(L306C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminusof a Dh2CpmFc(-)(N297G)(A287C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(L306C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C287 of the first polypeptide chain and C306 of the second polypeptide chain,

[0251] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)(N297G)(A287C)-GDF15(N3D):Dh2CpmFc(+)(N297U)(L306C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0252] More particularly, a tetramer is provided which comprises:

1. (a) two Dh2CpmFc(+)(N297G)(L306C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:297,
2. (b) two Dh2CpmFc(-)(N297G)(A287C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:192, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.24 Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDF15(Ndel3); Dh2CpmFc(+)(N297G)(L306C)(S354C)

[0253] The designation "Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(L306C)(S 354C)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G)(A287C)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(L306C)(S354C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C287 of the first polypeptide chain and C306 of the second polypeptide chain and between the C349 of the first polypeptide chain and C349 of the second polypeptide chain.

[0254] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDF15(Ndel3):Dh2CpmFc(+)(N297G)(L306C)(S3 54C) heterodimers in which the

two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0255] More particularly, a tetramer is provided which comprises:

1. (a) two Dh2CpmFc(+)(N297)(L306C)(S354C) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNC
   KTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:298),
2. (b) two Dh2CpmFc(-)(N297G)(A287C)(Y349C) domains (one each heterodimer) comprising the sequence:
   PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNC
   KTKPREEQYGSTYRVVSVCTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
   KAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
   ENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT
   QKSLSLSPG (SEQ ID NO:199),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.25 Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDFI5(N3D): Dh2CpmFc(+)(N297G)(L306C)(S354C)

[0256] The designation "Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(L306C)(S3 54C)" in the instant disclosure refers to a heterodimer comprising (i) a first monomer comprising GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh2CpmFc(-)(N297G)(A287C)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh2CpmFc(+)(N297G)(L306C)(S354C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C287 of the first polypeptide chain and C306 of the second polypeptide chain and between the C349 of the first polypeptide chain and C349 of the second polypeptide chain.

[0257] A tetramer is illustrated, comprising a dimer of two Dh2CpmFc(-)(N297G)(A287C)(Y349C)-GDF15(N3D):Dh2CpmFc(+)(N297G)(L306C)(S35 4C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective G.DF15 regions.

[0258] More particularly, a tetramer is illustrated which comprises:

1. (a) two Dh2CpmFc(+)(N297G)(L306C)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:298,
2. (b) two Dh2CpmFc(-)(N297G)(A287C)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO: 199, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of (SEQ ID NO:52).

II.H.26 GG-Dh2CpmFc(-)-GDF15(Ndel3):GG-Dh2CpmFc(+)

[0259] The designation "GG- Dh2CpmFc(-)-GDF15(Ndel3):GG-Dh2CpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a GG-Dh2CpmFc(-) domain, and (ii) a second polypeptide chain comprising a GG-Dh2CpmFc(+) domain.

[0260] A tetramer is illustrated comprising a dimer of two GG-Dh2CpinFc(-)-GDF15(Ndel3):GG-Dh2CpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0261] More particularly, the tetramer comprises:

1. (a) two GG-Dh2CpmFc(+) domains (one each heterodimer) comprising the sequence:
   GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
   NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
   ISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNG
   QPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
   YTQKSLSLSPG (SEQ ID NO:299),
2. (b) two GG-Dh2CpmFc(-) domains (one each heterodimer) comprising the sequence:
   GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
   NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
   ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
   QPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNH
   YTQKSLSLSPG (SEQ ID NO:206),
   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO.55.

II.H.27 GG-Dh2CpmFc(-)-GDF15(N3D):GG-Dh2CpmFc(+)

[0262] The designation "GG-Dh2CpmFc(-)-GDF15(N3D):GG-DhCpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a GG-Dh2CpmFc(-) domain, and (ii) a second polypeptide chain comprising a GG-DhCpmFc(+) domain.

[0263] A tetramer is illustrated, comprising a dimer of two GG-Dh2CpmFc(-)-GDF15(N3D):GG-Dh2CpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0264] More particularly, the tetramer comprises:

1. (a) two GG-Dh2CpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:299,
2. (b) two GG-Dh2CpmFc(-) domains (one each heterodimer) comprising the sequence of SEQ ID NO:206, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

II.H.28 GG-Dh2CpmFc(-)(Y349C)-GDF15(NdeI3): GG-Dh2CpmFc(+)(S354C)

[0265] The designation "GG-Dh2CpmFc(-)(Y349C)-GDF15(NdeI3):GG-Dh2CpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer, which comprises (i) a first polypeptide chain comprising GDF15(NdeI3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a GG-Dh2CpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a GG-Dh2CpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0266] A tetramer is illustrated comprising a dimer of two GG-Dh2CpmFc(-)(Y349C)-GDF15(NdeI3):GG-Dh2CpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0267] More particularly, the tetramer comprises:

1. (a) two GG-Dh2CpmFc(+)(S354C) (one each heterodimer) comprising the sequence:
   GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
   NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
   ISKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNG
   QPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
   YTQKSLSLSPG (SEQ ID NO:300),

2. (b) two GG-Dh2CpmFc(-)(Y349C) chains (one each heterodimer) comprising the sequence:

GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPG (SEQ ID NO:213),

and

3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

II.H.30 Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)

[0268] The designation "Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)" in the instant disclosure refers to a heterodimer, which comprises (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus vof a Dh3CpmFc(-) domain, and (ii) a second polypeptide chain comprising a Dh3CpmFc(+) domain.

[0269] In certain embodiments, a tetramer is provided, comprising a dimer of two Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0270] More particularly, in a specific embodiment, the tetramer comprises:

1. (a) two Dh3CpmFc(+) domains (one each heterodimer) comprising the sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPG (SEQ ID NO:301),

2. (b) two Dh3CpmFc(-) domains (one each heterodimer) comprising the sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPG (SEQ ID NO:220),

and

3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

[0271] In a preferred embodiment, the first polypeptide chain comprises the amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM
CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTD
TGVSLQTYDDLLAKDCHCI (SEQ ID NO:222),

which is encoded by the nucleic acid sequence:

ggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtggag
accactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccgc
gcgtcgctggaagacctgggctgggccgattgggtgctgtcgccacggga

ggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcgg
caaacatgcacgcgcagatcaagacgagcctgcaccgcctgaagcccgac
acggtgccagcgccctgctgcgtgcccgccagctacaatcccatggtgct
cattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttgt
tagccaaagactgccactgcata (SEQ ID NO:221).

[0272] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the first polypeptide chain comprises the amino acid sequence (signal sequence single underlined):

MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGDHCPLGPGRCCRLHTVR
ASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPD
TVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:255),

which is encoded by the nucleic acid sequence (signal sequence underlined):

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg

cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtggag
accactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccgc
gcgtcgctggaagacctgggctgggccgattgggtgctgtcgccacggga
ggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcgg
caaacatgcacgcgcagatcaagacgagcctgcaccgcctgaagcccgac
acggtgccagcgccctgctgcgtgcccgccagctacaatcccatggtgct

cattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttgt
tagccaaagactgccactgcata (SEQ ID NO:256).

[0273] In a preferred embodiment, the second polypeptide chain comprises the amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:219),

which is encoded by the nucleic acid sequence:

ggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccggaaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgc
tgaagtccgacggctccttcttcctctatagcaagctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO:223).

[0274] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the second polypeptide chain comprises the amino acid sequence (signal sequence single underlined):

MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL

NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:257),

which is encoded by the nucleic acid sequence (signal sequence underlined):

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccggaaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgc
tgaagtccgacggctccttcttcctctatagcaagctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID
NO:258).

[0275] As discussed above, a tetramer is provided comprising two polypeptide chains comprising the sequence of SEQ ID NO:222 and two polypeptide chains comprising the sequence of SEQ ID NO:219.

II.H.31 Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)

[0276] The designation "Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)" in the instant disclosure refers to a heterodimer comprising (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh3CpmFc(-) domain, and (ii) a second polypeptide chain comprising a Dh3CpmFc(+) domain.

[0277] In certain embodiments, a tetramer is provided, comprising a dimer of two Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0278] More particularly, in a specific embodiment, the tetramer comprises:

1. (a) two Dh3CpmFc(+) domains (one each heterodimer) comprising the sequence of SEQ ID NO:301,
2. (b) two Dh3CpmFc(-) (one each heterodimer) comprising the sequence of SEQ ID NO:220, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

[0279] In a preferred embodiment, the first polypeptide chain comprises the amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ
VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQ
KTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:225),

which is encoded by the nucleic acid sequence:

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttccccccaaaaccca
aggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtgcgc
gcgacggagaccactgtccgctcgggcccgggcgttgctgccgtctgcac
acggtccgcgcgtcgctggaagacctgggctgggccgattgggtgctgtc
gccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagt
tccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccgcctg
aagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaatcc
catggtgctcattcaaaagaccgacaccggggtgtcgctccagacctatg
atgacttgttagccaaagactgccactgcata (SEQ ID NO:224).

[0280] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the first polypeptide chain comprises the amino acid sequence (signal sequence single underlined):

MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARDGDHCPLGPGRCCRLH
TVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRL
KPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI(SEQ ID NO:259),

which is encoded by the nucleic acid sequence (signal sequence underlined):

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttccccccaaaaccca

aggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtgcgc
gcgacggagaccactgtccgctcgggcccgggcgttgctgccgtctgcac
acggtccgcgcgtcgctggaagacctgggctgggccgattgggtgctgtc
gccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagt
tccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccgcctg
aagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaatcc
catggtgctcattcaaaagaccgacaccggggtgtcgctccagacctatg
atgacttgttagccaaagactgccactgcata (SEQ ID NO:260).

[0281] In a preferred embodiment, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:219, which is encoded by the nucleic acid sequence of SEQ ID NO:223.

[0282] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:257, which is encoded by the nucleic acid sequence of SEQ ID NO:258.

[0283] As discussed above, a tetramer is provided comprising two polypeptide chains comprising the sequence of SEQ ID NO:225 and two polypeptide chains comprising the sequence of SEQ ID NO:219.

II.H.32 Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):Dh3CpmFc(+)(S354C)

[0284] The designation "Dh3CpmFc(-)(Y349C)-GDF 15(Ndel3):Dh3CpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer, which comprises (i) a first polypeptide chain comprising a GDF15(Ndel3) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh3CpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh3CpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide and C354 of the second polypeptide.

[0285] In certain embodiments, a tetramer is provided, comprising a dimer of two

Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):Dh3CpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0286] More particularly, in a specific embodiment, the tetramer comprises:

1. (a) two Dh3CpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence:
   GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
   AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
   SKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
   PENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
   TQKSLSLSPG (SEQ ID NO:302),
2. (b) two Dh3CpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence:
   GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
   AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
   SKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
   PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY
   TQKSLSLSPG (SEQ ID NO:227),

   and
3. (c) two GDF15(Ndel3) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:55.

[0287] In a preferred embodiment, the first polypeptide chain comprises the amino acid sequence:
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM
CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTD
TGVSLQTYDDLLAKDCHCI (SEQ ID NO:229),
which is encoded by the nucleic acid sequence:
atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtgcaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag

agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtggag
accactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccgc
gcgtcgctggaagacctgggctgggccgattgggtgctgtcgccacggga
ggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcgg
caaacatgcacgcgcagatcaagacgagcctgcaccgcctgaagcccgac
acggtgccagcgccctgctgcgtgcccgccagctacaatcccatggtgct
cattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttgt
tagccaaagactgccactgcata (SEQ ID NO:228).

[0288] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the first polypeptide :chain comprises the amino acid sequence (signal sequence single underlined):

MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGDHCPLGPGRCCRLHTVR
ASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPD
TVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:261),

which is encoded by the nucleic acid sequence (signal sequence underlined):

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtgcaccctgcccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtggag
accactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccgc
gcgtcgctggaagacctgggctgggccgattgggtgctgtcgccacggga
ggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcgg
caaacatgcacgcgcagatcaagacgagcctgcaccgcctgaagcccgac
acggtgccagcgccctgctgcgtgcccgccagctacaatcccatggtgct
cattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttgt
tagccaaagactgccactgcata (SEQ ID NO:262).

[0289] In a preferred embodiment, the second polypeptide chain comprises the amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN

AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPCRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ

PENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO:226),
which is encoded by the nucleic acid sequence:
ggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgccccatgccggaaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgc
tgaagtccgacggctccttcttcctctatagcaagctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 230).

[0290] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the second polypeptide chain comprises the amino acid sequence (signal sequence single underlined):
MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRKEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:263),
which is encoded by the nucleic acid sequence (signal sequence underlined):
atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtacaccctgccccatgccggaaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgc
tgaagtccgacggctccttcttcctctatagcaagctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID
NO:264).

[0291] As discussed above, a tetramer is provided comprising two polypeptide chains comprising the sequence of SEQ ID NO:229 and two polypeptide chains comprising the sequence of SEQ ID NO:226.

II.H.33 Dh3CpmFc(-)(Y349C)-GDF15(N3D):Dh3CpmFc(+)(S354C)

[0292] The designation "Dh3CpmFc(-)(Y349G)-GDF15(N3D):Dh3CpmFc(+)(S354C)" in the instant disclosure refers to a heterodimer, which comprises (i) a first polypeptide chain comprising a GDF15(N3D) polypeptide, the N-terminus of which is linked directly to the C-terminus of a Dh3CpmFc(-)(Y349C) domain, and (ii) a second polypeptide chain comprising a Dh3CpmFc(+)(S345C) domain. The cysteine clamp mutations allow the first and second polypeptide chains to be linked via an interchain disulfide bond between C349 of the first polypeptide chain and C354 of the second polypeptide chain.

[0293] In certain embodiments, a tetramer is provided, comprising a dimer of two Dh3CpmFc(-)(Y349C)-GDF15(N3D):Dh3CpmFc(+)(S354C) heterodimers in which the two first polypeptide chains of each heterodimer are linked via an interchain disulfide bond between their respective GDF15 regions.

[0294] More particularly, in a specific embodiment, the tetramer comprises:

1. (a) two Dh3CpmFc(+)(S354C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:302,
2. (b) two Dh3CpmFc(-)(Y349C) domains (one each heterodimer) comprising the sequence of SEQ ID NO:227, and
3. (c) two GDF15(N3D) polypeptides (one each heterodimer) comprising the sequence of SEQ ID NO:52.

[0295] In a preferred embodiment, the first polypeptide chain comprises the amino acid sequence:

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHY

TQKSLSLSPGARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ
VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQ
KTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO: 232),

which is encoded by the nucleic acid sequence:

ggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca

gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtgcaccctgccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtgcgc
gcgacggagaccactgtccgctcgggcccgggcgttgctgccgtctgcac
acggtccgcgcgtcgctggaagacctgggctgggccgattgggtgctgtc
gccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagt
tccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccgcctg
aagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaatcc
atgacttgttagccaaagactgccactgcata (SEQ ID NO:231).

[0296] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the first polypeptide chain comprises the amino acid sequence (signal sequence single underlined):

MDMRVPAQLLGLLLLWLRGARCGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARDGDHCPLGPGRCCRLH
TVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRL
KPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:265),

which is encoded by the nucleic acid sequence (signal sequence underlined):

atggacatgagggtgcccgctcagctcctggggctcctgctgctgtggct
gagaggtgcgcgctgtggcccgtcagtcttcctcttcccccaaaaccca
aggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtg
gacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacgg
cgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaaca
gcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctg
aatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccc
catcgagaaaaccatctccaaagccaaagggcagccccgagaaccacagg
tgtgcaccctgccccatcccgggaggagatgaccaagaaccaggtcagc
ctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtg
ggagagcaatgggcagccggagaacaactacgacaccacgcctcccgtgc
tggactccgacggctccttcttcctctatagcgacctcaccgtggacaag
agcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggc
tctgcacaaccactacacgcagaagagcctctccctgtctccgggtgcgc
gcgacggagaccactgtccgctcgggcccgggcgttgctgccgtctgcac
acggtccgcgcgtcgctggaagacctgggctgggccgattgggtgctgtc
gccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagt
tccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccgcctg
aagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaatcc

catggtgctcattcaaaagaccgacaccggggtgtcgctccagacctatg
atgacttgttagccaaagactgccactgcata (SEQ ID NO:266).

[0297] In a preferred embodiment, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:226, which is encoded by the nucleic acid sequence of SEQ ID NO:230.

[0298] In an embodiment employing the VK1 signal sequence, in a preferred embodiment, the second polypeptide chain comprises the amino acid sequence of SEQ ID NO:263, which is encoded by the nucleic acid sequence of SEQ ID NO:264.

[0299] As discussed above, a tetramer is provided comprising two polypeptide chains comprising the sequence of SEQ ID NO:232 and two polypeptide chains comprising the sequence of SEQ ID NO:226.

III. GDF15 Polypeptides and Constructs Comprising GDF15, Including Mutant Forms Thereof

[0300] As disclosed herein, the GDF15 polypeptides (including the full length and mature forms of human GDF15) and the constructs comprising GDF15 described in the instant disclosure can be engineered and/or produced using standard molecular biology methodology to form a mutant form of the GDF15 polypeptides and constructs provided herein. In various examples, a nucleic acid sequence encoding a mutant form of the GDF15 polypeptides and constructs provided herein, which can comprise all or a portion of SEQ ID NOs:4, 8 or 12 can be isolated and/or amplified from genomic DNA, or cDNA using appropriate oligonucleotide primers. Primers can be designed based on the nucleic and amino acid sequences provided herein according to standard (RT)-PCR amplification techniques. The amplified GDF15 mutant polypeptide nucleic acid can then be cloned into a suitable vector and characterized by DNA sequence analysis.

[0301] Oligonucleotides for use as probes in isolating or amplifying all or a portion of a mutant form of the GDF15 polypeptides and constructs provided herein can be designed and generated using standard synthetic techniques, e.g., automated DNA synthesis apparatus, or can be isolated from a longer sequence of DNA.

III.A. GDF15 Polypeptide and Polynucleotide Sequences

[0302] *In vivo,* GDF15 is expressed as a contiguous amino acid sequence comprising a signal sequence, a pro domain and an active domain.

[0303] The 308 amino acid sequence of full length human GDF15 is:

MPGQELRTVNGSQMLLVLLVLSWLPHGGALSLAEASRASFPGPSELHSED
SRFRELRKRYEDLLTRLRANQSWEDSNTDLVPAPAVRILTPEVRLGSGGH
LHLRISRAALPEGLPEASRLHRALFRLSPTASRSWDVTRPLRRQLSLARP
QAPALHLRLSPPPSQSDQLLAESSSARPQLELHLRPQAARGRRRARARNG

DHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRA
ANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDL
LAKDCHCI (SEQ ID NO:4)

and is encoded by the DNA sequence:

atgcccgggcaagaactcaggacggtgaatggctctcagatgctcctggt
gttgctggtgctctcgtggctgccgcatgggggcgccctgtctctggccg
aggcgagccgcgcaagtttcccgggaccctcagagttgcactccgaagac
tccagattccgagagttgcggaaacgctacgaggacctgctaaccaggct
gcgggccaaccagagctgggaagattcgaacaccgacctcgtcccggccc
ctgcagtccggatactcacgccagaagtgcggctgggatccggcggccac
ctgcacctgcgtatctctcgggccgcccttcccgaggggctccccgaggc
ctcccgccttcaccgggctctgttccggctgtccccgacggcgtcaaggt
cgtgggacgtgacacgaccgctgcggcgtcagctcagccttgcaagaccc
caggcgcccgcgctgcacctgcgactgtcgccgccgccgtcgcagtcgga
ccaactgctggcagaatcttcgtccgcacggccccagctggagttgcact
tgcggccgcaagccgccaggggcgccgcagagcgcgtgcgcgcaacggg
gaccactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccg
cgcgtcgctggaagacctgggctgggccgattgggtgctgtcgccacggg
aggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcg
gcaaacatgcacgcgcagatcaagacgagcctgcaccgcctgaagcccga
cacggtgccagcgccctgctgcgtgcccgccagctacaatcccatggtgc
tcattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttg
ttagccaaagactgccactgcatatga (SEQ ID NO:3).

The 303 amino acid sequence of full length murine GDF15 is:

MAPPALQAQPPGGSQLRFLLFLLLLLLLSWPSQGDALAMPEQRPSGPES
QLNADELRGRFQDLLSRLHANQSREDSNSEPSPDPAVRILSPEVRLGSHG
QLLLRVNRASLSQGLPEAYRVHRALLLLTPTARPWDITRPLKRALSLRGP
RAPALRLRLTPPPDLAMLPSGGTQLELRLRVAAGRGRRSAHAHPRDSCPL
GPGRCCHLETVQATLEDLGWSDWVLSPRQLQLSMCVGECPHLYRSANTHA
QIKARLHGLQPDKVPAPCCVPSSYTPVVLMHRTDSGVSLQTYDDLVARGC
HCA (SEQ ID NO:6)

and is encoded by the DNA sequence:

atggccccgcccgcgctccaggcccagcctccaggcggctctcaactgag
gttcctgctgttcctgctgctgttgctgctgctgtcatggccatcgc
aggggacgccctggcaatgcctgaacagcgaccctccggccctgagtcc
caactcaacgccgacgagctacggggtcgcttccaggacctgctgagccg
gctgcatgccaaccagagccgagaggactcgaactcagaaccaagtcctg
acccagctgtccggatactcagtccagaggtgagattggggtcccacggc
cagctgctactccgcgtcaaccgggcgtcgctgagtcagggtctccccga
agcctaccgcgtgcaccgagcgctgctcctgctgacgccgacggcccgcc
cctgggacatcactaggcccctgaagcgtgcgctcagcctccggggaccc
cgtgctcccgcattacgcctgcgcctgacgccgcctccggacctggctat
gctgccctctggcggcacgcagctggaactgcgcttacgggtagccgccg

gcagggggcgccgaagcgcgcatgcgcacccaagagactcgtgcccactg
ggtccggggcgctgctgtcacttggagactgtgcaggcaactcttgaaga
cttgggctggagcgactgggtgctgtccccgcgccagctgcagctgagca
tgtgcgtgggcgagtgtccccacctgtatcgctccgcgaacacgcatgcg
cagatcaaagcacgcctgcatggcctgcagcctgacaaggtgcctgcccc
gtgctgtgtcccctccagctacaccccggtggttcttatgcacaggacag
acagtggtgtgtcactgcagacttatgatgacctggtggcccggggctgc
cactgcgcttga (SEQ ID NO:5).

[0304] The amino acid sequence of human GDF15 following cleavage of the 29 residue signal sequence is:

LSLAEASRASFPGPSELHSEDSRFRELRKRYEDLLTRLRANQSWEDSNTD
LVPAPAVRILTPEVRLGSGGHLHLRISRAALPEGLPEASRLHRALFRLSP
TASRSWDVTRPLRRQLSLARPQAPALHLRLSPPPSQSDQLLAESSSARPQ
LELHLRPQAARGRRRARARNGDHCPLGPGRCCRLHTVRASLEDLGWADWV
LSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASY
NPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO:8)

and is encoded by the DNA sequence:

ctgtctctggccgaggcgagccgcgcaagtttcccgggaccctcagagtt
gcactccgaagactccagattccgagagttgcggaaacgctacgaggacc
tgctaaccaggctgcgggccaaccagagctgggaagattcgaacaccgac
ctcgtcccggcccctgcagtccggatactcacgccagaagtgcggctggg
atccggcggccacctgcacctgcgtatctctcgggccgcccttcccgagg
ggctccccgaggcctcccgccttcaccgggctctgttccggctgtccccg
acggcgtcaaggtcgtgggacgtgacacgaccgctgcggcgtcagctcag
ccttgcaagaccccaggcgcccgcgctgcacctgcgactgtcgccgccgc
cgtcgcagtcggaccaactgctggcagaatcttcgtccgcacggccccag
ctggagttgcacttgcggccgcaagccgccaggggggcgccgcagagcgcg

tgcgcgcaacggggaccactgtccgctcgggcccgggcgttgctgccgtc
tgcacacggtccgcgcgtcgctggaagacctgggctgggccgattgggtg
ctgtcgccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgag
ccagttccgggcggcaaacatgcacgcgcagatcaagacgagcctgcacc
gcctgaagcccgacacggtgccagcgccctgctgcgtgcccgccagctac
aatcccatggtgctcattcaaaagaccgacaccggggtgtcgctccagac
ctatgatgacttgttagccaaagactgccactgcatatga (SEQ ID NO:7)

[0305] The amino acid sequence of murine GDF 15 following cleavage of the 32 residue signal sequence is:

SQGDALAMPEQRPSGPESQLNADELRGRFQDLLSRLHANQSREDSNSEPS
PDPAVRILSPEVRLGSHGQLLLRVNRASLSQGLPEAYRVHRALLLLTPTA
RPWDITRPLKRALSLRGPRAPALRLRLTPPPDLAMLPSGGTQLELRLRVA
AGRGRRSAHAHPRDSCPLGPGRCCHLETVQATLEDLGWSDWVLSPRQLQL
SMCVGECPHLYRSANTHAQIKARLHGLQPDKVPAPCCVPSSYTPVVLMHR
TDSGVSLQTYDDLVARGCHCA (SEQ ID NO:10)

and is encoded by the DNA sequence:

tcgcaggggacgccctggcaatgcctgaacagcgaccctccggccctga

gtcccaactcaacgccgacgagctacggggtcgcttccaggacctgctga
gccggctgcatgccaaccagagccgagaggactcgaactcagaaccaagt
cctgacccagctgtccggatactcagtccagaggtgagattggggtccca
cggccagctgctactccgcgtcaaccgggcgtcgctgagtcagggtctcc
ccgaagcctaccgcgtgcaccgagcgctgctcctgctgacgccgacggcc
cgcccctgggacatcactaggcccctgaagcgtgcgctcagcctccgggg
accccgtgctcccgcattacgcctgcgcctgacgccgcctccggacctgg
ctatgctgccctctggcggcacgcagctggaactgcgcttacgggtagcc
gccggcaggggcgccgaagcgcgcatgcgcacccaagagactcgtgccc
actgggtccggggcgctgctgtcacttggagactgtgcaggcaactcttg
aagacttgggctggagcgactgggtgctgtccccgcgccagctgcagctg
agcatgtgcgtgggcgagtgtccccacctgtatcgctccgcgaacacgca
tgcgcagatcaaagcacgcctgcatggcctgcagcctgacaaggtgcctg
ccccgtgctgtgtcccctccagctacaccccggtggttcttatgcacagg
acagacagtggtgtgtcactgcagacttatgatgacctggtggcccgggg
ctgccactgcgcttga (SEQ ID NO:9)

[0306] The biologically active form of GDF15 comprises a homodimer comprising two mature GDF15 monomers, each of which comprises SEQ ID NO:12. The monomer that homodimerizes to form the native mature human GDF15 dimer is encoded by the nucleic acid sequence:

gcgcgcaacggggaccactgtccgctcgggcccgggcgttgctgccgtct
gcacacggtccgcgcgtcgctggaagacctgggctgggccgattgggtgc
tgtcgccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagc
cagttccgggcggcaaacatgcacgcgcagatcaagacgagcctgcaccg
cctgaagcccgacacggtgccagcgccctgctgcgtgcccgccagctaca
atcccatggtgctcattcaaaagaccgacaccggggtgtcgctccagacc
tatgatgacttgttagccaaagactgccactgcatatga (SEQ ID NO:11)

and comprises the amino acid sequence:

ARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPS
QFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQT
YDDLLAKDCHCI (SEQ ID NO:12).

[0307] Thus, the "native mature human GDF15 dimer" comprises two covalently associated monomers comprising SEQ ID NO:12.

[0308] The amino acid sequence of the recombinant active form of the human GDF15, which comprises a homodimer comprising nine cysteines in each monomer to form one interchain disulfide bond and four intrachain disulfide bonds (shown with an optional N-terminal methionine residue in parentheses), is:

(M)ARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGA
CPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVS
LQTYDDLLAKDCHCI (SEQ ID NO:189)

and is encoded by the DNA sequence (shown with an optional N-terminal methionine codon in parentheses):

(atg)gcgcgcaacggggaccactgtccgctcgggcccgggcgttgctgc

cgtctgcacacggtccgcgcgtcgctggaagacctgggctgggccgattg
ggtgctgtcgccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcc
cgagccagttccgggcggcaaacatgcacgcgcagatcaagacgagcctg
caccgcctgaagcccgacacggtgccagcgccctgctgcgtgcccgccag
ctacaatcccatggtgctcattcaaaagaccgacaccggggtgtcgctcc
agacctatgatgacttgttagccaaagactgccactgcatataa (SEQ ID
NO:190).

[0309] The amino acid sequence of the recombinant active form of the murine GDF15, which comprises a homodimer comprising nine cysteines in each monomer to form one interchain disulfide bond and four intrachain disulfide bonds, is:

(M)SAHAHPRDSCPLGPGRCCHLETVQATLEDLGWSDWVLSPRQLQLSMC
VGECPHLYRSANTHAQIKARLHGLQPDKVPAPCCVPSSYTPVVLMHRTDS
GVSLQTYDDLVARGCHCA (SEQ ID NO:14)

and is encoded by the DNA sequence:

(atg)agcgcgcatgcgcacccaagagactcgtgcccactgggtccgggg
cgctgctgtcacctggagactgtgcaggcaactcttgaagacttgggctg
gagcgactgggtgttgtccccgcgccagctgcagctgagcatgtgcgtgg
gcgagtgtccccacctgtatcgctccgcgaacacgcatgcgcagatcaaa
gcacgcctgcatggcctgcagcctgacaaggtgcctgccccgtgctgtgt
cccctccagctacaccccggtggttcttatgcacaggacagacagtggtg
tgtcactgcagacttatgatgacctggtggccccggggctgccactgcgct
tga (SEQ ID NO:13).

[0310] As stated herein, the term "GDF15 polypeptide" refers to a GDF polypeptide comprising the human amino acid sequences SEQ ID NOs:4, 8 and 12. The term "GDF15 mutant polypeptide," however, encompasses polypeptides comprising an amino acid sequence that differs from the amino acid sequence of a naturally-occurring GDF polypeptide sequence, *e.g.,* SEQ ID NOs: 4, 8 and 12, by one or more amino acids, such that the sequence is at least 85% identical to SEQ ID NOs: 4, 8 and 12. GDF15 polypeptides can be generated by introducing one or more amino acid substitutions, either conservative or non-conservative and using naturally or non-naturally-occurring amino acids, at particular positions of the GDF15 polypeptide, or by deleting particular residues or stretches of residues.

[0311] A "conservative amino acid substitution" can involve a substitution of a native amino acid residue (*i.e.,* a residue found in a given position of the wild-type GDF15 polypeptide sequence) with a non-native residue (*i.e.,* a residue that is not found in a given position of the wild-type GDF15 polypeptide sequence) such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Conservative amino acid substitutions also encompass non-naturally-occurring amino acid residues (as defined herein) that are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics, and other reversed or inverted forms of amino acid moieties.

[0312] Naturally-occurring residues can be divided into classes based on common side chain

properties:

1. (1) hydrophobic: norleucine, Met, Ala, Val, Leu, lie;
2. (2) neutral hydrophilic: Cys, Ser, Thr;
3. (3) acidic: Asp, Glu;
4. (4) basic: Asn, Gln, His, Lys, Arg;
5. (5) residues that influence chain orientation: Gly, Pro; and
6. (6) aromatic: Trp, Tyr, Phe.

[0313] Additional groups of amino acids can also be formulated using the principles described in, *e.g.,* Creighton (1984) PROTEINS: STRUCTURE AND MOLECULAR PROPERTIES (2d Ed. 1993), W.H. Freeman and Company. In some instances it can be useful to further characterize substitutions based on two or more of such features (*e.g.,* substitution with a "small polar" residue, such as a Thr residue, can represent a highly conservative substitution in an appropriate context).

[0314] Conservative substitutions can involve the exchange of a member of one of these classes for another member of the same class. Non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class.

[0315] Synthetic, rare, or modified amino acid residues having known similar physiochemical properties to those of an above-described grouping can be used as a "conservative" substitute for a particular amino acid residue in a sequence. For example, a D-Arg residue may serve as a substitute for a typical L-Arg residue. It also can be the case that a particular substitution can be described in terms of two or more of the above described classes (*e.g.,* a substitution with a small and hydrophobic residue means substituting one amino acid with a residue(s) that is found in both of the above-described classes or other synthetic, rare, or modified residues that are known in the art to have similar physiochemical properties to such residues meeting both definitions).

[0316] Nucleic acid sequences encoding a GDF15 mutant polypeptide provided herein, including those degenerate to SEQ ID NOs: 3, 7, 11 and 15, and those encoding polypeptide variants of SEQ ID NOs:4, 8 and 12, form other aspects of the instant disclosure.

III.B. Vectors Useful for Expressing GDF15 Polypeptides and Constructs Comprising GDF15, Including Mutant Forms Thereof

[0317] In order to express the nucleic acid sequences encoding a polypeptide comprising a GDF15 region, the appropriate coding sequences, *e.g.,* SEQ ID NOs:3, 7 and 11, can be cloned into a suitable vector and after introduction in a suitable host, the sequence can be expressed to produce the encoded polypeptide according to standard cloning and expression

techniques, which are known in the art (*e.g.,* as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. Molecular Cloning: A Laboratory Manual 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989). The invention also relates to such vectors comprising a nucleic acid sequence according to the invention.

[0318] A "vector" refers to a delivery vehicle that (a) promotes the expression of a polypeptide-encoding nucleic acid sequence; (b) promotes the production of the polypeptide therefrom; (c) promotes the transfection/transformation of target cells therewith; (d) promotes the replication of the nucleic acid sequence; (e) promotes stability of the nucleic acid; (f) promotes detection of the nucleic acid and/or transformed/transfected cells; and/or (g) otherwise imparts advantageous biological and/or physiochemical function to the polypeptide-encoding nucleic acid. A vector can be any suitable vector, , including chromosomal, non-chromosomal, and synthetic nucleic acid vectors (a nucleic acid sequence comprising a. suitable set of expression control elements). Examples of such vectors include derivatives of SV40, bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA, and viral nucleic acid (RNA or DNA) vectors.

[0319] A recombinant expression vector can be designed for expression of a polypeptide comprising a GDF15 region in prokaryotic (*e.g., E. coli*) or eukaryotic cells (*e.g.,* insect cells, using baculovirus expression vectors, yeast cells, or mammalian cells). Representative host cells include those hosts typically used for cloning and expression, including *Escherichia coli* strains TOP10F', TOP10, DH10B, DH5a, HB101, W3110, BL21(DE3) and BL21 (DE3)pLysS, BLUESCRIPT (Stratagene), mammalian cell lines CHO, CHO-K1, HEK293, 293-EBNA pIN vectors (Van Heeke & Schuster, J. Biol. Chem. 264: 5503-5509 (1989); pET vectors (Novagen, Madison Wis.). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro,* for example using T7 promoter regulatory sequences and T7 polymerase and an in vitro translation system. Preferably, the vector contains a promoter upstream of the cloning site containing the nucleic acid sequence encoding the polypeptide. Examples of promoters, which can be switched on and off, include the lac promoter, the T7 promoter, the trc promoter, the tac promoter and the trp promoter.

[0320] Thus, provided herein are vectors comprising a nucleic acid sequence encoding a polypeptide comprising a GDF15 region that facilitate the expression of the polypeptide or construct of interest. In various embodiments, the vectors comprise an operably linked nucleotide sequence which regulates the expression of a polypeptide comprising a GDF15 region. A vector can comprise or be associated with any suitable promoter, enhancer, and other expression-facilitating elements. Examples of such elements include strong expression promoters (*e.g.,* a human CMV IE promoter/enhancer, an RSV promoter, SV40 promoter, SL3-3 promoter, MMTV promoter, or HIV LTR promoter, EFlalpha promoter, CAG promoter), effective poly (A) termination sequences, an origin of replication for plasmid product in *E. coli,* an antibiotic resistance gene as a selectable marker, and/or a convenient cloning site (*e.g.,* a polylinker). Vectors also can comprise an inducible promoter as opposed to a constitutive promoter such as CMV IE. In one aspect, a nucleic acid comprising a sequence encoding a polypeptide comprising a GDF15 region which is operatively linked to a tissue specific

promoter which promotes expression of the sequence in a metabolically-relevant tissue, such as liver or pancreatic tissue is provided.

III.C. Host Cells

[0321] In another aspect of the instant disclosure, host cells comprising the nucleic acids and vectors disclosed herein are provided. In various embodiments, the vector or nucleic acid is integrated into the host cell genome, which in other embodiments the vector or nucleic acid is extra-chromosomal.

[0322] Recombinant cells, such as yeast, bacterial (*e.g., E. coli*), and mammalian cells (*e.g.,* immortalized mammalian cells) comprising such a nucleic acid, vector, or combinations of either or both thereof are provided. In various embodiments, cells comprising a non-integrated nucleic acid, such as a plasmid, cosmid, phagemid, or linear expression element, which comprises a sequence coding for expression of a polypeptide comprising a GDF15 region.

[0323] A vector comprising a nucleic acid sequence encoding a polypeptide comprising a GDF15 region can be introduced into a host cell by transformation or by transfection. Methods of transforming a cell with an expression vector are well known.

[0324] A nucleic acid encoding a polypeptide comprising a GDF15 region can be positioned in and/or delivered to a host cell or host animal via a viral vector. Any suitable viral vector can be used in this capacity. A viral vector can comprise any number of viral polynucleotides, alone or in combination with one or more viral proteins, which facilitate delivery, replication, and/or expression of the nucleic acid of the invention in a desired host cell. The viral vector can be a polynucleotide comprising all or part of a viral genome, a viral protein/nucleic acid conjugate, a virus-like particle (VLP), or an intact virus particle comprising viral nucleic acids and a nucleic acid encoding a polypeptide comprising a GDF15 region. A viral particle viral vector can comprise a wild-type viral particle or a modified viral particle. The viral vector can be a vector which requires the presence of another vector or wild-type virus for replication and/or expression (*e.g.,* a viral vector can be a helper-dependent virus), such as an adenoviral vector amplicon. Typically, such viral vectors consist of a wild-type viral particle, or a viral particle modified in its protein and/or nucleic acid content to increase transgene capacity or aid in transfection and/or expression of the nucleic acid (examples of such vectors include the herpes virus/AAV amplicons). Typically, a viral vector is similar to and/or derived from a virus that normally infects humans. Suitable viral vector particles in this respect, include, for example, adenoviral vector particles (including any virus of or derived from a virus of the adenoviridae), adeno-associated viral vector particles (AAV vector particles) or other parvoviruses and parvoviral vector particles, papillomaviral vector particles, flaviviral vectors, alphaviral vectors, herpes viral vectors, pox virus vectors, retroviral vectors, including lentiviral vectors.

III.D. Isolation of a GDF15 Polypeptide. Construct Comprising a GDF15 Polypeptide or a Mutant Form Thereof

[0325] A polypeptide comprising a GDF15 region can be isolated using standard protein purification methods. A polypeptide comprising a GDF15 region can be isolated from a cell that has been engineered to express a polypeptide comprising a GDF15 region, for example a cell that does not naturally express native GDF15.

[0326] Protein purification methods that can be employed to isolate polypeptide comprising a GDF15 region, as well as associated materials and reagents, are known in the art. Exemplary methods of purifying polypeptide comprising a GDF15 region are provided in the Examples herein below. Additional purification methods that may be useful for isolating polypeptide comprising a GDF15 region can be found in references such as Bootcov MR, 1997, Proc. Natl. Acad. Sci. USA 94:11514-9, Fairlie WD, 2000, Gene 254: 67-76.

IV. Pharmaceutical Compositions Comprising a GDF15 Polypeptide, Construct Comprising a GDF15 Polypeptide or a Mutant Form Thereof

[0327] Pharmaceutical compositions comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region are provided. Such polypeptide pharmaceutical compositions can comprise a therapeutically effective amount of a polypeptide comprising a monomer or multimer comprising a polypeptide: comprising a GDF15 region in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration. The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation agents suitable for accomplishing or enhancing the delivery of a monomer or multimer comprising a polypeptide comprising a GDF15 region into the body of a human or non-human subject. The term includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In some cases it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in a pharmaceutical composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the monomer or multimer comprising a polypeptide comprising a GDF15 region can also act as, or form a component of, a carrier. Acceptable pharmaceutically acceptable carriers are preferably nontoxic to recipients at the dosages and concentrations employed.

[0328] A pharmaceutical composition can contain formulation agent(s) for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption, or penetration of the

composition. Suitable formulation agents include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite, or sodium hydrogen-sulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, or other organic acids), bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin, or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrins), proteins (such as free serum albumin, gelatin, or immunoglobulins), coloring, flavoring and diluting agents, emulsifying agents, hydrophilic polymers (such as polyvinylpyrrolidone), low molecular weight polypeptides, salt-forming counterions (such as sodium), preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, or hydrogen peroxide), solvents (such as glycerin, propylene glycol, or polyethylene glycol), sugar alcohols (such as mannitol or sorbitol), suspending agents, surfactants or wetting agents (such as pluronics; PEG; sorbitan esters; polysorbates such as Polysorbate 20 or Polysorbate 80; Triton; tromethamine; lecithin; cholesterol or tyloxapal), stability enhancing agents (such as sucrose or sorbitol), tonicity enhancing agents (such as alkali metal halides - preferably sodium or potassium chloride - or mannitol sorbitol), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants (see, *e.g.,* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th edition, (1995); Berge et al., J. Pharm. Sci., 6661), 1-19 (1977). Additional relevant principles, methods, and agents are described in, *e.g.,* Lieberman et al., PHARMACEUTICAL DOSAGE FORMS-DISPERSE SYSTEMS (2nd ed., vol. 3, 1998); Ansel et al., PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS (7th ed. 2000); Martindale, THE EXTRA PHARMACOPEIA (31st edition), Remington's PHARMACEUTICAL SCIENCES (16th-20th and subsequent editions); The Pharmacological Basis Of Therapeutics, Goodman and Gilman, Eds. (9th ed.--1996); Wilson and Gisvolds' TEXTBOOK OF ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY, Delgado and Remers, Eds. (10th ed., 1998). Principles of formulating pharmaceutically acceptable compositions also are described in, e.g., Aulton, PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Churchill Livingstone (New York) (1988), EXTEMPORANEOUS ORAL LIQUID DOSAGE PREPARATIONS, CSHP (1998)).

[0329] The optimal pharmaceutical composition will be determined by a skilled artisan depending upon, for example, the intended route of administration, delivery format, and desired dosage (see, *e.g.,* Remington's PHARMACEUTICAL SCIENCES, *supra*). Such compositions can influence the physical state, stability, rate of i*n vivo* release, and rate of *in vivo* clearance of a GDF15 polypeptide, construct comprising a GDF15 polypeptide or a mutant form thereof.

[0330] The primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier for injection can be water, physiological saline solution, or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with free serum albumin are further exemplary vehicles. Other exemplary

pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute. In one embodiment of the present invention, compositions comprising a GDF15 polypeptide, construct comprising a GDF15 polypeptide or a mutant form thereof can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Furthermore, a product comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region can be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0331] The polypeptide pharmaceutical compositions can be selected for parenteral delivery. Alternatively, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the skill of the art.

[0332] The formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0333] When parenteral administration is contemplated, the therapeutic compositions for use in this invention can be in the form of a pyrogen-free, parenterally acceptable, aqueous solution comprising a desired GDF15 polypeptide, construct comprising a GDF15 polypeptide or a mutant form thereof, in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a GDF15 polypeptide, construct comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which can then be delivered via a depot injection. Hyaluronic acid can also be used, and this can have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

[0334] In one embodiment, a pharmaceutical composition can be formulated for inhalation. For example, a monomer or multimer comprising a polypeptide comprising a GDF15 region can be formulated as a dry powder for inhalation. Inhalation solutions comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region can also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions can be nebulized.. Pulmonary administration is further described in International Publication No. WO 94/20069, which describes the pulmonary delivery of chemically modified proteins.

[0335] It is also contemplated that certain formulations can be administered orally. In one embodiment of the present invention, a monomer or multimer comprising a polypeptide comprising a GDF15 region that is administered in this fashion can be formulated with or

without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of a monomer or multimer comprising a polypeptide comprising a GDF15 region. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

[0336] Another pharmaceutical composition can involve an effective quantity of a monomer or multimer comprising a polypeptide comprising a GDF15 region in a mixture with nontoxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0337] Additional pharmaceutical compositions comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region will be evident to those skilled in the art, including formulations comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region, in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art (see, *e.g.,* International Publication No. WO 93/15722, which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions, and Wischke & Schwendeman, 2008, Int. J. Pharm. 364: 298-327, and Freiberg & Zhu, 2004, Int. J. Pharm. 282: 1-18, which discuss microsphere/microparticle preparation and use). As described herein, a hydrogel is an example of a sustained- or controlled-delivery formulation.

[0338] Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S. Patent No. 3,773,919 and European Patent No. 0 058 481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 22: 547-56), poly(2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15: 167-277 and Langer, 1982, Chem. Tech. 12: 98-105), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (European Patent No. 0 133 988). Sustained-release compositions can also include liposomes, which can be prepared by any of several methods known in the art. See, *e.g.,* Epstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82: 3688-92; and European Patent Nos. 0 036 676, 0 088 046, and 0 143 949.

[0339] A pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region which is to be used for *in vivo* administration typically should be sterile. This can be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method can be conducted either

prior to, or following, lyophilization and reconstitution. The composition for parenteral administration can be stored in lyophilized form or in a solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0340] Once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (*e,g.,* lyophilized) requiring reconstitution prior to administration.

[0341] In a specific embodiment, the present invention is directed to kits for producing a single-dose administration unit. The kits can each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this invention are kits containing single and multi-chambered pre-filled syringes (*e.g.,* liquid syringes and lyosyringes).

[0342] The effective amount of pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region which is to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which a monomer or multimer comprising a polypeptide comprising a GDF15 region is being used, the route of administration, and the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage can range from about 0.1 µg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage can range from 0.1 µg/kg up to about 100 mg/kg; or 1 µg/kg up to about 100 mg/kg; or 5 µg/kg, 10 µg/kg, 15 µg/kg, 20 µg/kg, 25 µg/kg, 30 µg/kg, 35 µg/kg, 40 µg/kg, 45 µg/kg, 50 µg/kg, 55 µg/kg, 60 µg/kg, 65 µg/kg, 70 µg/kg, 75 µg/kg, 100 µg/kg, 200 µg/kg or up to about 10 mg/kg.

[0343] The frequency of dosing will depend upon the pharmacokinetic parameters of the a monomer or multimer comprising a polypeptide comprising a GDF15 region in the formulation being used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition can therefore be administered as a single dose, as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages can be ascertained through use of appropriate dose-response data.

[0344] The route of administration of the pharmaceutical composition is in accord with known methods, *e.g.,* orally; through injection by intravenous, intraperitoneal, intracerebral

(intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intraportal, or intralesional routes; by sustained release systems (which may also be injected): or by implantation devices. Where desired, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

[0345] Alternatively or additionally, the composition can be administered locally via implantation of a membrane, sponge, or other appropriate material onto which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

[0346] In order to deliver drug, *e.g.,* a monomer or multimer comprising a polypeptide comprising a GDF 15 region, at a predetermined rate such that the drug concentration can be maintained at a desired therapeutically effective level over an extended period, a variety of different approaches can be employed. In one example, a hydrogel comprising a polymer such as a gelatin (*e.g.,* bovine gelatin, human gelatin, or gelatin from another source) or a naturally-occurring or a synthetically generated polymer can be employed. Any percentage of polymer (*e.g.,* gelatin) can be employed in a hydrogel, such as 5, 10, 15 or 20%. The selection of an appropriate concentration can depend on a variety of factors, such as the therapeutic profile desired and the pharmacokinetic profile of the therapeutic molecule.

[0347] Examples of polymers that can be incorporated into a hydrogel include polyethylene glycol ("PEG"), polyethylene oxide, polyethylene oxide-co-polypropylene oxide, co-polyethylene oxide block or random copolymers, polyvinyl alcohol, poly(vinyl pyrrolidinone), poly(amino acids), dextran, heparin, polysaccharides, polyethers and the like.

[0348] Another factor that can be considered when generating a hydrogel formulation is the degree of crosslinking in the hydrogel and the crosslinking agent. In one embodiment, cross-linking can be achieved via a methacrylation reaction involving methacrylic anhydride. In some situations, a high degree of cross-linking may be desirable while in other situations a lower degree of crosslinking is preferred. In some cases a higher degree of crosslinking provides a longer sustained release. A higher degree of crosslinking may provide a firmer hydrogel and a longer period over which drug is delivered.

[0349] Any ratio of polymer to crosslinking agent (*e.g.,* methacrylic anhydride) can be employed to generate a hydrogel with desired properties. For example, the ratio of polymer to crosslinker can be, *e.g.,* 8:1, 16:1, 24:1, or 32:1. For example, when the hydrogel polymer is gelatin and the crosslinker is methacrylate, ratios of 8:1, 16:1, 24:1, or 32:1 methyacrylic anhydride:gelatin can be employed

V. Therapeutic Uses of a GDF15 Polypeptide, Construct Comprising a GDF15 Polypeptide or a Mutant Form Thereof

[0350] A monomer or multimer comprising a polypeptide comprising a GDF15 region can be used to treat, diagnose or ameliorate, a metabolic condition or disorder. In one embodiment, the metabolic disorder to be treated is diabetes, *e.g.,* type 2 diabetes. In another embodiment, the metabolic condition or disorder is obesity. In other embodiments the metabolic condition or disorder is dyslipidemia, elevated glucose levels, elevated insulin levels or diabetic nephropathy. For example, a metabolic condition or disorder that can be treated or ameliorated using a monomer or multimer comprising a polypeptide comprising a GDF15 region includes a state in which a human subject has a fasting blood glucose level of 125 mg/dL or greater, for example 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200 or greater than 200 mg/dL. Blood glucose levels can be determined in the fed or fasted state, or at random. The metabolic condition or disorder can also comprise a condition in which a subject is at increased risk of developing a metabolic condition. For a human subject, such conditions include a fasting blood glucose level of 100 mg/dL. Conditions that can be treated using a pharmaceutical composition comprising a GDF15 mutant polypeptide can also be found in the American Diabetes Association Standards of Medical Care in Diabetes Care-2011, American Diabetes Association, Diabetes Care Vol. 34, No. Supplement 1, S11-S61, 2010.

[0351] In application, a metabolic disorder or condition, such as Type 2 diabetes, elevated glucose levels, elevated insulin levels, dyslipidemia, obesity or diabetic nephropathy, can be treated by administering a therapeutically effective dose of a GDF15 polypeptide, construct comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region to a patient in need thereof. The administration can be performed as described herein, such as by IV injection, intraperitoneal (IP) injection, subcutaneous injection, intramuscular injection, or orally in the form of a tablet or liquid formation. In some situations, a therapeutically effective or preferred dose of a monomer or multimer comprising a polypeptide comprising a GDF15 region can be determined by a clinician. A therapeutically effective dose of a monomer or multimer comprising a polypeptide comprising a GDF15 region will depend, *inter alia,* upon the administration schedule, the unit dose of agent administered, whether the a monomer or multimer comprising a polypeptide comprising a GDF15 region is administered in combination with other therapeutic agents, the immune status and the health of the recipient. The term "therapeutically effective dose," as used herein, means an amount of a monomer or multimer comprising a polypeptide comprising a GDF15 region that elicits a biological or medicinal response in a tissue system, animal, or human being sought by a researcher, medical doctor, or other clinician, which includes alleviation or amelioration of the symptoms of the disease or disorder being treated, *i.e.,* an amount of a monomer or multimer comprising a polypeptide comprising a GDF15 region that supports an observable level of one or more desired biological or medicinal response, for example, lowering blood glucose, insulin, triglyceride, or cholesterol levels; reducing body weight; or improving glucose tolerance, energy expenditure, or insulin sensitivity.

[0352] It is noted that a therapeutically effective dose of a monomer or multimer comprising a polypeptide comprising a GDF15 region can also vary with the desired result. Thus, for example, in situations in which a lower level of blood glucose is indicated a dose of a monomer

or multimer comprising a polypeptide comprising a GDF15 region will be correspondingly higher than a dose in which a comparatively lower level of blood glucose is desired. Conversely, in situations in which a higher level of blood glucose is indicated at a dose of a monomer or multimer comprising a polypeptide comprising a GDF15 region will be correspondingly lower than a dose in which a comparatively higher level of blood glucose is desired.

[0353] In various embodiments, a subject is a human having a blood glucose level of 100 mg/dL or greater can be treated with a monomer or multimer comprising a polypeptide comprising a GDF15 region.

[0354] In one embodiment, a method of the instant disclosure comprises first measuring a baseline level of one or more metabolically-relevant compounds such as glucose, insulin, cholesterol, lipid in a subject. A pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region is then administered to the subject. After a desired period of time, the level of the one or more metabolically-relevant compounds (e.g., blood glucose, insulin, cholesterol, lipid) in the subject is again measured. The two levels can then be compared in order to determine the relative change in the metabolically-relevant compound in the subject. Depending on the outcome of that comparison another dose of the pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region can be administered to achieve a desired level of one or more metabolically-relevant compound.

[0355] It is noted that a pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region can be co-administered with another compound. The identity and properties of compound co-administered with the a monomer or multimer comprising a polypeptide comprising a GDF15 region will depend on the nature of the condition to be treated or ameliorated. A non-limiting list of examples of compounds that can be administered in combination with a pharmaceutical composition comprising a monomer or multimer comprising a polypeptide comprising a GDF15 region include rosiglitizone, pioglitizone, repaglinide, nateglitinide, metformin, exenatide, stiagliptin, pramlintide, glipizide, glimepriridеacarbose, and miglitol.

VI. Kits

[0356] Also provided are kits for practicing the disclosed methods. Such kits can comprise a pharmaceutical composition such as those described herein, including nucleic acids encoding the peptides or proteins provided herein, vectors and cells comprising such nucleic acids, and pharmaceutical compositions comprising such nucleic acid-containing compounds, which can be provided in a sterile container. Optionally, instructions on how to employ the provided phannaceutical composition in the treatment: of a metabolic disorder can also be included or be made available to a patient or a medical service provider.

[0357] In one aspect, a kit comprises (a) a pharmaceutical composition comprising a therapeutically effective amount of a monomer or multimer comprising a polypeptide comprising a GDF15 region; and (b) one or more containers for the pharmaceutical composition. Such a kit can also comprise instructions for the use thereof; the instructions can be tailored to the precise metabolic disorder being treated. The instructions can describe the use and nature of the materials provided in the kit. In certain embodiments, kits include instructions for a patient to carry out administration to treat a metabolic disorder, such as elevated glucose levels, elevated insulin levels, obesity, type 2 diabetes, dyslipidemia or diabetic nephropathy.

[0358] Instructions can be printed on a substrate, such as paper or plastic, etc, and can be present in the kits as a package insert, in the labeling of the container of the kit or components thereof ***(e.g.,*** associated with the packaging), etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, such as over the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded.

[0359] Often it will be desirable that some or all components of a kit are packaged in suitable packaging to maintain sterility. The components of a kit can be packaged in a kit containment element to make a single, easily handled unit, where the kit containment element, e.g., box or analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components of the kit.

EXAMPLES

[0360] The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

EXAMPLE 1

Preparation of Fc-GDF15 Molecules

[0361] GDF15 fusions with knob/holeFc, HemiFc, charged pair (delHinge) Fc and charged pair (delHinge) cysteine clamp Fc sequences were stably expressed in serum free, suspension adapted CHO-KI cell line. GDF15-Fc molecules were cloned into a stable expression vector containing puromycin resistance while the Fc chains were cloned into a hygromycin containing expression vector (Selexis, Inc.). The plasmids were transfected at a 1:1 ratio using

lipofectamine LTX and cells were selected 2 days post transfection in a proprietary growth media containing 10ug/mL puromycin and 600ug/mLhygromycin. Media was exchanged 2 times per week during selection. When cells reached about 90% viability, they were scaled up for a fedbatch production run. Cells were seeded at 1 e6/mL in a proprietary production media and fed on days 3, 6, and 8. The conditioned medium (CM) produced by the cells was harvested on day 10 and clarified. Endpoint viabilities typically were above 90%.

[0362] The Fc-GDF15 clarified, conditioned media was purified using a two-step chromatography procedure. Approximately 5 L of the CM was applied directly to a GE MabSelect SuRe column that had previously been equilibrated with Dulbecco's Phosphate Buffered Saline (PBS). The bound protein underwent three wash steps: first, 3 column volumes (CV) of PBS; next, 1 CV of 20 mM Tris, 100 mM sodium chloride, pH 7.4; and finally, 3 CV of 500 mM L-arginine, pH 7.5. These wash steps remove unbound or lightly bound media components and host cell impurities. The column was then re-equilibrated with 5 CV of 20 mM Tris, 100 mM sodium chloride at pH 7.4 which brings the UV absorbance back to baseline. The desired protein was eluted with 100 mM acetic acid at pH 3.6 and collected in bulk. The protein pool was quickly titrated to within a pH range of 5.0 to 5.5 with 1 M Tris-HCl, pH 9.2.

[0363] Tile pH adjusted protein pool was next loaded onto a GE SP Sepharose H.P column that had been previously equilibrated with 20 mM MES at pH 6.0. The bound protein was then washed with 5 CV of equilibration buffer, and finally eluted over a 20 CV, 0 to 50% linear gradient from 0 to 400 mM sodium chloride in 20 mM MES at pH 6.0. Fractions were collected during the elution and analyzed by analytical size-exclusion chromatography (Superdex 200) to determine the appropriate fractions to pool for a homogeneous product. The SP HP chromatography removes product-related impurities such as free Fc, clipped species, andFc-GDF15 multimers.
The SP HP pool was then buffer exchanged into 10 mM sodium acetate, 5% proline, pH 5.2 by dialysis. It was concentrated to approximately 15 mg/ml using the Sartorius Vivaspin 20 Ten kilo-Dalton molecular weight cut-off centrifugal device. Finally, it was sterile filtered and the resulting solution containing the purified Fc-GDF 15 molecules is stored at 5°C. Final products were assessed for identity and purity using,mass spectral analysis, sodium dodecyl sulfate polyacrylamide electrophoresis and size exclusion high performance liquid chromatography.

[0364] The purification method described above was employed to purify DhMonoFc-GDF15 fusion proteins. However, it was found that the addition of the H6D mutation to the DhMonoFc-GDF15 caused soluble aggregates to form in the SP elution. Therefore, the purification of the DhMonoFc-GFF15(H6D) included an additional SEC step (Superdex 200 with 20 mM phosphate, 250 mM NaCl, pH 6.8), followed by loading on Q-sepharose HP and eluting with a gradient from 0 to 0.6M NaCl in 20 mM tris, pH 8.5.

EXAMPLE 2

Preparation of GDF15-HSA and DhMonoFc Molecules

[0365] GDF15 fusions with HSA and DhMonoFc sequences were stably expressed in CHO-S cells (Invitrogen). For each of the constructs producing homodimers, the coding sequence was cloned into stable expression vector containing puromycin resistance (Selexis, Inc.). In the case of the HSA-$(G_4S)_4$-GDF15:GDF15 heterodimer, the HSA-$(G_4S)_4$-GDF15 fusion sequence was cloned into an expression vector containing puromycin resistance and the GDF15 sequence was cloned into an expression vector containing hygromycin resistance. CHO-S parental cells were maintained in CD-CHO medium (Invitrogen) supplemented with 8 mM L-glutamine and were transfected with 4µg of plasmid DNA using a Lipofectamine LTX transfection kit (Invitrogen) according to the manufacturer's instructions. In the case of the HSA-$(G_4S)_4$-GDF15:GDF15 heterodimer, the two plasmids were mixed at a 1:1 ratio prior to transfection. Stable cell lines were selected using 10 µg/mL of puromycin (homodimers) or 10 µg/mL of puromycin plus 400 µg/mL hygromicin (heterodimer). Upon recovery, which was defined as >90% viability using a Vi-Cell counter (Beckman Coulter), the stable CHO-S cell lines were expanded and used to seed either batch productions in shake flasks or fedbatch productions in WAVE bioreactors (GE Healthcare). Both processes were seeded at 1e6 viable cells/mL in production medium. Batch productions were harvested by centrifugation on day 6, while fedbatch productions were fed on days 3, 6, and 8. The CM produced by the cells was harvested by centrifugation on day 10 and clarified.

[0366] The HSA-GDF15 fusion proteins were purified from clarified conditioned media using two chromatographic steps. The clarified conditioned media containing the HSA-GDF15 fusion protein was applied to a Cibracon Blue Sepharose HP column that is equilibrated with 20mM Phosphate, 150mM NaCl pH 7.4. The column was next washed with equilibration buffer until a baseline ultraviolet (UV) level is obtained. Product and contaminants are eluted by a 20 mM Phosphate, 2M NaCl buffer and the elutions were collected and subsequently assayed by Coomasie-stained SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) to identify which eluate fractions contained a polypeptide that migrates at the predicted molecular weight of HSA-GDF15 fusion protein. Following the Blue Sepharose step, the pooled fractions containing product were dialyzed versus 10 mM tris, pH 8.0. The dialysis step allowed for the binding of HSA-GDF15 fusion protein when applied to anion exchange chromatographic resin. The final chromatography step was Q-Sepharose HP which applies a linear gradient (0 to 0.6M NaCl in 10 mM tris pH 8.0) to elute the bound fusion protein. The elution from the Q-Sepharose HP was collected as fractions and then assayed by SDS-PAGE and analytical size exclusion chromatography to determine the appropriate fractions to pool. LCMS and SDS-PAGE were run to confirm the identity of each protein. The resulting pool was buffer exchanged by dialysis into 10mM Sodium Acetate, 9% sucrose pH 4.5, sterile filtered, and finally stored at 5 C or frozen.

[0367] DhMonoFc-GDF15 fusion proteins were purified as set forth above in Example 2 for other Fc-GDF15 fusion proteins.

EXAMPLE 3

Suppression of Food Intake in Hyperphagic ob/ob Mice by Fc Fusion GDF15 Polypeptides and HSA Fusion GDF15 Polypeptides

[0368] GDF15 reduces food intake in hyperphagic ob/ob mice, and a food intake assay was used to evaluate efficacy of different forms of GDF15 analogs. As the half-life of human GDF15 polypeptide in mouse was observed to be approximately 3 hours, an Fc fusion strategy was used to extend protein half-life. Various multimers comprising a polypeptide comprising a GDF15 region were generated and analyzed for *in vivo* activity, by introducing the multimer into hyperphagic leptin-deficient ob/ob mice, and measuring the ability of a particular multimer comprising a polypeptide comprising a GDF15 region to suppress food intake in these animals. The multimer comprising a polypeptide comprising a GDF15 region to be tested was injected subcutaneously into a 7-8 week old ob/ob mouse (Jackson Laboratory) between 4-5pm on day 0. Animals were transferred after injection to cages where food had been premeasured, and food intake was measured between 9-10 AM the next day.

[0369] The results of representative experiments are provided in Figures 6-53. These experiments demonstrate that the described multimers comprising GDF15 regions exhibit a decrease in food intake in ob/ob mice, with greater potency than those of native mature hGDF15 homodimer.

EXAMPLE 4

Chronic Efficacy of GDF15 Constructs in DIO Mice

[0370] Certain multimers comprising GDF15 regions are administered chronically and subcutaneously into DIO mice, once per week. The constructs demonstrate efficacy in improving various metabolic parameters, including body weight, blood glucose levels and glucose tolerance, serum insulin levels, serum cholesterol levels, serum triglyceride levels and oral lipid tolerance.

EXAMPLE5

In Vivo Activity of GDF15 Constructs

[0371] Male C57B1/6 were fed a 60% high fat diet for 15 weeks and divided into different

treatment groups for each group to have the same pretreatment body weight, glucose, insulin, triglyceride and cholesterol levels. Animals were subcutaneously dosed with proteins or vehicle buffer weekly for 5 weeks. Three different dose levels were selected for the proteins: 10, 1, 0.1nmol/kg, which are equivalent to 1.25, 0.125, 0.0125 mg/kg. Studies were carried for 5 weeks, with the last dose on day 28.

[0372] Body weight was measured weekly during the 5 weeks of treatment and drug washout. One oral glucose tolerance tests (OGTT) was performed 2 weeks after the first protein injection in animals fasted for 4 hours. Another oral glucose tolerance tests (OGTT) was performed 5 weeks after the first protein injection in animals fasted for 16 hours. In OGTT, animals were orally administered with 2g/kg glucose solution, and glucose levels were measured by AlphaTRAK glucometer (Abbott) at 0, 15,30,60, 120min. Area under the curve (AUC) of the glucose levels during the OGTT were calculated to compare glucose tolerance of different treatment groups. Serum samples were collected at 3 weeks after first protein injection and used to measure insulin, triglyceride and cholesterol levels, as well as the levels of test articles. Insulin levels were measured using immunoassay kit (Alpco). Triglyceride and cholesterol levels were measured using enzymatic assays (Wako).

[0373] The results are shown in Figures 54-59 (asterisks indicate statistical significance). These experiments demonstrate that the described multimers comprising GDF15 regions reduce AUC of the glucose levels during the OGTT (Figures 55 and 59), reduce body weight (Figure 54) reduce insulin levels (Figure 56), reduce cholesterol (Figure 58) and reduce triglycerides (Figure 57).

EXAMPLE 6

<u>Thermal Stability of GDF15 Constructs</u>

[0374] The thermal stability of the selected GDF15 constructs was assessed by differential scanning calorimetry on a MicroCal Capillary VP-DSC system in which temperature differences between the reference and sample cell are continuously measured, and calibrated to power units. This data channel is referred to as the DP signal, or the differential power between the reference and sample cell. The unfolding of a protein molecule appears as an endothennic transition on the DSC thermogram and can characterized by the thermal transition midpoints (Tm). The samples were heated from 10°C to 100°C at a heating rate of 60°C/hour. The pre-scan time was 15 minutes and the filtering period was 10 seconds. The concentrations used in the DSC experiments were around 1.0 mg/mL. The data analysis for baseline correction and determination of Tm values was done using MicroCal Origin 7 software.

[0375] In particular, a dimer of DhCpmFc(-)-GDF15(N3D):DhCpmFc(+) was compared to a dimer of Dh3CpmFc(-)-GDF15(N3D):DhCpmFc(+); a dimer of DhCpmFc(-)-

GDF15(Ndel3):DhCpmFc(+) was compared to a dimer of Dh3CpmFc(-)-GDF15(Ndel3):DhCpmFc(+); a dimer of DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C) was compared to a dimer of Dh3CpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C); and a dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C) was compared to a dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C). The results are shown in Figure 61. These experiments demonstrate that the "Dh3CpmFc" domains confer greater stability than the corresponding "DhCpmFc" domains.

EXAMPLE 7

FcγReceptor Binding Analysis

[0376] Selected GDF15 constructs were analyzed for their binding activity to Fcγ receptors on BIA3000. Each Fcγ receptor was captured on anti-his antibody coated CM5 surface (captured RL ~ 200 RU). The GDF15 constructs were diluted to 250 nM in sample buffer (0.1 mg/ml BSA, 0.005% P20, PBS). Each GDF15 construct was injected over anti-his antibody captured Fcγ receptor surfaces at 50 µL/min for 3 minutes. After a 5-minute dissociation in instrument running buffer (0.005% P20 in PBS), each Fcγ receptor surface was regenerated by an injection of 8 mM Glycine, pH1.5, 1M NaCl for 30 seconds, followed by an injection of 10 mM Glycine, pH1.5 for 30 seconds. The resulting sensorgrams were analyzed using BIAcore BIAEvaluation (v. 4.1). The binding response in the unit of RU was read at 10 seconds before end of injection.

[0377] In particular, FcγRI, FcγRIIA and FcγRIIA were determined with respect to a dimer of DhCpmFc(-)-GDF15(Ndel3):DhCpmFc(+),a dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3): DhCpmFc(+)(S354C); a dimer ofDh3CpmFc(-)-GDF15(Ndel3); a dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3)-Dh3CpmFc(+)(S354C); a dimer of Dh3CpmFc(-)-GDF15(N3D); and a dimer of Dh3CpmFc(-)(Y349C)-GDF15(N3D):Dh3CpmFc(+)(S354C). The results are shown in Figure 60. These experiments demonstrate that the "Dh3CpmFc" domains essentially eliminate FcγRI, FcγRIIIA and FcγRIIA binding.

SEQUENCE LISTING

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cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 900

ttagccaaag actgccactg catatga 927

<210> 4

<211> 308

<212> PRT

<213> Homo sapiens

<400> 4

Met Pro Gly Gln Glu Leu Arg Thr Val Asn Gly Ser Gln Met Leu Leu
1 5 10 15

Val Leu Leu Val Leu Ser Trp Leu Pro His Gly Gly Ala Leu Ser Leu
20 25 30

Ala Glu Ala Ser Arg Ala Ser Phe Pro Gly Pro Ser Glu Leu His Ser
35 40 45

Glu Asp Ser Arg Phe Arg Glu Leu Arg Lys Arg Tyr Glu Asp Leu Leu
50 55 60

Thr Arg Leu Arg Ala Asn Gln Ser Trp Glu Asp Ser Asn Thr Asp Leu
65 70 75 80

Val Pro Ala Pro Ala Val Arg Ile Leu Thr Pro Glu Val Arg Leu Gly
85 90 95

Ser Gly Gly His Leu His Leu Arg Ile Ser Arg Ala Ala Leu Pro Glu
100 105 110

Gly Leu Pro Glu Ala Ser Arg Leu His Arg Ala Leu Phe Arg Leu Ser
115 120 125

Pro Thr Ala Ser Arg Ser Trp Asp Val Thr Arg Pro Leu Arg Arg Gln
130 135 140

Leu Ser Leu Ala Arg Pro Gln Ala Pro Ala Leu His Leu Arg Leu Ser
145 150 155 160

Pro Pro Pro Ser Gln Ser Asp Gln Leu Leu Ala Glu Ser Ser Ser Ala
165 170 175

Arg Pro Gln Leu Glu Leu His Leu Arg Pro Gln Ala Ala Arg Gly Arg
180 185 190

Arg Arg Ala Arg Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly
195 200 205

Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly
210 215 220

Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys
225 230 235 240

Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln
245 250 255

Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro
260 265 270

Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr
275 280 285

Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp
290 295 300

Cys His Cys Ile
305

<210> 5
<211> 912
<212> DNA
<213> Mus sp.

<400> 5
atggccccgc ccgcgctcca ggcccagcct ccaggcggct ctcaactgag gttcctgctg 60

ttcctgctgc tgttgctgct gctgctgtca tggccatcgc aggggggacgc cctggcaatg 120

cctgaacagc gaccctccgg ccctgagtcc caactcaacg ccgacgagct acggggtcgc 180

ttccaggacc tgctgagccg gctgcatgcc aaccagagcc gagaggactc gaactcagaa 240

ccaagtcctg acccagctgt ccggatactc agtccagagg tgagattggg gtcccacggc 300

cagctgctac tccgcgtcaa ccgggcgtcg ctgagtcagg gtctccccga agcctaccgc 360

gtgcaccgag cgctgctcct gctgacgccg acggcccgcc cctgggacat cactaggccc 420

ctgaagcgtg cgctcagcct ccggggaccc cgtgctcccg cattacgcct gcgcctgacg 480

ccgcctccgg acctggctat gctgccctct ggcggcacgc agctggaact gcgcttacgg 540

gtagccgccg gcaggggggcg ccgaagcgcg catgcgcacc caagagactc gtgcccactg 600

ggtccggggc gctgctgtca cttggagact gtgcaggcaa ctcttgaaga cttgggctgg 660

agcgactggg tgctgtcccc gcgccagctg cagctgagca tgtgcgtggg cgagtgtccc 720

cacctgtatc gctccgcgaa cacgcatgcg cagatcaaag cacgcctgca tggcctgcag 780

gctgagaaag tggctgaggg gtggtgtgtg aggtgaagct agaggggagt ggttgttatg 840

cctgacaagg tgcctgcccc gtgctgtgtc ccctccagct acacccctgt ggttcttatg 840

cacaggacag acagtggtgt gtcactgcag acttatgatg acctggtggc ccggggctgc 900

cactgcgctt ga 912

<210> 6
<211> 303
<212> PRT
<213> Mus sp.

<400> 6

Met Ala Pro Pro Ala Leu Gln Ala Gln Pro Pro Gly Gly Ser Gln Leu
1 5 10 15

Arg Phe Leu Leu Phe Leu Leu Leu Leu Leu Leu Leu Leu Ser Trp Pro
20 25 30

Ser Gln Gly Asp Ala Leu Ala Met Pro Glu Gln Arg Pro Ser Gly Pro
35 40 45

Glu Ser Gln Leu Asn Ala Asp Glu Leu Arg Gly Arg Phe Gln Asp Leu
50 55 60

Leu Ser Arg Leu His Ala Asn Gln Ser Arg Glu Asp Ser Asn Ser Glu
65 70 75 80

Pro Ser Pro Asp Pro Ala Val Arg Ile Leu Ser Pro Glu Val Arg Leu
85 90 95

Gly Ser His Gly Gln Leu Leu Leu Arg Val Asn Arg Ala Ser Leu Ser
100 105 110

Gln Gly Leu Pro Glu Ala Tyr Arg Val His Arg Ala Leu Leu Leu Leu
115 120 125

Thr Pro Thr Ala Arg Pro Trp Asp Ile Thr Arg Pro Leu Lys Arg Ala
130 135 140

Leu Ser Leu Arg Gly Pro Arg Ala Pro Ala Leu Arg Leu Arg Leu Thr
145 150 155 160

Pro Pro Pro Asp Leu Ala Met Leu Pro Ser Gly Gly Thr Gln Leu Glu
165 170 175

Leu Arg Leu Arg Val Ala Ala Gly Arg Gly Arg Arg Ser Ala His Ala
180 185 190

His Pro Arg Asp Ser Cys Pro Leu Gly Pro Gly Arg Cys Cys His Leu
195 200 205

Glu Thr Val Gln Ala Thr Leu Glu Asp Leu Gly Trp Ser Asp Trp Val
210 215 220

Leu Ser Pro Arg Gln Leu Gln Leu Ser Met Cys Val Gly Glu Cys Pro
225 230 235 240

```
His Leu Tyr Arg Ser Ala Asn Thr His Ala Gln Ile Lys Ala Arg Leu
                245                 250                 255

His Gly Leu Gln Pro Asp Lys Val Pro Ala Pro Cys Cys Val Pro Ser
            260                 265                 270

Ser Tyr Thr Pro Val Val Leu Met His Arg Thr Asp Ser Gly Val Ser
        275                 280                 285

Leu Gln Thr Tyr Asp Asp Leu Val Ala Arg Gly Cys His Cys Ala
    290                 295                 300
```

<210> 7
<211> 840
<212> DNA
<213> Homo sapiens

<400> 7

```
ctgtctctgg ccgaggcgag ccgcgcaagt ttcccgggac cctcagagtt gcactccgaa      60

gactccagat tccgagagtt gcggaaacgc tacgaggacc tgctaaccag gctgcgggcc     120

aaccagagct gggaagattc gaacaccgac ctcgtcccgg cccctgcagt ccggatactc     180

acgccagaag tgcggctggg atccggcggc cacctgcacc tgcgtatctc tcgggccgcc     240

cttcccgagg ggctccccga ggcctcccgc cttcaccggg ctctgttccg gctgtccccg     300

acggcgtcaa ggtcgtggga cgtgacacga ccgctgcggc gtcagctcag ccttgcaaga     360

ccccaggcgc ccgcgctgca cctgcgactg tcgccgccgc cgtcgcagtc ggaccaactg     420

ctggcagaat cttcgtccgc acggccccag ctggagttgc acttgcggcc gcaagccgcc     480

aggggcgccc gcagagcgcg tgcgcgcaac ggggaccact gtccgctcgg gcccgggcgt     540

tgctgccgtc tgcacacggt ccgcgcgtcg ctggaagacc tgggctgggc cgattgggtg     600

ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg     660

gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg     720

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac     780

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcatatga     840
```

<210> 8
<211> 279
<212> PRT
<213> Homo sapiens

<400> 8

```
Leu Ser Leu Ala Glu Ala Ser Arg Ala Ser Phe Pro Gly Pro Ser Glu
1               5                  10                  15

Leu His Ser Glu Asp Ser Arg Phe Arg Glu Leu Arg Lys Arg Tyr Glu
            20                  25                  30

Asp Leu Leu Thr Arg Leu Arg Ala Asn Gln Ser Trp Glu Asp Ser Asn
        35                  40                  45
```

Thr Asp Leu Val Pro Ala Pro Ala Val Arg Ile Leu Thr Pro Glu Val
50 55 60

Arg Leu Gly Ser Gly Gly His Leu His Leu Arg Ile Ser Arg Ala Ala
65 70 75 80

Leu Pro Glu Gly Leu Pro Glu Ala Ser Arg Leu His Arg Ala Leu Phe
85 90 95

Arg Leu Ser Pro Thr Ala Ser Arg Ser Trp Asp Val Thr Arg Pro Leu
100 105 110

Arg Arg Gln Leu Ser Leu Ala Arg Pro Gln Ala Pro Ala Leu His Leu
115 120 125

Arg Leu Ser Pro Pro Pro Ser Gln Ser Asp Gln Leu Leu Ala Glu Ser
130 135 140

Ser Ser Ala Arg Pro Gln Leu Glu Leu His Leu Arg Pro Gln Ala Ala
145 150 155 160

Arg Gly Arg Arg Arg Ala Arg Ala Arg Asn Gly Asp His Cys Pro Leu
165 170 175

Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu
180 185 190

Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val
195 200 205

Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met
210 215 220

His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val
225 230 235 240

Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile
245 250 255

Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu
260 265 270

Ala Lys Asp Cys His Cys Ile
275

<210> 9
<211> 816
<212> DNA
<213> Mus sp.

<400> 9
tcgcaggggg acgccctggc aatgcctgaa cagcgaccct ccggccctga gtcccaactc 60

aacgccgacg agctacgggg tcgcttccag gacctgctga gccggctgca tgccaaccag 120

agccgagagg actcgaactc agaaccaagt cctgacccag ctgtccggat actcagtcca 180

gaggtgagat tggggtccca cggccagctg ctactccgcg tcaaccgggc gtcgctgagt 240

cagggtctcc ccgaagccta ccgcgtgcac cgagcgctgc tcctgctgac gccgacggcc 300

cgcccctggg acatcactag gcccctgaag cgtgcgctca gcctccgggg accccgtgct 360

cccgcattac gcctgcgcct gacgccgcct ccggacctgg ctatgctgcc ctctggcggc 420

acgcagctgg aactgcgctt acgggtagcc gccggcaggg ggcgccgaag cgcgcatgcg 480

cacccaagag actcgtgccc actgggtccg gggcgctgct gtcacttgga gactgtgcag 540

gcaactcttg aagacttggg ctggagcgac tgggtgctgt ccccgcgcca gctgcagctg 600

agcatgtgcg tgggcgagtg tccccacctg tatcgctccg cgaacacgca tgcgcagatc 660

aaagcacgcc tgcatggcct gcagcctgac aaggtgcctg ccccgtgctg tgtcccctcc 720

agctacaccc cggtggttct tatgcacagg acagacagtg gtgtgtcact gcagacttat 780

gatgacctgg tggcccgggg ctgccactgc gcttga 816

<210> 10

<211> 271

<212> PRT

<213> Mus sp.

<400> 10

```
Ser Gln Gly Asp Ala Leu Ala Met Pro Glu Gln Arg Pro Ser Gly Pro
1               5                  10                  15

Glu Ser Gln Leu Asn Ala Asp Glu Leu Arg Gly Arg Phe Gln Asp Leu
            20                  25                  30

Leu Ser Arg Leu His Ala Asn Gln Ser Arg Glu Asp Ser Asn Ser Glu
        35                  40                  45

Pro Ser Pro Asp Pro Ala Val Arg Ile Leu Ser Pro Glu Val Arg Leu
    50                  55                  60

Gly Ser His Gly Gln Leu Leu Leu Arg Val Asn Arg Ala Ser Leu Ser
65                  70                  75                  80

Gln Gly Leu Pro Glu Ala Tyr Arg Val His Arg Ala Leu Leu Leu Leu
                85                  90                  95

Thr Pro Thr Ala Arg Pro Trp Asp Ile Thr Arg Pro Leu Lys Arg Ala
            100                 105                 110

Leu Ser Leu Arg Gly Pro Arg Ala Pro Ala Leu Arg Leu Arg Leu Thr
        115                 120                 125

Pro Pro Pro Asp Leu Ala Met Leu Pro Ser Gly Gly Thr Gln Leu Glu
    130                 135                 140

Leu Arg Leu Arg Val Ala Ala Gly Arg Gly Arg Arg Ser Ala His Ala
145                 150                 155                 160
```

```
His Pro Arg Asp Ser Cys Pro Leu Gly Pro Gly Arg Cys Cys His Leu
                165                 170                 175

Glu Thr Val Gln Ala Thr Leu Glu Asp Leu Gly Trp Ser Asp Trp Val
            180                 185                 190

Leu Ser Pro Arg Gln Leu Gln Leu Ser Met Cys Val Gly Glu Cys Pro
        195                 200                 205

His Leu Tyr Arg Ser Ala Asn Thr His Ala Gln Ile Lys Ala Arg Leu
    210                 215                 220

His Gly Leu Gln Pro Asp Lys Val Pro Ala Pro Cys Cys Val Pro Ser
225                 230                 235                 240

Ser Tyr Thr Pro Val Val Leu Met His Arg Thr Asp Ser Gly Val Ser
                245                 250                 255

Leu Gln Thr Tyr Asp Asp Leu Val Ala Arg Gly Cys His Cys Ala
            260                 265                 270
```

<210> 11

<211> 339

<212> DNA

<213> Homo sapiens

<400> 11

```
gcgcgcaacg gggaccactg tccgctcggg cccgggcgtt gctgccgtct gcacacggtc      60

cgcgcgtcgc tggaagacct gggctgggcc gattgggtgc tgtcgccacg ggaggtgcaa     120

gtgaccatgt gcatcggcgc gtgcccgagc cagttccggg cggcaaacat gcacgcgcag     180

atcaagacga gcctgcaccg cctgaagccc gacacggtgc cagcgccctg ctgcgtgccc     240

gccagctaca atcccatggt gctcattcaa aagaccgaca ccggggtgtc gctccagacc     300

tatgatgact tgttagccaa agactgccac tgcatatga                            339
```

<210> 12

<211> 112

<212> PRT

<213> Homo sapiens

<400> 12

```
Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
1               5                  10                  15

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
            20                  25                  30

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
        35                  40                  45

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
    50                  55                  60
```

```
Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
65                  70                  75                  80

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val
                85                  90                  95

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            100                 105                 110
```

<210> 13
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 13

```
atgagcgcgc atgcgcaccc aagagactcg tgcccactgg gtccggggcg ctgctgtcac      60

ctggagactg tgcaggcaac tcttgaagac ttgggctgga gcgactgggt gttgtccccg     120

cgccagctgc agctgagcat gtgcgtgggc gagtgtcccc acctgtatcg ctccgcgaac     180

acgcatgcgc agatcaaagc acgcctgcat ggcctgcagc ctgacaaggt gcctgccccg     240

tgctgtgtcc cctccagcta caccccggtg gttcttatgc acaggacaga cagtggtgtg     300

tcactgcaga cttatgatga cctggtggcc cggggctgcc actgcgcttg a              351
```

<210> 14
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14

```
Met Ser Ala His Ala His Pro Arg Asp Ser Cys Pro Leu Gly Pro Gly
1               5                   10                  15

Arg Cys Cys His Leu Glu Thr Val Gln Ala Thr Leu Glu Asp Leu Gly
            20                  25                  30

Trp Ser Asp Trp Val Leu Ser Pro Arg Gln Leu Gln Leu Ser Met Cys
        35                  40                  45

Val Gly Glu Cys Pro His Leu Tyr Arg Ser Ala Asn Thr His Ala Gln
    50                  55                  60

Ile Lys Ala Arg Leu His Gly Leu Gln Pro Asp Lys Val Pro Ala Pro
65                  70                  75                  80
```

```
Cys Cys Val Pro Ser Ser Tyr Thr Pro Val Val Leu Met His Arg Thr
                85                  90                  95

Asp Ser Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Val Ala Arg Gly
            100                 105                 110

Cys His Cys Ala
        115
```

<210> 15

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 15

```
Glu Arg Lys Ser Ser Val Glu Cys Pro Pro Cys Pro
1               5                   10
```

<210> 16

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 16

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
```

```
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 17

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 17

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125
```

```
Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 18

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 18

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15

Gly Gly Gly Ser
            20
```

<210> 19

<211> 1047

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 19

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc     360
```

ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgtggtg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

tccggaggcg gtggaagcgg aggtggtgga tctggaggcg gtggaagcgc gcgcaacgga 720

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 780

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 840

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 900

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 960

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 1020

ttagccaaag actgccactg catatga 1047

<210> 20
<211> 348
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 20

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn Gly
225                 230                 235                 240

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
                245                 250                 255

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
            260                 265                 270

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
        275                 280                 285

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
    290                 295                 300

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
305                 310                 315                 320

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
                325                 330                 335

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            340                 345
```

<210> 21

<211> 654

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 21

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

gcgggggaag aggagtacaa gagcacgtac cgtgtggtca gcgtcctgac cgtcctgcac     240
```

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgagctg cgcggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcgt cagcaagctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga 654

<210> 22

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 22

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175
```

```
Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 23
<211> 1046
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 23

```
cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc      60

tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc     120

ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc aagacaaagc     180

cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc     240

aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc ctcccagccc     300

ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag gtgaccaccc     360

tgcccccatc ccgggaggag atgaccaaga accaggtcag cctgacctgc ctggtcaaag     420

gcttctatcc cagcgacatc gccgtggagt gggagagcaa tgggcagccg gagaacaact     480

acgacaccac gcctcccgtg ctggactccg acggctcctt cttcctctat agcgacctca     540

ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg atgcatgagg     600

ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtgga ggtggtggat     660

ccggaggcgg tggaagcgga ggtggtggat ctggaggcgg tggaagcgcg cgcaacggag     720

accactgtcc gctcgggccc gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg     780

aagacctggg ctgggccgat tgggtgctgt cgccacggga ggtgcaagtg accatgtgca     840

tcggcgcgtg cccgagccag ttccgggcgg caaacatgca cgcgcagatc aagacgagcc     900

tgcaccgcct gaagcccgac acggtgccag cgccctgctg cgtgcccgcc agctacaatc     960

ccatggtgct cattcaaaag accgacaccg gggtgtcgct ccagacctat gatgacttgt    1020

tagccaaaga ctgccactgc atatga                                         1046
```

<210> 24
<211> 348
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 24

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn Gly
225                 230                 235                 240

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
                245                 250                 255

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
            260                 265                 270
```

```
Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
        275                 280                 285

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
    290                 295                 300

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
305                 310                 315                 320

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
                325                 330                 335

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            340                 345
```

<210> 25

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 25

```
Ala Arg Asn Gly Asp Asp Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
1               5                   10                  15

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
            20                  25                  30

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
        35                  40                  45

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
    50                  55                  60

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
65                  70                  75                  80

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val
                85                  90                  95

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            100                 105                 110
```

<210> 26

<211> 1047

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 26
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgaccacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

tccggaggcg gtggaagcgg aggtggtgga tctggaggcg gtggaagcgc gcgcaacgga 720

gacgactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 780

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 840

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 900

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 960

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 1020

ttagccaaag actgccactg catatga 1047

<210> 27
<211> 348
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 27
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

```
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn Gly
225                 230                 235                 240

Asp Asp Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
                245                 250                 255

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
            260                 265                 270

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
        275                 280                 285

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
    290                 295                 300

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
305                 310                 315                 320

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
                325                 330                 335

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            340                 345
```

<210> 28

<211> 230

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 28

```
Gly Gly Gly Glu Arg Lys Ser Ser Val Glu Cys Pro Pro Cys Pro Ala
1               5                  10                  15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65                  70                  75                  80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly
225                 230
```

<210> 29

<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 29

Glu	Arg	Lys	Ser	Ser	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val
1				5				10					15		
Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
			20					25					30		
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
		35					40					45			
His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
	50					55					60				
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr
65					70					75					80
Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn
				85					90					95	
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro
			100					105					110		
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
		115					120					125			
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val
	130					135					140				
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val
145					150					155					160
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro
				165					170					175	
Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr
			180					185					190		
Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val
		195					200					205			
Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu
	210					215					220				
Ser	Pro	Gly													
225															

<210> 30
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 30

```
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15

Gly Gly Gly Gly Ser
            20
```

<210> 31
<211> 1833
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 31

```
ggaggtggag agcgcaaatc ttctgtcgag tgcccaccgt gcccagcacc acctgtggca      60

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc     120

cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac     180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa aaccacggga ggagcagttc     240

aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc     300

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag ccccccatcga gaaaaccatc     360

tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag     420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac     480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc     540

atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg     600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac     660

acgcagaaga gcctctccct gtctccgggt ggaggtggcg gtagcggtgg cggaggttca     720

ggtggcggcg gaagcggtgg aggaggttca gagcggaaat ccagcgttga atgtcctccg     780

tgccctgctc cacccgtcgc ggggcctagt gtcttccttt tccctccaaa accaaaggat     840

acactgatga tcagccggac ccccgaggtt acgtgcgtcg tcgtcgatgt ctcccacgag     900

gatccagagg tccaattcaa ctggtacgtg gacggggtcg aggtgcataa tgcaaagaca     960

aagccacggg aagagcagtt taactctact ttccgcgtgg tttctgtgct gaccgtggtg    1020
```

caccaagatt ggctcaacgg caaggagtac aagtgcaagg taagcaataa ggggctccct 1080

gcccccattg agaagactat ctccaagaca aagggacagc cacgcgagcc acaagtctat 1140

acactccccc cttcccgcga agaaatgacc aagaatcagg ttagcctgac atgcttggtt 1200

aagggtttct acccctctga catagccgtg gagtgggaga gcaatggaca accagagaac 1260

aactacaaga ccaccccacc catgctggat agcgacggtt cattctttct gtatagtaag 1320

cttaccgtgg acaagtcccg gtggcaacaa ggaaatgtct tttcatgctc tgtgatgcac 1380

gaggccttgc ataatcacta tactcagaag agcttgagcc tcagccccgg atctggaggt 1440

ggcggatccg ggggcggtgg aagcggaggt ggtggatcgg gaggcggtgg aagcgcgcgc 1500

aacggcgacc actgtccgct cgggcccgga cgttgctgcc gtctgcacac ggtccgcgcg 1560

tcgctggaag acctgggctg ggccgattgg gtgctgtcgc cacgggaggt gcaagtgacc 1620

atgtgcatcg gcgcgtgccc gagccagttc cgggcggcaa acatgcacgc gcagatcaag 1680

acgagcctgc accgcctgaa gcccgacacg gtgccagcgc cctgctgcgt gcccgccagc 1740

tacaatccca tggtgctcat tcaaaagacc gacaccgggg tgtcgctcca gacctatgat 1800

gacttgttag ccaaagactg ccactgcata tga 1833

<210> 32
<211> 610
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32

```
Gly Gly Gly Glu Arg Lys Ser Ser Val Glu Cys Pro Pro Cys Pro Ala
1               5                  10                  15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65                  70                  75                  80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        115                 120                 125
```

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Arg Lys Ser Ser Val
                245                 250                 255

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
            260                 265                 270

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
        275                 280                 285

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
    290                 295                 300

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
305                 310                 315                 320

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
                325                 330                 335

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
            340                 345                 350

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
        355                 360                 365

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
    370                 375                 380

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
385                 390                 395                 400

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
                405                 410                 415

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
            420                 425                 430
```

```
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
        435                 440                 445

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
    450                 455                 460

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Gly Gly
465                 470                 475                 480

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                485                 490                 495

Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
            500                 505                 510

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
        515                 520                 525

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly

    530                 535                 540

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
545                 550                 555                 560

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
                565                 570                 575

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
            580                 585                 590

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
        595                 600                 605

Cys Ile
    610
```

<210> 33

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 33

```
Gly Gly Gly Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
1               5                   10                  15

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            20                  25                  30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
```

```
        35                  40                  45

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    50                  55                  60

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
65                  70                  75                  80

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                85                  90                  95

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
            100                 105                 110

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu

        115                 120                 125

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
    130                 135                 140

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
145                 150                 155                 160

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
                165                 170                 175

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
            180                 185                 190

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
        195                 200                 205

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 34

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 34

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
            20                  25
```

<210> 35

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 35

```
Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1               5                  10                  15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            180                 185                 190

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 36

<211> 1809

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 36

ggcggtggag ctccgccggt ggctggaccc tcagtgttcc tctttccacc gaagccgaag 60

gacaccctta tgattagccg gaccccagag gtcacttgcg tcgtcgtgga cgtgtcccat 120

gaggatcccg aagtgcagtt taactggtat gtggacggag tggaggtcca taacgccaag 180

accaagccaa gggaagaaca gttcaatagc accttccggg tggtgtccgt gctcaccgtg 240

gtgcatcaag actggctgaa tggcaaagag tacaaatgta aggtgtcaaa caaggggctc 300

ccagccccta ttgaaaagac catctcaaag actaagggac agccacgcga acctcaagtg 360

tataccctcc cgccttcacg cgaagaaatg actaagaatc aggtcagcct tacttgtctg 420

gtcaagggct tctacccgag cgacattgca gtcgaatggg agagcaatgg tcagccagag 480

aataactaca agaccactcc tcccatgctt gatagcgatg gaagcttttt cctttacagc 540

aagcttactg tggataagtc tcgctggcaa cagggaaatg tgttcagctg ttcagtgatg 600

catgaagcac tccacaatca ttacacccag aagtcactca gcctctcacc cggaggagga 660

ggcggttctg gtggaggagg gtctggaggt ggagggagcg gcggaggcgg gtctggcggt 720

ggtgggtctg agaggaagtc atcagtggaa tgcccaccat gccctgctcc tcccgtggcc 780

ggtccgagcg tgtttctctt cccacctaag cccaaggaca ctctgatgat ctcacggact 840

ccggaagtga cttgtgtggt ggtggacgtg tctcatgagg accctgaagt gcagttcaac 900

tggtacgtgg acggcgtgga ggtgcacaat gctaagacca agcctagaga ggaacagttc 960

aattccacct ttcgcgtggt gagcgtcctg accgtcgtgc accaggactg gcttaacgga 1020

aaggaataca agtgcaaggt gtccaacaaa ggccttccag ctcccattga gaaaaccatc 1080

tctaaaacta agggtcaacc aagggaaccc caagtctaca ccctccctcc gtctagagaa 1140

gagatgacca aaaaccaggt gtccctgacc tgtctggtga agggatttta cccctcagac 1200

atcgccgtgg agtgggaaag caacggacag cccgaaaaca actataagac tacccctcct 1260

atgctggact cagacggatc tttcttcctc tatagcaagc tcactgtgga caaatccaga 1320

tggcaacaag ggaatgtgtt ctcatgcagc gtgatgcacg aggctcttca caaccactat 1380

acccagaaga gcctgtctct ttcacctggt tccggaggtg gtgggagcgg aggggtggga 1440

tcaggtggtg gagggtccgg aggcggagga tccgcacgga atggcgacca ctgtccactg 1500

ggacccggaa gatgttgtcg cctccacacc gtgagggcct ctctggagga ccttggctgg 1560

gccgactggg tcctgtcacc tcgggaggtc caagtcacca tgtgtatcgg agcctgcccc 1620

agccaattca gagcagcaaa tatgcacgca cagattaaga ccagcctgca tcggcttaaa 1680

cctgatactg tgccggctcc ttgttgcgtg ccagcatctt acaacccgat ggtgctgatc 1740

cagaaaaccg ataccggtgt ctccctccag acttacgacg acctccttgc aaaggactgc 1800

cattgcatc 1809

<210> 37

<211> 591
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 37

```
Gly Gly Gly Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
1               5                  10                  15

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            20                  25                  30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
        35                  40                  45

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    50                  55                  60

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
65                  70                  75                  80

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                85                  90                  95

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
            100                 105                 110

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
        115                 120                 125

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
    130                 135                 140

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
145                 150                 155                 160

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
                165                 170                 175

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
            180                 185                 190

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
        195                 200                 205

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly
    210                 215                 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
225                 230                 235                 240

Gly Gly Ser Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
```

245 250 255

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
260 265 270

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
275 280 285

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
290 295 300

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
305 310 315 320

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
325 330 335

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
340 345 350

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
355 360 365

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
370 375 380

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385 390 395 400

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
405 410 415

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Gly Gly Gly Gly Ser
450 455 460

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
465 470 475 480

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
485 490 495

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
500 505 510

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
515 520 525

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
530 535 540

530 535 540

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
545 550 555 560

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
565 570 575

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
580 585 590

<210> 38
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 39
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

```
Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 40

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 40

```
Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Val Ala Ser Ser Gly
1               5                   10                  15

Ser Gly Ser Ala Thr His Leu
            20
```

<210> 41

<211> 1053

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 41

```
gccccagagc tgcttggtgg accatccgtg ttcctgtttc ctccaaagcc gaaggacacc      60

ctgatgatct caagaactcc ggaagtgact tgcgtcgtcg tggacgtgtc acatgaggat     120

ccagaggtca agttcaattg gtatgtggac ggagtggaag tgcataacgc caagaccaaa     180

ccccgcgaag aacagtacaa tagcacctac cgcgtggtga gcgtccttac tgtgctccac     240

caggactggc ttaatgggaa ggaatacaag tgtaaggtgt ccaacaaggc ctccccgct      300

cccatcgaaa agaccatctc aaaggcaaag gggcaaccaa gggaacctca agtgtacacc     360

ctgcctccga gcaggaagga gatgaccaag aaccaggtca gcctgacttg tctcgtgaag     420

ggcttctatc ccagcgatat tgctgtggaa tgggagtcaa atggccagcc cgagaataac     480

tacaaaacta ccccacccgt gctgaaatct gatgggtcct tcttccttta ctccaagctg     540

accgtggaca agagccgctg gcaacaaggc aatgtcttta gctgctcagt gatgcatgag     600

gctctccata atcactacac tcagaagtca ctgtccctgt cacctggcgg atccggttct     660

gctactggtg gttccggctc cgtcgcaagc tctggttcag gcagtgcgac tcatctggca     720

cgaaacgaga accattatcc cctgaggacc gatcggtact gccgacttca caccatcaga     780
```

gcctctctgg aggaccttgg atgggctgat tgggtgctga gccctcggga ggtgcaagtc 840

accatgtgca tcggggcctg ccctagccag ttccgcgcag ccaacatgca cgctcagatc 900

aaaacctctc ttcacagact gaagcccgac accgtgccag caccttgctg tgtgccggcc 960

tcttataacc ccatggtcct cattcagaaa accgacaccg gagtgtcact tcagacttac 1020

gatgacctcc tggccaagga ctgccactgc ata 1053

<210> 42
<211> 351
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
```

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Ser Gly Ser Ala Thr Gly Gly
210 215 220

Ser Gly Ser Val Ala Ser Ser Gly Ser Gly Ser Ala Thr His Leu Ala
225 230 235 240

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
245 250 255

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
260 265 270

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
275 280 285

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
290 295 300

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
305 310 315 320

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
325 330 335

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
340 345 350

<210> 43

<211> 651

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 43

gcgccggaac tgctgggcgg cccgagcgtg tttctgtttc cgccgaaacc gaaagatacc 60

ctgatgatta gccgcacccc ggaagtgacc tgcgtggtgg tggatgtgag ccatgaagat 120

ccggaagtga aatttaactg gtatgtggat ggcgtggaag tgcataacgc gaaaaccaaa 180

ccgcgcgaag aacagtataa cagcacctat cgcgtggtga gcgtgctgac cgtgctgcat 240

caggattggc tgaacggcaa agaatataaa tgcaaagtga gcaacaaagc gctgccggcg 300

ccgattgaaa aaaccattag caaagcgaaa ggccagccgc gcgaaccgca ggtgtatacc 360

ctgccgccga gccgcgaaga aatgaccaaa aaccaggtga gcctgacctg cctggtgaaa 420

ggcttttatc cgagcgatat tgcggtggaa tgggaaagca acggccagcc ggaaaacaac 480

tatgatacca ccccgccggt gctggatagc gatggcagct tttttctgta tagcgatctg 540

accgtggata aaagccgctg gcagcagggc aacgtgttta gctgcagcgt gatgcatgaa 600

gcgctgcata accattatac ccagaaaagc ctgagcctga gcccgggcaa a 651

<210> 44

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 44

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 45
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 45
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgaccacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcaacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 46
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asn Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 47
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 48
<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 49

<211> 984

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 49

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcaacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 50

<211> 328

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 50

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

```
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asn Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 51

<211> 654

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 51

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc     360

ctgccccccat cccggaagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa     420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac     480

tacaagacca cgcctcccgt gctgaagtcc gacggctcct tcttcctcta tagcaagctc     540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag     600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga           654
```

<210> 52

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 52

```
Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
1               5                  10                  15

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
            20                  25                  30

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
        35                  40                  45

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
    50                  55                  60

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
65                  70                  75                  80

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val
                85                  90                  95

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            100                 105                 110
```

100 105 110

<210> 53
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 53
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 54
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 54
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320
```

Leu Ala Lys Asp Cys His Cys Ile
325

<210> 55

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 55

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
1 5 10 15

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
20 25 30

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
35 40 45

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
50 55 60

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
65 70 75 80

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
85 90 95

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
100 105

<210> 56

<211> 975

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 56

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

gtgggggcat gcgggcagga gatgaggaag aaggaggtga cggtgaggtg cgtggtgaaa 420

ctgccccccat cccgggaggg gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660

ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720

ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780

tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840

ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900

ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960

gactgccact gcata 975

<210> 57
<211> 325
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 57

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
    210                 215                 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225                 230                 235                 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
                245                 250                 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
            260                 265                 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
        275                 280                 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
    290                 295                 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305                 310                 315                 320

Asp Cys His Cys Ile
                325
```

<210> 58

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 58

```
Gly Gly Gly Gly
1
```

<210> 59

<211> 996

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 59

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

gcgcgcgacg gagaccactg tccgctcggg cccgggcgtt gctgccgtct gcacacggtc 720

cgcgcgtcgc tggaagacct gggctgggcc gattgggtgc tgtcgccacg ggaggtgcaa 780

gtgaccatgt gcatcggcgc gtgcccgagc cagttccggg cggcaaacat gcacgcgcag 840

atcaagacga gcctgcaccg cctgaagccc gacacggtgc cagcgccctg ctgcgtgccc 900

gccagctaca atcccatggt gctcattcaa aagaccgaca ccggggtgtc gctccagacc 960

tatgatgact tgttagccaa agactgccac tgcata 996

<210> 60

<211> 332

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 60

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

```
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ala Arg Asp Gly
    210                 215                 220

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
225                 230                 235                 240

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
                245                 250                 255

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
            260                 265                 270

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
        275                 280                 285

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
    290                 295                 300

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
305                 310                 315                 320

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
                325                 330
```

<210> 61

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 61

```
Gly Gly Gly Gly Ser
1               5
```

<210> 62

<211> 1002

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 62

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc     360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa     420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac     480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc     540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag     600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga     660

tccgcgcgca acggagacca ctgtccgctc gggcccgggc gttgctgccg tctgcacacg     720

gtccgcgcgt cgctggaaga cctgggctgg gccgattggg tgctgtcgcc acgggaggtg     780

caagtgacca tgtgcatcgg cgcgtgcccg agccagttcc gggcggcaaa catgcacgcg     840

cagatcaaga cgagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg     900

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag     960

acctatgatg acttgttagc caaagactgc cactgcatat ga                       1002
```

<210> 63

<211> 333

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 63

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Ala Arg Asn
    210                 215                 220

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
225                 230                 235                 240

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
                245                 250                 255

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
            260                 265                 270
```

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
275 280 285

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
290 295 300

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
305 310 315 320

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
325 330

<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 64
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 65
<211> 1014
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 65
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

tccggaggcg gtggaagcgc gcgcaacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 1014

<210> 66

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 66

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205
```

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225 230 235 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
245 250 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
260 265 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
275 280 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
290 295 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305 310 315 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
325 330 335

Cys Ile

<210> 67
<211> 1014
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 67
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

tccggaggcg gtggaagcgc gcgcgacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 1014

<210> 68

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 68

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
```

```
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225                 230                 235                 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
                245                 250                 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
            260                 265                 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
        275                 280                 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
    290                 295                 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305                 310                 315                 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
                325                 330                 335

Cys Ile
```

<210> 69
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 69

```
Gly Gly Gly Gly Pro
1               5
```

<210> 70
<211> 999
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 70

```
gcacctgaaa tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc        60
```

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

cccgcgcgca acggagacca ctgtccgctc gggcccgggc gttgctgccg tctgcacacg 720

gtccgcgcgt cgctggaaga cctgggctgg gccgattggg tgctgtcgcc acgggaggtg 780

caagtgacca tgtgcatcgg cgcgtgcccg agccagttcc gggcggcaaa catgcacgcg 840

cagatcaaga cgagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg 900

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag 960

acctatgatg acttgttagc caaagactgc cactgcata 999

<210> 71

<211> 333

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 71

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
```

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Pro Ala Arg Asn
210 215 220

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
225 230 235 240

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
245 250 255

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
260 265 270

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
275 280 285

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
290 295 300

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
305 310 315 320

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
325 330

<210> 72
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 72

```
Gly Gly Gly Gly Pro Gly Gly Gly Gly Pro
1               5                   10
```

<210> 73

<211> 1017

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 73

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc     360
ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa     420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac     480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc     540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag     600
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga     660
cctggaggcg gtggaccagc gcgcaacgga gaccactgtc cgctcgggcc cgggcgttgc     720
tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg     780
tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg     840
gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca     900
gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc     960
ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg catatga       1017
```

<210> 74

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 74

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15
```

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Pro Gly Gly Gly
    210                 215                 220

Gly Pro Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225                 230                 235                 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
                245                 250                 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
            260                 265                 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
        275                 280                 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
    290                 295                 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305                 310                 315                 320
```

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
325 330 335

Cys Ile

<210> 75

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 75

Gly Gly Gly Gly Gln
1 5

<210> 76

<211> 1002

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 76

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

actgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

caggcgcgca acggagacca ctgtccgctc gggcccgggc gttgctgccg tctgcacacg 720

gtccgcgcgt cgctggaaga cctgggctgg gccgattggg tgctgtcgcc acgggaggtg 780

caagtgacca tgtgcatcgg cgcgtgcccg agccagttcc gggcggcaaa catgcacgcg 840

cagatcaaga cgagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg 900

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag 960

acctatgatg acttgttagc caaagactgc cactgcatat ga 1002

<210> 77
<211> 333
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 77

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Gln Ala Arg Asn
```

```
    210                 215                 220

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
225                 230                 235                 240

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
                245                 250                 255

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
            260                 265                 270

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
        275                 280                 285

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
    290                 295                 300

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
305                 310                 315                 320

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
                325                 330
```

<210> 78

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 78

```
Gly Gly Gly Gly Gln Gly Gly Gly Gly Gln
1               5                   10
```

<210> 79

<211> 1017

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 79

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300
```

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

cagggaggcg gtggacaggc gcgcaacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg catatga 1017

<210> 80
<211> 338
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 80

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Gln Gly Gly Gly
    210                 215                 220

Gly Gln Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225                 230                 235                 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
                245                 250                 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
            260                 265                 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
        275                 280                 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
    290                 295                 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305                 310                 315                 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
                325                 330                 335

Cys Ile
```

<210> 81

<211> 1014

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 81

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180
```

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

cagggaggcg gtggacaggc gcgcgacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 1014

<210> 82

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 82

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125
```

115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Gln Gly Gly Gly
210 215 220

Gly Gln Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225 230 235 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
245 250 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
260 265 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
275 280 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
290 295 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305 310 315 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
325 330 335

Cys Ile

<210> 83

<211> 1005

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 83

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

cagggaggcg gtggacaggg agaccactgt ccgctcgggc ccgggcgttg ctgccgtctg 720

cacacggtcc gcgcgtcgct ggaagacctg ggctgggccg attgggtgct gtcgccacgg 780

gaggtgcaag tgaccatgtg catcggcgcg tgcccgagcc agttccgggc ggcaaacatg 840

cacgcgcaga tcaagacgag cctgcaccgc ctgaagcccg acacggtgcc agcgccctgc 900

tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg 960

ctccagacct atgatgactt gttagccaaa gactgccact gcata 1005

<210> 84

<211> 335

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 84

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
```

```
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Gln Gly Gly Gly
    210                 215                 220

Gly Gln Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
225                 230                 235                 240

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
                245                 250                 255

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
            260                 265                 270

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
        275                 280                 285

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
    290                 295                 300

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
305                 310                 315                 320

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
                325                 330                 335
```

<210> 85

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 85

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15
```

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 86

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 86

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 87

<211> 984

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 87

```
gccccagagc tgcttggtgg accatccgtg ttcctgtttc ctccaaagcc gaaggacacc      60

ctgatgatct caagaactcc ggaagtgact tgcgtcgtcg tggacgtgtc acatgaggat     120

ccagaggtca agttcaattg gtatgtggac ggagtggaag tgcataacgc caagaccaaa     180

ccccgcgaag aacagtacaa tagcacctac cgcgtggtga gcgtccttac tgtgctccac     240

caggactggc ttaatgggaa ggaatacaag tgtaaggtgt ccaacaaggc cctccccgct     300
```

cccatcgaaa agaccatctc aaaggcaaag gggcaaccaa gggaacctca agtgtacacc 360

ctgcctccgt gcaggaagga gatgaccaag aaccaggtca gcctgacttg tctcgtgaag 420

ggcttctatc ccagcgatat tgctgtggaa tgggagtcaa atggccagcc cgagaataac 480

tacaaaacta ccccacccgt gctgaaatct gatgggtcct tcttccttta ctccaagctg 540

accgtggaca agagccgctg gcaacaaggc aatgtcttta gctgctcagt gatgcatgag 600

gctctccata atcactacac tcagaagtca ctgtccctgt cacctggcgc gcgcgacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 88
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 88

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 89

<211> 651

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 89

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300
```

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a 651

<210> 90

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 90

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
```

180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys

210 215

<210> 91
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 91

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 92
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 92
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcaacgga 660
gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720
gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780
atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840
ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900
cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960
ttagccaaag actgccactg cata 984

<210> 93
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 93

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asn Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300
```

290 295 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305 310 315 320

Leu Ala Lys Asp Cys His Cys Ile
325

<210> 94
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 94
gccccagagc tgcttggtgg accatccgtg ttcctgtttc ctccaaagcc gaaggacacc 60
ctgatgatct caagaactcc ggaagtgact tgcgtcgtcg tggacgtgtc acatgaggat 120
ccagaggtca agttcaattg gtatgtggac ggagtggaag tgcataacgc caagaccaaa 180
ccccgcgaag aacagtacaa tagcacctac cgcgtggtga gcgtccttac tgtgctccac 240
caggactggc ttaatgggaa ggaatacaag tgtaaggtgt ccaacaaggc ctccccgct 300
cccatcgaaa agaccatctc aaaggcaaag gggcaaccaa gggaacctca agtgtacacc 360
ctgcctccgt gcaggaagga gatgaccaag aaccaggtca gcctgacttg tctcgtgaag 420
ggcttctatc ccagcgatat tgctgtggaa tgggagtcaa atggccagcc cgagaataac 480
tacaaaacta ccccacccgt gctgaaatct gatgggtcct tcttccttta ctccaagctg 540
accgtggaca agagccgctg gcaacaaggc aatgtcttta gctgctcagt gatgcatgag 600
gctctccata atcactacac tcagaagtca ctgtccctgt ctccgggtaa a 651

<210> 95
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 95
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 96
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 96

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
```

```
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 97

<211> 975

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 97

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300
```

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660

ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720

ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780

tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840

ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900

ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960

gactgccact gcata 975

<210> 98
<211> 325
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 98

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
    ---                 ---                 ---

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
    210                 215                 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225                 230                 235                 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met

                245                 250                 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
            260                 265                 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
        275                 280                 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
    290                 295                 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305                 310                 315                 320

Asp Cys His Cys Ile
                325
```

<210> 99

<211> 996

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 99

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac     240
```

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg tggaggtggt 660

gcgcgcgacg gagaccactg tccgctcggg cccgggcgtt gctgccgtct gcacacggtc 720

cgcgcgtcgc tggaagacct gggctgggcc gattgggtgc tgtcgccacg ggaggtgcaa 780

gtgaccatgt gcatcggcgc gtgcccgagc cagttccggg cggcaaacat gcacgcgcag 840

atcaagacga gcctgcaccg cctgaagccc gacacggtgc cagcgccctg ctgcgtgccc 900

gccagctaca atcccatggt gctcattcaa aagaccgaca ccggggtgtc gctccagacc 960

tatgatgact tgttagccaa agactgccac tgcata 996

<210> 100
<211> 332
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 100

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125
```

```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ala Arg Asp Gly
    210                 215                 220

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
225                 230                 235                 240

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
                245                 250                 255

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
            260                 265                 270

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
        275                 280                 285

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
    290                 295                 300

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
305                 310                 315                 320

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
                325                 330
```

<210> 101

<211> 1014

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 101

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag     180
```

```
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac      240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc      300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc      360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa      420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac      480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc      540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag      600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga      660
tccggaggcg gtggaagcgc gcgcgacgga gaccactgtc cgctcgggcc cgggcgttgc      720
tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg      780
tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg      840
gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca      900
gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc      960
ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata            1014
```

<210> 102
<211> 338
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 102

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
```

```
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225                 230                 235                 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
                245                 250                 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
            260                 265                 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
        275                 280                 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
    290                 295                 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305                 310                 315                 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
                325                 330                 335

Cys Ile
```

<210> 103

<211> 1014

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 103

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc        60
```

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

cagggaggcg gtggacaggc gcgcgacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 1014

<210> 104

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 104

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
```

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Gln Gly Gly Gly
210 215 220

Gly Gln Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225 230 235 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
245 250 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
260 265 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
275 280 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
290 295 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305 310 315 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
325 330 335

Cys Ile

<210> 105
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 105

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 106

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 106

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15
```

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 107

<211> 1014

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 107

```
gcgccggaac tgctgggcgg cccgagcgtg tttctgtttc cgccgaaacc gaaagatacc        60

ctgatgatta gccgcacccc ggaagtgacc tgcgtggtgg tggatgtgag ccatgaagat       120

ccggaagtga aatttaactg gtatgtggat ggcgtggaag tgcataacgc gaaaaccaaa       180

ccgcgcgaag aacagtataa cagcacctat cgcgtggtga gcgtgctgac cgtgctgcat       240
```

caggattggc tgaacggcaa agaatataaa tgcaaagtga gcaacaaagc gctgccggcg 300

ccgattgaaa aaaccattag caaagcgaaa ggccagccgc gcgaaccgca ggtgtatacc 360

tgcccgccga gccgcgaaga aatgaccaaa aaccaggtga gcctgacctg cctggtgaaa 420

ggcttttatc cgagcgatat tgcggtggaa tgggaaagca acggccagcc ggaaaacaac 480

tatgatacca ccccgccggt gctggatagc gatggcagct tttttctgta tagcgatctg 540

accgtggata aaagccgctg gcagcagggc aacgtgttta gctgcagcgt gatgcatgaa 600

gcgctgcata accattatac ccagaaaagc ctgagcctga gcccgggcgg cggcggcggc 660

agcggcggcg gcggcagcgc gcgcaacggc gatcattgcc cgctgggccc gggccgctgc 720

tgccgcctgc ataccgtgcg cgcgagcctg gaagatctgg gctgggcgga ttgggtgctg 780

agcccgcgcg aagtgcaggt gaccatgtgc attggcgcgt gcccgagcca gtttcgcgcg 840

gcgaacatgc atgcgcagat taaaaccagc ctgcatcgcc tgaaaccgga taccgtgccg 900

gcgccgtgct gcgtgccggc gagctataac ccgatggtgc tgattcagaa aaccgatacc 960

ggcgtgagcc tgcagaccta tgatgatctg ctggcgaaag attgccattg catt 1014

<210> 108
<211> 338
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 108

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Glu Glu Met
        115                 120                 125
```

```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
    210                 215                 220

Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225                 230                 235                 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
                245                 250                 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
            260                 265                 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
        275                 280                 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
    290                 295                 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305                 310                 315                 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
                325                 330                 335

Cys Ile
```

<210> 109

<211> 651

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 109

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag cgaagaggac     120
```

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

tgtcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a 651

<210> 110
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 110

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 111
<211> 2154
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 111
gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

```
cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa      720
gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt      780
gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa      840
aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct      900
gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct      960
gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat     1020
tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc     1080
tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt     1140
gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag     1200
tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact     1260
ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat     1320
cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta     1380
tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc     1440
ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa     1500
gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag     1560
agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca     1620
aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag     1680
gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag     1740
gccgccttag gcttaggagg tggtggatcc ggaggcggtg gaagcggagg tggtggatct     1800
ggaggcggtg gaagcgcgcg caacggagac cactgtccgc tcgggcccgg gcgttgctgc     1860
cgtctgcaca cggtccgcgc gtcgctggaa gacctgggct gggccgattg ggtgctgtcg     1920
ccacgggagg tgcaagtgac catgtgcatc ggcgcgtgcc cgagccagtt ccgggcggca     1980
aacatgcacg cgcagatcaa gacgagcctg caccgcctga agcccgacac ggtgccagcg     2040
ccctgctgcg tgcccgccag ctacaatccc atggtgctca ttcaaaagac cgacaccggg     2100
gtgtcgctcc agacctatga tgacttgtta gccaaagact gccactgcat atga            2154
```

<210> 112
<211> 717
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 112

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45
```

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr

340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser Gly Gly
580 585 590

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn
595 600 605

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
610 615 620

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
625 630 635 640

```
Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
                645                 650                 655

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
            660                 665                 670

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
        675                 680                 685

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
    690                 695                 700

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705                 710                 715
```

<210> 113

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 113

```
Gly Ser Pro Ala Pro Ala Pro Gly Ser
1               5
```

<210> 114

<211> 2121

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 114

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gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa       60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta      120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa      180

aattgtgaca aatcacttca taccctttt ggagacaaat tatgcacagt tgcaactctt       240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa      300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt      360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat      420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg      480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca      540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt      600
```

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggatc cccagctcca gctccaggaa gcgcgcgcaa cggagaccac 1800

tgtccgctcg ggcccgggcg ttgctgccgt ctgcacacgg tccgcgcgtc gctggaagac 1860

ctgggctggg ccgattgggt gctgtcgcca cgggaggtgc aagtgaccat gtgcatcggc 1920

gcgtgcccga gccagttccg ggcggcaaac atgcacgcgc agatcaagac gagcctgcac 1980

cgcctgaagc ccgacacggt gccagcgccc tgctgcgtgc ccgccagcta caatcccatg 2040

gtgctcattc aaaagaccga caccggggtg tcgctccaga cctatgatga cttgttagcc 2100

aaagactgcc actgcatatg a 2121

<210> 115
<211> 706
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 115

Asp	Ala	His	Lys	Ser	Glu	Val	Ala	His	Arg	Phe	Lys	Asp	Leu	Gly	Glu
1				5				10					15		

```
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
```

325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Pro Ala Pro Ala Pro
580 585 590

Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
595 600 605

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
610 615 620

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly

```
Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
625                 630                 635                 640

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
                645                 650                 655

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
            660                 665                 670

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
        675                 680                 685

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
    690                 695                 700

Cys Ile
705
```

<210> 116

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 116

```
Gly Ser Pro Ala Pro Ala Pro Pro Ala Pro Ala Pro Gly Ser
1               5                   10
```

<210> 117

<211> 2136

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 117

```
gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa       60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta      120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa      180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt      240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa      300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt      360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat      420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg      480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca      540
```

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggatc cccagctcca gctccacccg cacctgcccc tggaagcgcg 1800

cgcaacggag accactgtcc gctcgggccc gggcgttgct gccgtctgca cacggtccgc 1860

gcgtcgctgg aagacctggg ctgggccgat tgggtgctgt cgccacggga ggtgcaagtg 1920

accatgtgca tcggcgcgtg cccgagccag ttccgggcgg caaacatgca cgcgcagatc 1980

aagacgagcc tgcaccgcct gaagcccgac acggtgccag cgccctgctg cgtgcccgcc 2040

agctacaatc ccatggtgct cattcaaaag accgacaccg gggtgtcgct ccagacctat 2100

gatgacttgt tagccaaaga ctgccactgc atatga 2136

<210> 118

<211> 711

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 118

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15
```

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Pro Ala Pro Ala Pro
580 585 590

Pro Ala Pro Ala Pro Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu
595 600 605

```
Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu
    610                 615                 620

Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val
625                 630                 635                 640

Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met
                645                 650                 655

His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val
            660                 665                 670

Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile
        675                 680                 685

Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu
    690                 695                 700

Ala Lys Asp Cys His Cys Ile
705                 710
```

<210> 119

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 119

```
Gly Ser Ala Ala Gln Ala Ala Gln Gln Gly Ser
1               5                   10
```

<210> 120

<211> 2127

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 120

```
gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa      60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta     120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa     180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt     240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa     300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt     360
```

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggatc cgccgctcag gctgcacagc aaggaagcgc gcgcaacgga 1800

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 1860

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 1920

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 1980

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 2040

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 2100

ttagccaaag actgccactg catatga 2127

<210> 121
<211> 708
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 121

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300
```

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Ala Ala Gln Ala Ala
580 585 590

Gln Gln Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly
595 600 605

Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly
610 615 620

Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys
625 630 635 640

Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln
645 650 655

Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro
660 665 670

Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr
675 680 685

Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp
690 695 700

Cys His Cys Ile
705

<210> 122

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 122

Gly Ser Ala Ala Gln Ala Ala Gln Gln Ala Ala Gln Ala Ala Gln Gln
1 5 10 15

Gly Ser

<210> 123

<211> 2148

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 123

gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca taccctttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggatc cgccgctcag gctgcacagc aagcagccca agcagctcag 1800

cagggaagcg cgcgcaacgg agaccactgt ccgctcgggc ccgggcgttg ctgccgtctg 1860

cacacggtcc gcgcgtcgct ggaagacctg ggctgggccg attgggtgct gtcgccacgg 1920

gaggtgcaag tgaccatgtg catcggcgcg tgcccgagcc agttccgggc ggcaaacatg 1980

cacgcgcaga tcaagacgag cctgcaccgc ctgaagcccg acacggtgcc agcgccctgc 2040

tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg 2100

ctccagacct atgatgactt gttagccaaa gactgccact gcatatga 2148

<210> 124

<211> 715

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 124

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255
```

```
Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560
```

```
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Ala Ala Gln Ala Ala
            580                 585                 590

Gln Gln Ala Ala Gln Ala Ala Gln Gln Gly Ser Ala Arg Asn Gly Asp
        595                 600                 605

His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg
    610                 615                 620

Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg
625                 630                 635                 640

Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg
                645                 650                 655

Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys
            660                 665                 670

Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro
        675                 680                 685

Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr
    690                 695                 700

Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705                 710                 715
```

<210> 125

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 125

```
Gly Gly Asn Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala
1               5                   10                  15

Ala Ala Lys Ala Gly Gly
            20
```

<210> 126

<211> 2175

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 126

gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggagg caacgccgag gctgccgcta aggaagccgc tgccaaggag 1800

gccgcagcaa aagaggctgc agctaaggcc ggaggagcgc gcaacggaga ccactgtccg 1860

ctcgggcccg ggcgttgctg ccgtctgcac acggtccgcg cgtcgctgga agacctgggc 1920

tgggccgatt gggtgctgtc gccacgggag gtgcaagtga ccatgtgcat cggcgcgtgc 1980

ccgagccagt tccgggcggc aaacatgcac gcgcagatca agacgagcct gcaccgcctg 2040

aagcccgaca cggtgccagc gccctgctgc gtgcccgcca gctacaatcc catggtgctc 2100

attcaaaaga ccgacaccgg ggtgtcgctc cagacctatg atgacttgtt agccaaagac 2160

tgccactgca tatga 2175

<210> 127
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 127

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220
```

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

```
Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Asn Ala Glu Ala Ala
            580                 585                 590

Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala
        595                 600                 605

Lys Ala Gly Gly Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly
    610                 615                 620

Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly
625                 630                 635                 640

Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys
                645                 650                 655

Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln
            660                 665                 670

Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro
        675                 680                 685

Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr
    690                 695                 700

Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp
705                 710                 715                 720

Cys His Cys Ile
```

<210> 128

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 128

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
```

20 25 30

<210> 129
<211> 2184
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 129

gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggagg tggtggctct ggaggcggtg gaagcggagg cggtggatcc 1800

ggaggcggtg gaagcggagg tggtggatct ggaggcggtg gaagcgcgcg caacggagac 1860

cactgtccgc tcgggcccgg gcgttgctgc cgtctgcaca cggtccgcgc gtcgctggaa 1920

gacctgggct gggccgattg ggtgctgtcg ccacgggagg tgcaagtgac catgtgcatc 1980

ggcgcgtgcc cgagccagtt ccgggcggca aacatgcacg cgcagatcaa gacgagcctg 2040

caccgcctga agcccgacac ggtgccagcg ccctgctgcg tgcccgccag ctacaatccc 2100

atggtgctca ttcaaaagac cgacaccggg gtgtcgctcc agacctatga tgacttgtta 2160

gccaaagact gccactgcat atga 2184

<210> 130

<211> 777

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 130

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
50 55 60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65 70 75 80

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
85 90 95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
100 105 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
115 120 125

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
130 135 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145 150 155 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
165 170 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
180 185 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
195 200 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
210 215 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225 230 235 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
245 250 255

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
260 265 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
275 280 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
290 295 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305 310 315 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
325 330 335

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
340 345 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
355 360 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
370 375 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385 390 395 400

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
405 410 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
420 425 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
435 440 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
450 455 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465 470 475 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
485 490 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
500 505 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
515 520 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
530 535 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545 550 555 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
565 570 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
580 585 590

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
595 600 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
610 615 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Gly Gly Ser
625 630 635 640

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
645 650 655

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn Gly Asp His Cys
660 665 670

Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser
675 680 685

Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val
690 695 700

Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala
705 710 715 720

Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp
725 730 735

Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val
740 745 750

```
Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp
        755                 760                 765

Leu Leu Ala Lys Asp Cys His Cys Ile
    770                 775
```

<210> 131

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 131

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205
```

```
Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 132

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 132

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 133
<211> 975
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 133
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180
ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660
ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720
ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780
tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840
ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900
ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960
gactgccact gcata 975

<210> 134
<211> 325
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 134
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
    210                 215                 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225                 230                 235                 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
                245                 250                 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
            260                 265                 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
        275                 280                 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
    290                 295                 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305                 310                 315                 320
```

Asp Cys His Cys Ile
325

<210> 135
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 135
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccggaagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacaagacca cgcctcccgt gctgaagtcc gacggctcct tcttcctcta tagcaagctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa atga 654

<210> 136
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 136
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcaagctc 540

tacgacacca cgcctcccgt gctggacttc gacggcttct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 137

<211> 328

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 137

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asn Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
```

```
Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 138

<211> 996

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 138

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc       60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac      120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag      180

ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac      240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc      300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc      360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa      420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac      480
```

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

gcgcgcgacg gagaccactg tccgctcggg cccgggcgtt gctgccgtct gcacacggtc 720

cgcgcgtcgc tggaagacct gggctgggcc gattgggtgc tgtcgccacg ggaggtgcaa 780

gtgaccatgt gcatcggcgc gtgcccgagc cagttccggg cggcaaacat gcacgcgcag 840

atcaagacga gcctgcaccg cctgaagccc gacacggtgc cagcgccctg ctgcgtgccc 900

gccagctaca atcccatggt gctcattcaa aagaccgaca ccggggtgtc gctccagacc 960

tatgatgact tgttagccaa agactgccac tgcata 996

<210> 139

<211> 332

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 139

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160
```

```
Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ala Arg Asp Gly
    210                 215                 220

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
225                 230                 235                 240

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
                245                 250                 255

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
            260                 265                 270

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
        275                 280                 285

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
    290                 295                 300

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
305                 310                 315                 320

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
                325                 330
```

<210> 140

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 140

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60
```

```
Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 141

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 141

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80
```

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 142
<211> 975
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 142
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660

ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720

ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780

tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840

ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900

ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960

gactgccact gcata 975

<210> 143

<211> 325

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 143

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175
```

```
Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
    210                 215                 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225                 230                 235                 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
                245                 250                 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
            260                 265                 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
        275                 280                 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
    290                 295                 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305                 310                 315                 320

Asp Cys His Cys Ile
                325
```

<210> 144
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 144

```
gccccagagc tgcttggtgg accatccgtg ttcctgtttc ctccaaagcc gaaggacacc      60

ctgatgatct caagaactcc ggaagtgact tgcgtcgtcg tggacgtgtc acatgaggat     120

ccagaggtca agttcaattg gtatgtggac ggagtggaag tgcataacgc caagaccaaa     180

ccccgcgaag aacagtacgg gagcacctac cgcgtggtga gcgtccttac tgtgctccac     240

caggactggc ttaatgggaa ggaatacaag tgtaaggtgt ccaacaaggc ctccccgct      300

cccatcgaaa agaccatctc aaaggcaaag gggcaaccaa gggaacctca agtgtacacc     360

ctgcctccgt gcaggaagga gatgaccaag aaccaggtca gcctgacttg tctcgtgaag     420

ggcttctatc ccagcgatat tgctgtggaa tgggagtcaa atggccagcc cgagaataac     480

tacaaaacta ccccacccgt gctgaaatct gatgggtcct tcttccttta ctccaagctg     540

accgtggaca agagccgctg gcaacaaggc aatgtcttta gctgctcagt gatgcatgag     600
```

gctctccata atcactacac tcagaagtca ctgtccctgt ctccgggtaa a 651

<210> 145
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 145
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180
ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga 660
gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720
gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780
atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840
ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900
cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960
ttagccaaag actgccactg cata 984

<210> 146
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 146
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
210 215 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225 230 235 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
245 250 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
260 265 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
275 280 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
290 295 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305 310 315 320

Leu Ala Lys Asp Cys His Cys Ile
325

<210> 147

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 147

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215

<210> 148
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 148

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 149

<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 149
gcgccggaac tgctgggcgg cccgagcgtg tttctgtttc cgccgaaacc gaaagatacc 60

ctgatgatta gccgcacccc ggaagtgacc tgcgtggtgg tggatgtgag ccatgaagat 120

ccggaagtga aatttaactg gtatgtggat ggcgtggaag tgcataacgc gaaaaccaaa 180

ccgcgcgaag aacagtatgg cagcacctat cgcgtggtga gcgtgctgac cgtgctgcat 240

caggattggc tgaacggcaa agaatataaa tgcaaagtga gcaacaaagc gctgccggcg 300

ccgattgaaa aaaccattag caaagcgaaa ggccagccgc gcgaaccgca ggtgtatacc 360

tgcccgccga gccgcaaaga aatgaccaaa aaccaggtga gcctgacctg cctggtgaaa 420

ggcttttatc cgagcgatat tgcggtggaa tgggaaagca acggccagcc ggaaaacaac 480

tataaaacca ccccgccggt gctgaaaagc gatggcagct tttttctgta tagcaaactg 540

accgtggata aaagccgctg gcagcagggc aacgtgttta gctgcagcgt gatgcatgaa 600

gcgctgcata accattatac ccagaaaagc ctgagcctga gcccgggcgc gcgcaacggc 660

gatcattgcc cgctgggccc gggccgctgc tgccgcctgc ataccgtgcg cgcgagcctg 720

gaagatctgg gctgggcgga ttgggtgctg agcccgcgcg aagtgcaggt gaccatgtgc 780

attggcgcgt gcccgagcca gtttcgcgcg gcgaacatgc atgcgcagat taaaaccagc 840

ctgcatcgcc tgaaaccgga taccgtgccg gcgccgtgct gcgtgccggc gagctataac 900

ccgatggtgc tgattcagaa aaccgatacc ggcgtgagcc tgcagaccta tgatgatctg 960

ctggcgaaag attgccattg catt 984

<210> 150
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 150
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

```
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asn Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 151

<211> 651

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 151
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg gagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

tgtcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a 651

<210> 152
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 152
gcgccggaac tgctgggcgg cccgagcgtg tttctgtttc cgccgaaacc gaaagatacc 60

ctgatgatta gccgcacccc ggaagtgacc tgcgtggtgg tggatgtgag ccatgaagat 120

ccggaagtga aatttaactg gtatgtggat ggcgtggaag tgcataacgc gaaaaccaaa 180

ccgcgcgaag aacagtatgg cagcacctat cgcgtggtga gcgtgctgac cgtgctgcat 240

caggattggc tgaacggcaa agaatataaa tgcaaagtga gcaacaaagc gctgccggcg 300

ccgattgaaa aaaccattag caaagcgaaa ggccagccgc gcgaaccgca ggtgtatacc 360

tgcccgccga gccgcaaaga aatgaccaaa aaccaggtga gcctgacctg cctggtgaaa 420

ggcttttatc cgagcgatat tgcggtggaa tgggaaagca acggccagcc ggaaaacaac 480

tataaaacca ccccgccggt gctgaaaagc gatggcagct tttttctgta tagcaaactg 540

accgtggata aaagccgctg gcagcagggc aacgtgttta gctgcagcgt gatgcatgaa 600

gcgctgcata accattatac ccagaaaagc ctgagcctga gcccgggcgc gcgcgatggc 660

gatcattgcc cgctgggccc gggccgctgc tgccgcctgc ataccgtgcg cgcgagcctg 720

gaagatctgg gctgggcgga ttgggtgctg agcccgcgcg aagtgcaggt gaccatgtgc 780

attggcgcgt gcccgagcca gtttcgcgcg gcgaacatgc atgcgcagat taaaaccagc 840

ctgcatcgcc tgaaaccgga taccgtgccg gcgccgtgct gcgtgccggc gagctataac 900

ccgatggtgc tgattcagaa aaccgatacc ggcgtgagcc tgcagaccta tgatgatctg 960

ctggcgaaag attgccattg catt 984

<210> 153

<211> 328

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 153

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
```

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
210 215 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225 230 235 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
245 250 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
260 265 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
275 280 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
290 295 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305 310 315 320

Leu Ala Lys Asp Cys His Cys Ile
325

<210> 154

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 154

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
50 55 60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65 70 75 80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
85 90 95

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

<210> 155

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 155

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110
```

```
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 156

<211> 954

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 156

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac     180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag     240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc     300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag     360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc     420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg     480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg     540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg     600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc     660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg     720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg     780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca     840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc     900
```

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 157
<211> 318
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 157

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
    210                 215                 220
```

```
Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225                 230                 235                 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
                245                 250                 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
            260                 265                 270

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
        275                 280                 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
    290                 295                 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 158

<211> 633

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 158

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac     180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag     240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc     300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccggaaggag     360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc     420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg     480

ctgaagtccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg     540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg     600

cagaagagcc tctccctgtc tccgggtaaa tga                                  633
```

<210> 159

<211> 963

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 159

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac     180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag     240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc     300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag     360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc     420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg     480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg     540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg     600

cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc     660

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat     720

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag     780

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac     840

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag     900

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc     960

ata                                                                  963
```

<210> 160

<211> 321

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 160

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80
```

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
85 90 95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
100 105 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
115 120 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145 150 155 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
210 215 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
225 230 235 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
245 250 255

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
260 265 270

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
275 280 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
290 295 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305 310 315 320

Ile

<210> 161
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 161

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

<210> 162

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 162

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 163

<211> 954

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 163

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct        60
```

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc 660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 900

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 164

<211> 318

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 164

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
```

```
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
    210                 215                 220

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225                 230                 235                 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
                245                 250                 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
            260                 265                 270

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
        275                 280                 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
    290                 295                 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 165

<211> 630

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 165

```
ccatccgtgt tcctgtttcc tccaaagccg aaggacaccc tgatgatctc aagaactccg      60

gaagtgactt gcgtcgtcgt ggacgtgtca catgaggatc cagaggtcaa gttcaattgg     120

tatgtggacg gagtggaagt gcataacgcc aagaccaaac cccgcgaaga acagtacaat     180
```

agcacctacc gcgtggtgag cgtcccttact gtgctccacc aggactggct taatgggaag 240

gaatacaagt gtaaggtgtc caacaaggcc ctccccgctc ccatcgaaaa gaccatctca 300

aaggcaaagg ggcaaccaag ggaacctcaa gtgtacaccc tgcctccgtg caggaaggag 360

atgaccaaga accaggtcag cctgacttgt ctcgtgaagg gcttctatcc cagcgatatt 420

gctgtggaat gggagtcaaa tggccagccc gagaataact acaaaactac cccacccgtg 480

ctgaaatctg atgggtcctt cttcctttac tccaagctga ccgtggacaa gagccgctgg 540

caacaaggca atgtctttag ctgctcagtg atgcatgagg ctctccataa tcactacact 600

cagaagtcac tgtccctgtc tccgggtaaa 630

<210> 166
<211> 963
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 166
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc 660

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 720

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 780

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 840

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 900

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 960

ata 963

<210> 167
<211> 321
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 167

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
    210                 215                 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
225                 230                 235                 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
                245                 250                 255

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
            260                 265                 270
```

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
275 280 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
290 295 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305 310 315 320

Ile

<210> 168
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 168
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 169
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 169
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
165 170 175

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly
225
```

<210> 170
<211> 1005
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 170

```
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc      60

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca     120

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac     180

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac     240

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag     300

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa     360

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag     420

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag     480

tgggagagca atgggcagcc ggagaacaac tacgacacca cgcctcccgt gctggactcc     540

gacggctcct tcttcctcta tagcgacctc accgtggaca agagcaggtg gcagcagggg     600

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc     660

ctctccctgt ctccgggtgg agaccactgt ccgctcgggc ccgggcgttg ctgccgtctg     720

cacacggtcc gcgcgtcgct ggaagacctg ggctgggccg attgggtgct gtcgccacgg     780

gaggtgcaag tgaccatgtg catcggcgcg tgcccgagcc agttccgggc ggcaaacatg     840

cacgcgcaga tcaagacgag cctgcaccgc ctgaagcccg acacggtgcc agcgccctgc     900

tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg     960

ctccagacct atgatgactt gttagccaaa gactgccact gcata                    1005
```

<210> 171
<211> 335
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 171

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
225                 230                 235                 240

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
                245                 250                 255

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
            260                 265                 270
```

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
275 280 285

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
290 295 300

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
305 310 315 320

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
325 330 335

<210> 172
<211> 681
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 172
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 60

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 120

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 180

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac 240

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 300

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 360

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccggaagga gatgaccaag 420

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 480

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctgaagtcc 540

gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg 600

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 660

ctctccctgt ctccgggtaa a 681

<210> 173
<211> 1014
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 173
gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 60

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 120

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 180

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgg cagcacgtac 240

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 300

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 360

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggagga gatgaccaag 420

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 480

tgggagagca atgggcagcc ggagaacaac tacgacacca cgcctcccgt gctggactcc 540

gacggctcct tcttcctcta tagcgacctc accgtggaca agagcaggtg gcagcagggg 600

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 660

ctctccctgt ctccgggtgc gcgcgacgga gaccactgtc cgctcgggcc cgggcgttgc 720

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 780

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 840

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 900

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 960

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 1014

<210> 174

<211> 338

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 174

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95
```

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
225 230 235 240

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
245 250 255

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
260 265 270

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
275 280 285

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
290 295 300

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
305 310 315 320

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
325 330 335

Cys Ile

<210> 175
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 175

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

<210> 176

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 176

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 177

<211> 954

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 177

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120
```

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacggg 180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc 660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 900

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 178

<211> 318

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 178

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110
```

```
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
    210                 215                 220

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225                 230                 235                 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
                245                 250                 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
            260                 265                 270

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
        275                 280                 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
    290                 295                 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 179

<211> 633

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 179

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacggg     180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag     240
```

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccggaaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 480

ctgaagtccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtaaa tga 633

<210> 180
<211> 963
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 180
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacggg 180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc 660

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 720

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 780

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 840

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 900

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 960

ata 963

<210> 181
<211> 321
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 181

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
    210                 215                 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp

225                 230                 235                 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
                245                 250                 255
```

```
Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
            260                 265                 270

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
        275                 280                 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
    290                 295                 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305                 310                 315                 320

Ile
```

<210> 182

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 182

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160
```

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly Lys
210

<210> 183
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 183
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
50 55 60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65 70 75 80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
85 90 95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
100 105 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
115 120 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145 150 155 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly

<210> 184
<211> 954
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 184
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacggc 180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc 660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 900

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 185
<211> 318
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 185

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
    210                 215                 220

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225                 230                 235                 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
                245                 250                 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
            260                 265                 270
```

```
Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
        275                 280                 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
    290                 295                 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 186
<211> 630
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 186

```
ccatccgtgt tcctgtttcc tccaaagccg aaggacaccc tgatgatctc aagaactccg      60

gaagtgactt gcgtcgtcgt ggacgtgtca catgaggatc cagaggtcaa gttcaattgg     120

tatgtggacg gagtggaagt gcataacgcc aagaccaaac cccgcgaaga acagtacggg     180

agcacctacc gcgtggtgag cgtccttact gtgctccacc aggactggct taatgggaag     240

gaatacaagt gtaaggtgtc caacaaggcc ctccccgctc ccatcgaaaa gaccatctca     300

aaggcaaagg ggcaaccaag ggaacctcaa gtgtacaccc tgcctccgtg caggaaggag     360

atgaccaaga accaggtcag cctgacttgt ctcgtgaagg gcttctatcc cagcgatatt     420

gctgtggaat gggagtcaaa tggccagccc gagaataact acaaaactac cccacccgtg     480

ctgaaatctg atgggtcctt cttcctttac tccaagctga ccgtggacaa gagccgctgg     540

caacaaggca atgtctttag ctgctcagtg atgcatgagg ctctccataa tcactacact     600

cagaagtcac tgtccctgtc tccgggtaaa                                      630
```

<210> 187
<211> 963
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 187

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacggg     180

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag     240

gagtacaagt gcaaggtgtc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc     300
```

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc 660

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 720

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 780

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 840

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 900

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 960

ata 963

<210> 188
<211> 321
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 188

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
```

Xaa Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145 150 155 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
210 215 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
225 230 235 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
245 250 255

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
260 265 270

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
275 280 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
290 295 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305 310 315 320

Ile

<210> 189

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 189

Met Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
1 5 10 15

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
20 25 30

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala

35 40 45

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
50 55 60

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
65 70 75 80

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
85 90 95

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
100 105 110

Ile

<210> 190
<211> 342
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 190
atggcgcgca acggggacca ctgtccgctc gggcccgggc gttgctgccg tctgcacacg 60

gtccgcgcgt cgctggaaga cctgggctgg gccgattggg tgctgtcgcc acgggaggtg 120

caagtgacca tgtgcatcgg cgcgtgcccg agccagttcc gggcggcaaa catgcacgcg 180

cagatcaaga cgagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg 240

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag 300

acctatgatg acttgttagc caaagactgc cactgcatat aa 342

<210> 191
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 191
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

```
Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

<210> 192

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 192

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
```

```
     50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 193
<211> 954
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 193

```
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct      60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg     120

tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc     180

agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag     240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc     300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag     360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc     420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg     480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg     540
```

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc 660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 900

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 194

<211> 318

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 194

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
```

165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
210 215 220

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225 230 235 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
245 250 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
260 265 270

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
275 280 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
290 295 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305 310 315

<210> 195
<211> 630
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 195
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc 180

agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccggaaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 480

ctgaagtccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtaaa 630

<210> 196
<211> 963
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 196
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60
gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120
tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc 180
agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag 240
gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 360
atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420
gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480
ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600
cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc 660
gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 720
tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 780
ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 840
acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 900
accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 960
ata 963

<210> 197
<211> 321
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 197
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

```
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
    210                 215                 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
225                 230                 235                 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
                245                 250                 255

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
            260                 265                 270

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
        275                 280                 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
    290                 295                 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305                 310                 315                 320
```

Ile

<210> 198
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 198

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

<210> 199
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 199

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 200
<211> 954

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 200
ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc 180

agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgga gaccactgtc cgctcgggcc cgggcgttgc 660

tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg 720

tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 780

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 840

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 900

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 954

<210> 201
<211> 318
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 201
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg

```
     50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
    210                 215                 220

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
225                 230                 235                 240

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
                245                 250                 255

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
            260                 265                 270

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
        275                 280                 285

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
    290                 295                 300

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 202

<211> 630

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 202

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc 180

agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatg ccggaaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 480

ctgaagtccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtaaa 630

<210> 203

<211> 963

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 203

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 60

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 120

tacgtggacg gcgtggaggt gcataattgc aagacaaagc cgcgggagga gcagtacggc 180

agcacgtacc gtgtggtcag cgtctgcacc gtcctgcacc aggactggct gaatggcaag 240

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 300

aaagccaaag ggcagccccg agaaccacag gtgtgcaccc tgcccccatc ccgggaggag 360

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc 420

gccgtggagt gggagagcaa tgggcagccg gagaacaact acgacaccac gcctcccgtg 480

ctggactccg acggctcctt cttcctctat agcgacctca ccgtggacaa gagcaggtgg 540

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg 600

cagaagagcc tctccctgtc tccgggtgcg cgcgacggag accactgtcc gctcgggccc 660

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 720

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 780

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 840

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 900

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 960

ata 963

<210> 204

<211> 321

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 204

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205
```

Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
210 215 220

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
225 230 235 240

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
245 250 255

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
260 265 270

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
275 280 285

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
290 295 300

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
305 310 315 320

Ile

<210> 205

<211> 212

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 205

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1 5 10 15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
20 25 30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
35 40 45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
50 55 60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65 70 75 80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
85 90 95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
100 105 110

Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val

```
Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly Lys
    210
```

<210> 206

<211> 211

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 206

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                   10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        115                 120                 125
```

```
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly
    210
```

<210> 207

<211> 960

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 207

```
ggtggcccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg      60

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     180

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc      300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     360

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc     420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacga caccacgcct     480

cccgtgctgg actccgacgg ctccttcttc ctctatagcg acctcaccgt ggacaagagc     540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     600

tacacgcaga agagcctctc cctgtctccg ggtggagacc actgtccgct cgggcccggg     660

cgttgctgcc gtctgcacac ggtccgcgcg tcgctggaag acctgggctg ggccgattgg     720

gtgctgtcgc cacgggaggt gcaagtgacc atgtgcatcg gcgcgtgccc gagccagttc     780

cgggcggcaa acatgcacgc gcagatcaag acgagcctgc accgcctgaa gcccgacacg     840

gtgccagcgc cctgctgcgt gcccgccagc tacaatccca tggtgctcat tcaaaagacc     900

gacaccgggg tgtcgctcca gacctatgat gacttgttag ccaaagactg ccactgcata     960
```

<210> 208

<211> 320
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 208

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
    210                 215                 220

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
225                 230                 235                 240

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
```

```
Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
                245                 250                 255

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
            260                 265                 270

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
        275                 280                 285

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val
    290                 295                 300

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315                 320
```

<210> 209

<211> 636

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 209

```
ggtggcccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg       60

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      180

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc       300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      360

aaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc      420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      480

cccgtgctga agtccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc      540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      600

tacacgcaga agagcctctc cctgtctccg ggtaaa                                 636
```

<210> 210

<211> 969

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 210

```
ggtggcccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg       60
```

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 180

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 360

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacga caccacgcct 480

cccgtgctgg actccgacgg ctccttcttc ctctatagcg acctcaccgt ggacaagagc 540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 600

tacacgcaga agagcctctc cctgtctccg ggtgcgcgcg acggagacca ctgtccgctc 660

gggcccgggc gttgctgccg tctgcacacg gtccgcgcgt cgctggaaga cctgggctgg 720

gccgattggg tgctgtcgcc acgggaggtg caagtgacca tgtgcatcgg cgcgtgcccg 780

agccagttcc gggcggcaaa catgcacgcg cagatcaaga cgagcctgca ccgcctgaag 840

cccgacacgg tgccagcgcc ctgctgcgtg cccgccagct acaatcccat ggtgctcatt 900

caaaagaccg acaccggggt gtcgctccag acctatgatg acttgttagc caaagactgc 960

cactgcata 969

<210> 211

<211> 323

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 211

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
```

100 105 110

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
115 120 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
130 135 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145 150 155 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
165 170 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
180 185 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
195 200 205

Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg
210 215 220

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
225 230 235 240

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
245 250 255

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
260 265 270

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
275 280 285

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
290 295 300

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
305 310 315 320

His Cys Ile

<210> 212
<211> 212
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 212

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1 5 10 15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
20 25 30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
35 40 45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
50 55 60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65 70 75 80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
85 90 95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
100 105 110

Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val
115 120 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
130 135 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
145 150 155 160

Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
165 170 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
180 185 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
195 200 205

Ser Pro Gly Lys
210

<210> 213
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 213

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1 5 10 15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
20 25 30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
35 40 45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
50 55 60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65 70 75 80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
85 90 95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
100 105 110

Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
115 120 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
130 135 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145 150 155 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
165 170 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
180 185 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
195 200 205

Ser Pro Gly
210

<210> 214
<211> 960
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 214
ggtggcccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg 60

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 180

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt gcaccctgcc cccatcccgg 360

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacga caccacgcct 480

cccgtgctgg actccgacgg ctccttcttc ctctatagcg acctcaccgt ggacaagagc 540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 600

tacacgcaga agagcctctc cctgtctccg ggtggagacc actgtccgct cgggcccggg 660

cgttgctgcc gtctgcacac ggtccgcgcg tcgctggaag acctgggctg ggccgattgg 720

gtgctgtcgc cacgggaggt gcaagtgacc atgtgcatcg gcgcgtgccc gagccagttc 780

cgggcggcaa acatgcacgc gcagatcaag acgagcctgc accgcctgaa gcccgacacg 840

gtgccagcgc cctgctgcgt gcccgccagc tacaatccca tggtgctcat tcaaaagacc 900

gacaccgggg tgtcgctcca gacctatgat gacttgttag ccaaagactg ccactgcata 960

<210> 215

<211> 320

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 215

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110
```

```
Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
    210                 215                 220

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
225                 230                 235                 240

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
                245                 250                 255

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
            260                 265                 270

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
        275                 280                 285

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val
    290                 295                 300

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315                 320
```

<210> 216

<211> 636

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 216

```
ggtggcccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg        60

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       180
```

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatgccgg 360

aaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 480

cccgtgctga agtccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc 540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 600

tacacgcaga agagcctctc cctgtctccg ggtaaa 636

<210> 217
<211> 969
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 217
ggtggcccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg 60

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 120

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 180

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 240

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 300

atctccaaag ccaaagggca gccccgagaa ccacaggtgt gcaccctgcc cccatcccgg 360

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 420

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacga caccacgcct 480

cccgtgctgg actccgacgg ctccttcttc ctctatagcg acctcaccgt ggacaagagc 540

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 600

tacacgcaga agagcctctc cctgtctccg ggtgcgcgcg acggagacca ctgtccgctc 660

gggcccgggc gttgctgccg tctgcacacg gtccgcgcgt cgctggaaga cctgggctgg 720

gccgattggg tgctgtcgcc acgggaggtg caagtgacca tgtgcatcgg cgcgtgcccg 780

agccagttcc gggcggcaaa catgcacgcg cagatcaaga cgagcctgca ccgcctgaag 840

cccgacacgg tgccagcgcc ctgctgcgtg cccgccagct acaatcccat ggtgctcatt 900

caaaagaccg acaccggggt gtcgctccag acctatgatg acttgttagc caaagactgc 960

cactgcata 969

<210> 218
<211> 323
<212> PRT
<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 218

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg
    210                 215                 220

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
225                 230                 235                 240

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
                245                 250                 255

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
```

260 265 270

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
275 280 285

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
290 295 300

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
305 310 315 320

His Cys Ile

<210> 219
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 219
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
50 55 60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65 70 75 80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
85 90 95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
100 105 110

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
115 120 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
130 135 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
145 150 155 160

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
165 170 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
180 185 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
195 200 205

Pro Gly Lys
210

<210> 220
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 220
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
50 55 60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65 70 75 80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
85 90 95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
100 105 110

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
115 120 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
130 135 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145 150 155 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
165 170 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

180 185 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
195 200 205

Pro Gly
210

<210> 221

<211> 957

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 221

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 60

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 120

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 180

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 240

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 300

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 360

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 420

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 480

gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 540

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 600

acgcagaaga gcctctccct gtctccgggt ggagaccact gtccgctcgg gcccgggcgt 660

tgctgccgtc tgcacacggt ccgcgcgtcg ctggaagacc tgggctgggc cgattgggtg 720

ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg 780

gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 840

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 900

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 957

<210> 222

<211> 319

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 222

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

[illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
50 55 60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65 70 75 80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
85 90 95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
100 105 110

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
115 120 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
130 135 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145 150 155 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
165 170 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
180 185 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
195 200 205

Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
210 215 220

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
225 230 235 240

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
245 250 255

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
260 265 270

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
275 280 285

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
290 295 300

290 295 300

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305 310 315

<210> 223

<211> 633

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 223

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 60

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 120

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 180

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 240

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 300

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccggaag 360

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 420

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 480

gtgctgaagt ccgacggctc cttcttcctc tatagcaagc tcaccgtgga caagagcagg 540

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 600

acgcagaaga gcctctccct gtctccgggt aaa 633

<210> 224

<211> 1032

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 224

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 420

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg 540

cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660

cactacacgc agaagagcct ctccctgtct ccgggtgcgc gcgacggaga ccactgtccg 720

ctcgggcccg ggcgttgctg ccgtctgcac acggtccgcg cgtcgctgga agacctgggc 780

tgggccgatt gggtgctgtc gccacgggag gtgcaagtga ccatgtgcat cggcgcgtgc 840

ccgagccagt tccgggcggc aaacatgcac gcgcagatca agacgagcct gcaccgcctg 900

aagcccgaca cggtgccagc gccctgctgc gtgcccgcca gctacaatcc catggtgctc 960

attcaaaaga ccgacaccgg ggtgtcgctc cagacctatg atgacttgtt agccaaagac 1020

tgccactgca ta 1032

<210> 225
<211> 322
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 225

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
50 55 60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65 70 75 80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
85 90 95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
100 105 110

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
115 120 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

130 135 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145 150 155 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
165 170 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
180 185 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
195 200 205

Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
210 215 220

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
225 230 235 240

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
245 250 255

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
260 265 270

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
275 280 285

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
290 295 300

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
305 310 315 320

Cys Ile

<210> 226

<211> 211

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 226

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
50 55 60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65 70 75 80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
85 90 95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
100 105 110

Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser
115 120 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
130 135 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
145 150 155 160

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
165 170 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
180 185 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
195 200 205

Pro Gly Lys
210

<210> 227

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 227

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1 5 10 15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
20 25 30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
35 40 45

```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145                 150                 155                 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly
    210
```

<210> 228

<211> 1023

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 228

```
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg   60
cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc   120
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag   180
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag   240
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg   300
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa   360
accatctcca aagccaaagg gcagccccga gaaccacagg tgtgcaccct gcccccatcc   420
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc   480
```

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg 540

cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660

cactacacgc agaagagcct ctccctgtct ccgggtggag accactgtcc gctcgggccc 720

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 780

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 840

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 900

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 960

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 1020

ata 1023

<210> 229
<211> 319
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 229

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1               5                  10                  15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            20                  25                  30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        35                  40                  45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145                 150                 155                 160
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
    210                 215                 220

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
225                 230                 235                 240

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
                245                 250                 255

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
            260                 265                 270

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
        275                 280                 285

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
    290                 295                 300

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
305                 310                 315
```

<210> 230

<211> 633

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 230

```
ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc       60

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac      120

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac      180

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc      240

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc      300

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atgccggaag      360

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac      420

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc      480

gtgctgaagt ccgacggctc cttcttcctc tatagcaagc tcaccgtgga caagagcagg      540

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac      600
```

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 600

acgcagaaga gcctctccct gtctccgggt aaa 633

<210> 231
<211> 966
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 231
ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 60

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 120

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 180

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 240

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 300

tccaaagcca aagggcagcc ccgagaacca caggtgtgca ccctgccccc atcccgggag 360

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 420

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 480

gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 540

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 600

acgcagaaga gcctctccct gtctccgggt gcgcgcgacg gagaccactg tccgctcggg 660

cccgggcgtt gctgccgtct gcacacggtc cgcgcgtcgc tggaagacct gggctgggcc 720

gattgggtgc tgtcgccacg ggaggtgcaa gtgaccatgt gcatcggcgc gtgcccgagc 780

cagttccggg cggcaaacat gcacgcgcag atcaagacga gcctgcaccg cctgaagccc 840

gacacggtgc cagcgccctg ctgcgtgccc gccagctaca atcccatggt gctcattcaa 900

aagaccgaca ccggggtgtc gctccagacc tatgatgact tgttagccaa agactgccac 960

tgcata 966

<210> 232
<211> 322
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 232
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1 5 10 15

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            20                  25                  30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        35                  40                  45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
145                 150                 155                 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys
    210                 215                 220

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
225                 230                 235                 240

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
                245                 250                 255

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
            260                 265                 270

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
        275                 280                 285

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
    290                 295                 300

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
305                 310                 315                 320
```

Cys Ile

<210> 233
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 233

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 234
<211> 984
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 234
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgaccacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcaacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 235
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 235
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asn Gly Asp His Cys Pro
    210                 215                 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225                 230                 235                 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
                245                 250                 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
            260                 265                 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
        275                 280                 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
    290                 295                 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 236
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 236

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 237
<211> 1044

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 237
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgaccacc 360

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

tccggaggcg gtggaagcgg aggtggtgga tctggaggcg gtggaagcgc gcgcaacgga 720

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 780

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 840

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 900

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 960

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 1020

ttagccaaag actgccactg cata 1044

<210> 238
<211> 348
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 238
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Arg Asn Gly
225 230 235 240

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
245 250 255

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
260 265 270

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
275 280 285

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
290 295 300

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
305 310 315 320

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr

325 330 335

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
340 345

<210> 239

<211> 996

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 239

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgaccacc 360

ctgccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg aggtggtgga 660

gcgcgcaacg gagaccactg tccgctcggg cccgggcgtt gctgccgtct gcacacggtc 720

cgcgcgtcgc tggaagacct gggctgggcc gattgggtgc tgtcgccacg ggaggtgcaa 780

gtgaccatgt gcatcggcgc gtgcccgagc cagttccggg cggcaaacat gcacgcgcag 840

atcaagacga gcctgcaccg cctgaagccc gacacggtgc cagcgccctg ctgcgtgccc 900

gccagctaca atcccatggt gctcattcaa aagaccgaca ccggggtgtc gctccagacc 960

tatgatgact tgttagccaa agactgccac tgcata 996

<210> 240

<211> 332

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 240

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ala Arg Asn Gly
    210                 215                 220

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
225                 230                 235                 240

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
                245                 250                 255

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
            260                 265                 270

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
        275                 280                 285

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
    290                 295                 300
```

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
305 310 315 320

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
325 330

<210> 241

<211> 2145

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 241

gatgcacaca agagtgaggt tgctcatcga tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc ggccagtcag 1740

gccgccttag gcttaggatc cgccgctcag gctgcacagc aagcagccca agcagctcag 1800

cagggaagcg cgcgcgacgg agaccactgt ccgctcgggc ccgggcgttg ctgccgtctg 1860

cacacggtcc gcgcgtcgct ggaagacctg ggctgggccg attgggtgct gtcgccacgg 1920

gaggtgcaag tgaccatgtg catcggcgcg tgcccgagcc agttccgggc ggcaaacatg 1980

cacgcgcaga tcaagacgag cctgcaccgc ctgaagcccg acacggtgcc agcgccctgc 2040

tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg 2100

ctccagacct atgatgactt gttagccaaa gactgccact gcata 2145

<210> 242
<211> 715
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 242

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg

145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Ala Ala Gln Ala Ala
580 585 590

Gln Gln Ala Ala Gln Ala Ala Gln Gln Gly Ser Ala Arg Asp Gly Asp
595 600 605

His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg
610 615 620

Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg
625 630 635 640

Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg
645 650 655

Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys
660 665 670

Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro
675 680 685

Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr
690 695 700

Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 243

<211> 339

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 243

```
Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1               5                  10                  15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
                165                 170                 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg
225                 230                 235                 240

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
                245                 250                 255

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
            260                 265                 270
```

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
275 280 285

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
290 295 300

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
305 310 315 320

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
325 330 335

His Cys Ile

<210> 244
<211> 1017
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 244
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt 60

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 120

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 240

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 300

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 360

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 540

gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660

acgcagaaga gcctctccct gtctccgggt ggagaccact gtccgctcgg gcccgggcgt 720

tgctgccgtc tgcacacggt ccgcgcgtcg ctggaagacc tgggctgggc cgattgggtg 780

ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg 840

gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 900

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 960

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 1017

<210> 245
<211> 231
<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 245

```
Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1               5                  10                  15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 246

<211> 693

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 246
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt 60

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 120

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 240

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 300

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 360

tccaaagcca agggcagccc cgagaacca caggtgtaca ccctgccccc atcccggaag 420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 540

gtgctgaagt ccgacggctc cttcttcctc tatagcaagc tcaccgtgga caagagcagg 600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660

acgcagaaga gcctctccct gtctccgggt aaa 693

<210> 247
<211> 342
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 247
Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp

85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly
225 230 235 240

Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp
245 250 255

Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr
260 265 270

Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His
275 280 285

Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro
290 295 300

Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln
305 310 315 320

Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala
325 330 335

Lys Asp Cys His Cys Ile
340

<210> 248

<211> 1026

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 248

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt 60

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 120

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 240

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 300

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 360

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 540

gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660

acgcagaaga gcctctccct gtctccgggt gcgcgcgacg gagaccactg tccgctcggg 720

cccgggcgtt gctgccgtct gcacacggtc cgcgcgtcgc tggaagacct gggctgggcc 780

gattgggtgc tgtcgccacg ggaggtgcaa gtgaccatgt gcatcggcgc gtgcccgagc 840

cagttccggg cggcaaacat gcacgcgcag atcaagacga gcctgcaccg cctgaagccc 900

gacacggtgc cagcgccctg ctgcgtgccc gccagctaca atcccatggt gctcattcaa 960

aagaccgaca ccggggtgtc gctccagacc tatgatgact tgttagccaa agactgccac 1020

tgcata 1026

<210> 249

<211> 339

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 249

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
50 55 60

50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro Gly Arg
225 230 235 240

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
245 250 255

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
260 265 270

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
275 280 285

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
290 295 300

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
305 310 315 320

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
325 330 335

His Cys Ile

<210> 250
<211> 1017
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 250
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt 60
ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 120
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 180
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 240
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 300
aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc 360
tccaaagcca aagggcagcc ccgagaacca caggtgtgca ccctgccccc atcccgggag 420
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 540
gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 600
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660
acgcagaaga gcctctccct gtctccgggt ggagaccact gtccgctcgg gcccgggcgt 720
tgctgccgtc tgcacacggt ccgcgcgtcg ctggaagacc tgggctgggc cgattgggtg 780
ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg 840
gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 900
ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 960
accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 1017

<210> 251
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 251
Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 252

<211> 693

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 252

```
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt      60

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc     120

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac     180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac     240
```

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 300

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag cccccatcga gaaaaccatc 360

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atgccggaag 420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 540

gtgctgaagt ccgacggctc cttcttcctc tatagcaagc tcaccgtgga caagagcagg 600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660

acgcagaaga gcctctccct gtctccgggt aaa 693

<210> 253

<211> 342

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 253

```
Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1               5                  10                  15

Val His Ser Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr

65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160
```

```
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
                165                 170                 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro Leu Gly
225                 230                 235                 240

Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp
                245                 250                 255

Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr
            260                 265                 270

Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His
        275                 280                 285

Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro
    290                 295                 300

Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln
305                 310                 315                 320

Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala
                325                 330                 335

Lys Asp Cys His Cys Ile
            340
```

<210> 254

<211> 1026

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 254

```
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa cgactggtgt ccactccggt      60

ggcccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc     120

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac     180

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac     240

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc     300

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc     360
```

tccaaagcca aagggcagcc ccgagaacca caggtgtgca ccctgccccc atcccgggag 420

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 480

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacgacac cacgcctccc 540

gtgctggact ccgacggctc cttcttcctc tatagcgacc tcaccgtgga caagagcagg 600

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 660

acgcagaaga gcctctccct gtctccgggt gcgcgcgacg gagaccactg tccgctcggg 720

cccgggcgtt gctgccgtct gcacacggtc cgcgcgtcgc tggaagacct gggctgggcc 780

gattgggtgc tgtcgccacg ggaggtgcaa gtgaccatgt gcatcggcgc gtgcccgagc 840

cagttccggg cggcaaacat gcacgcgcag atcaagacga gcctgcaccg cctgaagccc 900

gacacggtgc cagcgccctg ctgcgtgccc gccagctaca atcccatggt gctcattcaa 960

aagaccgaca ccggggtgtc gctccagacc tatgatgact tgttagccaa agactgccac 1020

tgcata 1026

<210> 255
<211> 341
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 255

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140
```

```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
225                 230                 235                 240

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
                245                 250                 255

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
            260                 265                 270

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
        275                 280                 285

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
    290                 295                 300

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
305                 310                 315                 320

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
                325                 330                 335

Asp Cys His Cys Ile
            340
```

<210> 256

<211> 1023

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 256

```
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg      60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc     120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag     180
```

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 420

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg 540

cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660

cactacacgc agaagagcct ctccctgtct ccgggtggag accactgtcc gctcgggccc 720

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 780

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 840

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 900

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 960

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 1020

ata 1023

<210> 257

<211> 233

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 257

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110
```

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 258

<211> 699

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 258

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 420

cggaaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 540

cctcccgtgc tgaagtccga cggctccttc ttcctctata gcaagctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660

cactacacgc agaagagcct ctccctgtct ccgggtaaa 699

<210> 259

<211> 344

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 259

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro

225                 230                 235                 240
```

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
245 250 255

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
260 265 270

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
275 280 285

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
290 295 300

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
305 310 315 320

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
325 330 335

Leu Ala Lys Asp Cys His Cys Ile
340

<210> 260

<211> 1032

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 260

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 420

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg 540

cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660

cactacacgc agaagagcct ctccctgtct ccgggtgcgc gcgacggaga ccactgtccg 720

ctcgggcccg ggcgttgctg ccgtctgcac acggtccgcg cgtcgctgga agacctgggc 780

tgggccgatt gggtgctgtc gccacgggag gtgcaagtga ccatgtgcat cggcgcgtgc 840

ccgagccagt tccgggcggc aaacatgcac gcgcagatca agacgagcct gcaccgcctg 900

aagcccgaca cggtgccagc gccctgctgc gtgcccgcca gctacaatcc catggtgctc 960

attcaaaaga ccgacaccgg ggtgtcgctc cagacctatg atgacttgtt agccaaagac 1020

tgccactgca ta 1032

<210> 261

<211> 341

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 261

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205
```

```
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
225                 230                 235                 240

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
                245                 250                 255

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
            260                 265                 270

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
        275                 280                 285

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
    290                 295                 300

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
305                 310                 315                 320

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
                325                 330                 335

Asp Cys His Cys Ile
            340
```

<210> 262
<211> 1023
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 262

```
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg      60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc     120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag     180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag     240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg     300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa     360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtgcaccct gcccccatcc     420

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc     480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg     540

cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag     600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac     660
```

cactacacgc agaagagcct ctccctgtct ccgggtggag accactgtcc gctcgggccc 720

gggcgttgct gccgtctgca cacggtccgc gcgtcgctgg aagacctggg ctgggccgat 780

tgggtgctgt cgccacggga ggtgcaagtg accatgtgca tcggcgcgtg cccgagccag 840

ttccgggcgg caaacatgca cgcgcagatc aagacgagcc tgcaccgcct gaagcccgac 900

acggtgccag cgccctgctg cgtgcccgcc agctacaatc ccatggtgct cattcaaaag 960

accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 1020

ata 1023

<210> 263

<211> 233

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 263

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175
```

```
Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 264
<211> 699
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 264

```
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg      60

cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc     120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag     180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag     240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg     300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa     360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatgc     420

cggaaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc     480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg     540

cctcccgtgc tgaagtccga cggctccttc ttcctctata gcaagctcac cgtggacaag     600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac     660

cactacacgc agaagagcct ctccctgtct ccgggtaaa                            699
```

<210> 265
<211> 344
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 265

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15
```

```
Leu Arg Gly Ala Arg Cys Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
225                 230                 235                 240

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
                245                 250                 255

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
            260                 265                 270

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
        275                 280                 285

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
    290                 295                 300

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
```

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
305 310 315 320

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
325 330 335

Leu Ala Lys Asp Cys His Cys Ile
340

<210> 266
<211> 1032
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 266
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60
cgctgtggcc cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 120
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 180
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300
aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 360
accatctcca aagccaaagg gcagccccga gaaccacagg tgtgcaccct gccccatcc 420
cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta cgacaccacg 540
cctcccgtgc tggactccga cggctccttc ttcctctata gcgacctcac cgtggacaag 600
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 660
cactacacgc agaagagcct ctccctgtct ccgggtgcgc gcgacggaga ccactgtccg 720
ctcgggcccg ggcgttgctg ccgtctgcac acggtccgcg cgtcgctgga agacctgggc 780
tgggccgatt gggtgctgtc gccacgggag gtgcaagtga ccatgtgcat cggcgcgtgc 840
ccgagccagt tccgggcggc aaacatgcac gcgcagatca agacgagcct gcaccgcctg 900
aagcccgaca cggtgccagc gccctgctgc gtgcccgcca gctacaatcc catggtgctc 960
attcaaaaga ccgacaccgg ggtgtcgctc cagacctatg atgacttgtt agccaaagac 1020
tgccactgca ta 1032

<210> 267
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 267

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu

    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 268

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 268

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met

        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 269

<211> 325

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 269

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
210 215 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225 230 235 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
245 250 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
260 265 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
275 280 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
290 295 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305 310 315 320

Asp Cys His Cys Ile
325

<210> 270
<211> 975
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 270
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag 180
ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtctgcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480
tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660
ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720
ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780
tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840
ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900
ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960
gactgccact gcata 975

<210> 271
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 271

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag     180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtctgcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc     360

ctgccccccat cccggaagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa     420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac     480

tacaagacca cgcctcccgt gctgaagtcc gacggctcct tcttcctcta tagcaagctc     540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag     600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a              651
```

<210> 272
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 272

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
210 215 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225 230 235 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
245 250 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
260 265 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
275 280 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu
290 295 300

Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305 310 315 320

Leu Ala Lys Asp Cys His Cys Ile
325

<210> 273

<211> 984

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 273

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtcctgcac cgtcctgcac 240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 360

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga 660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg 720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc 780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 960

ttagccaaag actgccactg cata 984

<210> 274
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 274

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 275

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 275

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160
```

145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 276

<211> 325

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 276

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Gly Asp His Cys Pro Leu Gly Pro
210 215 220

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
225 230 235 240

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
245 250 255

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
260 265 270

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
275 280 285

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
290 295 300

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
305 310 315 320

Asp Cys His Cys Ile
325

<210> 277
<211> 975
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 277
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag 180
ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtctgcac cgtcctgcac 240
caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 300
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc 360
ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 420
ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc 540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgg agaccactgt 660

ccgctcgggc ccgggcgttg ctgccgtctg cacacggtcc gcgcgtcgct ggaagacctg 720

ggctgggccg attgggtgct gtcgccacgg gaggtgcaag tgaccatgtg catcggcgcg 780

tgcccgagcc agttccgggc ggcaaacatg cacgcgcaga tcaagacgag cctgcaccgc 840

ctgaagcccg acacggtgcc agcgccctgc tgcgtgcccg ccagctacaa tcccatggtg 900

ctcattcaaa agaccgacac cggggtgtcg ctccagacct atgatgactt gttagccaaa 960

gactgccact gcata 975

<210> 278
<211> 651
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 278
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag 180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtctgcac cgtgctccac 240

caggactggc ttaatgggaa ggaatacaag tgtaaggtgt ccaacaaggc ctccccgct 300

cccatcgaaa agaccatctc aaaggcaaag gggcaaccaa gggaacctca agtgtacacc 360

ctgcctccgt gcaggaagga gatgaccaag aaccaggtca gcctgacttg tctcgtgaag 420

ggcttctatc ccagcgatat tgctgtggaa tgggagtcaa atggccagcc cgagaataac 480

tacaaaacta ccccacccgt gctgaaatct gatgggtcct tcttccttta ctccaagctg 540

accgtggaca agagccgctg gcaacaaggc aatgtcttta gctgctcagt gatgcatgag 600

gctctccata atcactacac tcagaagtca ctgtccctgt ctccgggtaa a 651

<210> 279
<211> 328
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 279

Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
1				5					10					15	

- - -- --

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Ala Arg Asp Gly Asp His Cys Pro
210 215 220

Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu
225 230 235 240

Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln
245 250 255

Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn
260 265 270

Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr
275 280 285

Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu

290 295 300

```
Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu
305                 310                 315                 320

Leu Ala Lys Asp Cys His Cys Ile
                325
```

<210> 280

<211> 984

<212> DNA

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 280

```
gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc      60

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac     120

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataattg caagacaaag     180

ccgcgggagg agcagtacgg cagcacgtac cgtgtggtca gcgtctgcac cgtcctgcac     240

caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc     300

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtgcacc     360

ctgccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa     420

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac     480

tacgacacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcgacctc     540

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag     600

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtgc gcgcgacgga     660

gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg     720

gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc     780

atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc     840

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat     900

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg     960

ttagccaaag actgccactg cata                                            984
```

<210> 281

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 281

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 282

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 282

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15
```

```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 283

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 283

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 284

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 284

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45
```

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Glu Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 285

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 285

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 286

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 286

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Lys Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 287

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 287

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
115 120 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 288

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 288

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

```
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 289

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 289

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110
```

```
Pro Arg Glu Pro Gln Val Tyr Thr Cys Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 290

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 290

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met
        115                 120                 125
```

```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 291

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 291

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                   10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Cys Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Cys Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215
```

<210> 292

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 292

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160
```

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly

<210> 293
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 293
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
50 55 60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65 70 75 80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
85 90 95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
100 105 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
115 120 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145 150 155 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
165 170 175

```
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 294

<211> 226

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 294

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
```

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly
225
```

<210> 295
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 295

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                   10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190
```

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly

<210> 296

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 296

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1 5 10 15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
20 25 30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
35 40 45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
50 55 60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65 70 75 80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
85 90 95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
100 105 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
115 120 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
130 135 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145 150 155 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
165 170 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
180 185 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
195 200 205

Gly

<210> 297
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 297

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 298
<211> 209
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 298

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Cys Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Cys Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly
```

<210> 299

<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 299

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly
    210
```

<210> 300

<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 300

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly
    210
```

<210> 301
<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 301

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1               5                  10                  15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            20                  25                  30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        35                  40                  45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

145                 150                 155                 160

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly
    210
```

<210> 302

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 302

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1               5                  10                  15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            20                  25                  30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        35                  40                  45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Tyr Thr Leu Pro Pro Cys Arg Lys Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
145                 150                 155                 160

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly
    210
```

<210> 303

<211> 212

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 303

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1               5                  10                  15

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            20                  25                  30

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        35                  40                  45

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    50                  55                  60

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
65                  70                  75                  80

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                85                  90                  95

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            100                 105                 110

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        115                 120                 125

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    130                 135                 140

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
145                 150                 155                 160

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                165                 170                 175

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            180                 185                 190

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        195                 200                 205

Ser Pro Gly Lys
    210
```

<210> 304

<211> 211

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 304

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
1               5                  10                  15

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            20                  25                  30

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        35                  40                  45

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    50                  55                  60

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
65                  70                  75                  80

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                85                  90                  95

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            100                 105                 110

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        115                 120                 125

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    130                 135                 140

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
145                 150                 155                 160

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                165                 170                 175

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            180                 185                 190

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        195                 200                 205

Pro Gly Lys
    210
```

<210> 305

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 305

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
1               5                  10                  15

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            20                  25                  30

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        35                  40                  45

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    50                  55                  60

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
65                  70                  75                  80

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

                85                  90                  95

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            100                 105                 110

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        115                 120                 125

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    130                 135                 140

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
145                 150                 155                 160

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

                165                 170                 175

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            180                 185                 190

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        195                 200                 205

Gly Lys
    210
```

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO9906445A [0007]
- WO2010048670A [0007]
- WO2006000448A [0007]
- WO2011064758A [0007]
- US2012032415W [0011]
- US2013023465W [0011]
- WO9420069A [0334]
- WO9315722A [0337]
- US3773919A [0338]
- EP0058481A [0338]
- EP0133988A [0338]
- EP0036676A [0338]
- EP0088046A [0338]
- EP0143949A [0338]
- WO61860723A [0378]

Non-patent literature cited in the description

- **BOOTCOV MR**Proc Natl Acad Sci, 1997, vol. 94, 11514-9 [0002]
- **HROMAS R**Biochim Biophys Acta, 1997, vol. 1354, 40-4 [0002]
- **LAWTON LN**Gene, 1997, vol. 203, 17-26 [0002]
- **PARALKAR VM**J Biol Chem., 1998, vol. 273, 13760-7 [0002]
- **BAEK SJ**J Biol Chem., 2001, vol. 276, 33384-92 [0002]
- **BOTTNER M**Gene, 1999, vol. 237, 105-11 [0003] [0004]
- **KATOH M**Int J Mol Med., 2006, vol. 17, 951-5 [0003]
- **BAUSKIN AR**EMBO J, 2000, vol. 19, 2212-20 [0004]
- **MOORE AG**J Clin Endocrinol Metab, 2000, vol. 85, 4781-4788 [0006]
- **TANNO T**Nat Med, 2007, vol. 13, 1096-101 [0006]
- **ZIMMERMANN MB**Am J Clin Nutr, 2008, vol. 88, 1026-31 [0006]
- **TAMARY H**Blood, 2008, vol. 112, 5241-4 [0006]
- **KEMPF T**Circ Res., 2006, vol. 98, 351-60 [0006]

- **XU J**Circ Res., 2006, vol. 98, 342-50 [0006]
- **STRELAU J**J Neurasci., 2009, vol. 29, 13640-8 [0006]
- **JOHNEN H**Nat Med., 2007, vol. 11, 1333-40 [0006]
- **BAEK SJ**Gastroenterology, 2006, vol. 131, 1553-60 [0006]
- **CEKANOVA M**Cancer Prev Res, 2009, vol. 2, 450-8 [0006]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press19890000 [0012]
- Current Protocols in Molecular BiologyGreen Publishers Inc. and Wiley and Sons19940000 [0012]
- Computational Molecular BiologyOxford University Press19880000 [0048]
- Biocomputing Informatics and Genome ProjectsAcademic Press19930000 [0048]
- Computer Analysis of Sequence DataHumana Press19940000 [0048]
- **HEINJE, G.**Sequence Analysis in Molecular BiologyAcademic Press19870000 [0048]
- Sequence Analysis PrimerStockton Press19910000 [0048]
- **CARILLO et al.**SIAM J. Applied Math., 1988, vol. 48, 1073- [0048]
- **DEVEREUX et al.**Nucl. Acid Res., 1984, vol. 12, 387- [0049]
- Genetics Computer GroupUniversity of Wisconsin [0049]
- **DAYHOFF et al.**Atlas of Protein Sequence, and Structure19780000vol. 5, 345-352 [0049]
- **HENIKOFF et al.**Proc. Natl. Acad. Sci. U.S.A., 1992, vol. 89, 10915-10919 [0049]
- **NEEDLEMAN et al.**J. Mol, Biol, 1970, vol. 48, 443-13 [0050]
- **ELLISON et al.**Nucleic Acids Res., 1982, vol. 10, 4071-9 [0057]
- **DEISENHOFER J**Biochem, 1981, vol. 20, 2361-2370 [0067]
- **HUBER R**Behring Inst Mitt, 1984, vol. 76, 1-14 [0067]
- **ROUX KH**Int Arch Allergy Immunol, 1999, vol. 120, 85-99 [0067]
- **PAPADEA C**Crit Rev Clin Lab Sci, 1989, vol. 27, 27-58 [0067]
- **MARTIN WL**Mol Cell, 2001, vol. 7, 867-877 [0067]
- **TAMM A**Int. Rev. Immunol., 1997, vol. 16, 57-85 [0156]
- **RADAEV S et al.**J. Biol. Chem., vol. 276, 16469-16477 [0156]
- **SONDERMANN, P et al.**Nature, 2000, vol. 406, 267-273 [0156]
- **CREIGHTON**PROTEINS: STRUCTURE AND MOLECULAR PROPERTIESW.H. Freeman and Company19840000 [0313]
- **SAMBROOK, J.FRITSH, E. F.MANIATIS, T.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Laboratory Press19890000 [0317]
- **VAN HEEKESCHUSTER**J. Biol. Chem., 1989, vol. 264, 5503-5509 [0319]
- **BOOTCOV MR**Proc. Natl. Acad. Sci. USA, 1997, vol. 94, 11514-9 [0326]
- **FAIRLIE WD**Gene, 2000, vol. 254, 67-76 [0326]
- REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY19950000 [0328]
- **BERGE et al.**J. Pharm. Sci., 1977, vol. 6661, 1-19 [0328]
- **LIEBERMAN et al.**PHARMACEUTICAL DOSAGE FORMS-DISPERSE SYSTEMS19980000vol. 3, [0328]
- **ANSEL et al.**PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS20000000 [0328]
- **MARTINDALE**THE EXTRA PHARMACOPEIA [0328]

- Remington's PHARMACEUTICAL SCIENCES [0328]
- The Pharmacological Basis Of Therapeutics19960000 [0328]
- **WILSONGISVOLDS**TEXTBOOK OF ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRYDelgado and Remers19980000 [0328]
- **AULTON**PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGNChurchill Livingstone19880000 [0328]
- EXTEMPORANEOUS ORAL LIQUID DOSAGE PREPARATIONSCSHP19980000 [0328]
- **WISCHKESCHWENDEMAN**Int. J. Pharm., 2008, vol. 364, 298-327 [0337]
- **FREIBERGZHU**Int. J. Pharm., 2004, vol. 282, 1-18 [0337]
- **SIDMAN et al.**Biopolymers, 1983, vol. 22, 547-56 [0338]
- **LANGER et al.**J. Biomed. Mater. Res., 1981, vol. 15, 167-277 [0338]
- **LANGER**Chem. Tech., 1982, vol. 12, 98-105 [0338]
- **EPSTEIN et al.**Proc. Natl. Acad. Sci. U.S.A., 1985, vol. 82, 3688-92 [0338]
- American Diabetes Association Standards of Medical Care in Diabetes Care-2011American Diabetes Association, Diabetes Care20100000vol. 34, S11-S61 [0350]

Patentkrav

1. Fusionsprotein, der omfatter en GDF15-region og et Fc-domæne, hvor
a) Fc-domænet omfatter sekvensen ifølge SEQ ID NO: 220, og hvor Fc-domænet er et Dh3CpmFc(-)-domæne, hvor Dh3CpmFc(-)-domænet er en sekvens med en N-terminal sekvens, der er sekvensen ifølge SEQ ID NO: 220; eller
b) Fc-domænet omfatter sekvensen ifølge SEQ ID NO: 227, og hvor Fc-domænet er et Dh3CpmFc(-)(Y349C)-domæne, hvor Dh3CpmFc(-)(Y349C)-domænet er en sekvens med en N-terminal sekvens, der er sekvensen ifølge SEQ ID NO: 227.

2. Fusionsprotein ifølge krav 1, hvor fusionsproteinet omfatter en sekvens ifølge en hvilken som helst af SEQ ID NO: 222, 225, 229 eller 232.

3. Fusionsprotein ifølge krav 1, hvor Fc-domænet af fusionsproteinet har sekvensen ifølge SEQ ID NO: 220.

4. Fusionsprotein ifølge krav 1, hvor Fc-domænet af fusionsproteinet har sekvensen ifølge SEQ ID NO: 227.

5. Fusionsprotein ifølge krav 1, hvor fusionsproteinet omfatter to eller flere Fc-domæner.

6. Dimer, der omfatter (i) en første polypeptidkæde, der omfatter en GDF15-region og et første Fc-domæne, hvor
a) Fc-domænet omfatter sekvensen ifølge SEQ ID NO: 220, og hvor Fc-domænet er et Dh3CpmFc(-)-domæne, hvor Dh3CpmFc(-)-domænet er en sekvens med en N-terminal sekvens, der er sekvensen ifølge SEQ ID NO: 220; eller
b) hvor Fc-domænet omfatter sekvensen ifølge SEQ ID NO: 227, og hvor Fc-domænet er et Dh3CpmFc(-)(Y349C)-domæne, hvor Dh3CpmFc(-)(Y349C)-domænet er en sekvens med en N-terminal sekvens, der er sekvensen ifølge SEQ ID NO: 227,
og (ii) en anden polypeptidkæde, der omfatter et andet Fc-domæne.

7. Dimer ifølge krav 6, hvor den første polypeptidkæde omfatter sekvensen ifølge en hvilken som helst af SEQ ID NO: 222, 225, 229 eller 232.

8. Dimer ifølge krav 6, hvor Fc-domænet af den første polypeptidkæde har sekvensen ifølge SEQ ID NO: 220.

9. Dimer ifølge krav 6, hvor Fc-domænet af den første polypeptidkæde har sekvensen ifølge SEQ ID NO: 227.

10. Dimer ifølge krav 6, hvor den første polypeptidkæde omfatter to eller flere Fc-domæner.

11. Dimer ifølge et hvilket som helst af kravene 6-10, hvor andet Fc-domæne omfatter en sekvens valgt fra gruppen, der består af SEQ ID NO: 16, 22, 28, 29, 33, 35, 38, 48, 85, 91, 106, 132, 141, 148, 155, 162, 169, 176, 183, 192, 199, 206, 213, 219, 220, 226, 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 og 302.

12. Dimer ifølge et hvilket som helst af kravene 6-10, hvor den første og anden polypeptidkæde er ikke-kovalent forbundet.

13. Dimer ifølge et hvilket som helst af kravene 6-10, hvor den første og anden polypeptidkæde er kovalent forbundet.

14. Dimer ifølge krav 13, hvor den første og anden polypeptidkæde er kovalent forbundet via disulfidbindinger mellem deres respektive Fc-domæner.

15. Tetramer, der omfatter (i) en første dimer og (ii) en anden dimer, hvor den første og anden dimer uafhængigt omfatter en dimer ifølge et hvilket som helst af kravene 6-14.

16. Tetramer ifølge krav 15, hvor den første polypeptidkæde af den første dimer er koblet til den første polypeptidkæde af

den anden dimer via en interkæde-disulfidbinding mellem deres respektive GDF15-regioner.

17. Fusionsprotein ifølge et hvilket som helst af kravene 1-5, dimer ifølge et hvilket som helst af kravene 6-14 eller tetramer ifølge et hvilket som helst af kravene 15-16, hvor henholdsvis GDF15-regionen eller GDF15-regionen af det første polypeptid omfatter en aminosyresekvens, der er mindst ca. 85 % identisk med SEQ ID NO: 4, 8 eller 12.

18. Fusionsprotein ifølge et hvilket som helst af kravene 1-5, dimer ifølge et hvilket som helst af kravene 6-14 eller tetramer ifølge et hvilket som helst af kravene 15-16, hvor henholdsvis GDF15-regionen eller GDF15-regionen af det første polypeptid omfatter en sekvens valgt fra gruppen, der består af SEQ ID NO: 4, 8, 12, 25, 52 og 55.

19. Fusionsprotein ifølge et hvilket som helst af kravene 1-5, dimer ifølge et hvilket som helst af kravene 6-14 eller tetramer ifølge et hvilket som helst af kravene 15-16, hvor GDF15-regionen og Fc-domænet er forbundet via en polypeptidlinker.

20. Fusionsprotein, dimer eller tetramer ifølge krav 19, hvor polypeptidlinkeren er valgt fra gruppen, der består af SEQ ID NO: 18, 30, 34, 40, 58, 61, 64, 69, 72, 75, 78, 113, 116, 119, 122, 125 og 128.

21. Fusionsprotein ifølge et hvilket som helst af kravene 1-5, dimer ifølge et hvilket som helst af kravene 6-14 eller tetramer ifølge et hvilket som helst af kravene 15-16 til anvendelse til behandling af en metabolisk forstyrrelse hos et individ, der har brug for det.

22. Fusionsprotein, dimer eller tetramer til anvendelse ifølge krav 21, hvor den metaboliske forstyrrelse er diabetes, obesitas, dyslipidæmi eller diabetisk nefropati.

DRAWINGS

Figure 1

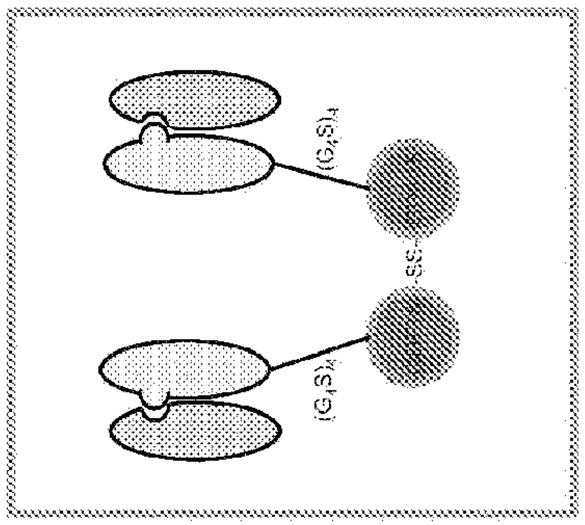


Figure 2

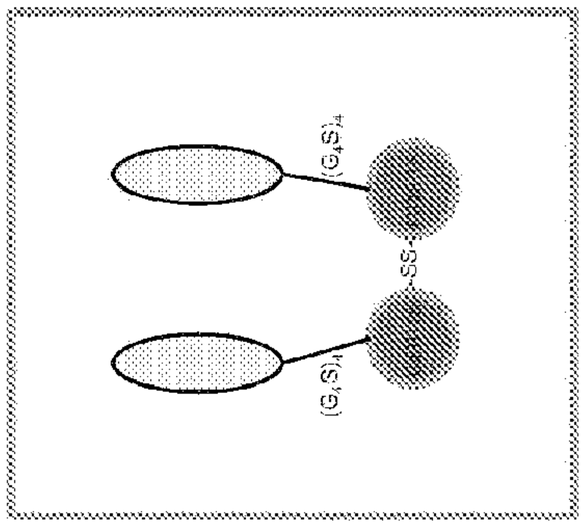
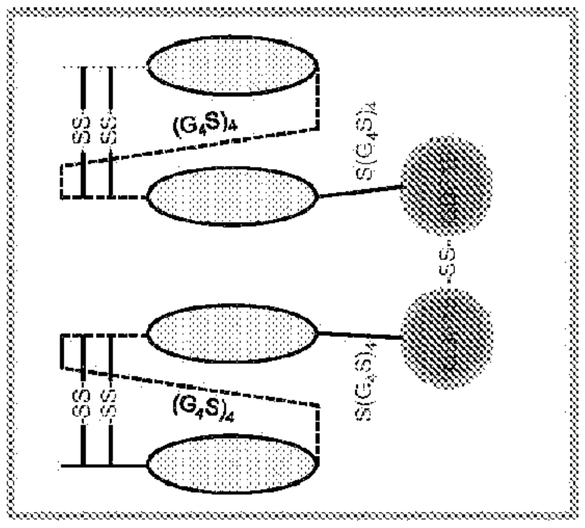


Figure 3



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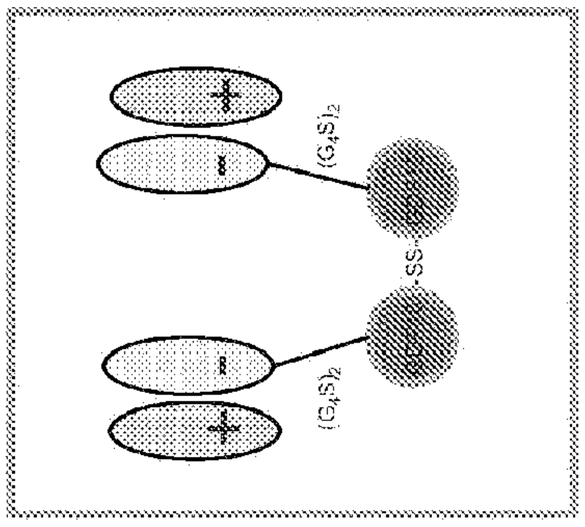

Figure 5

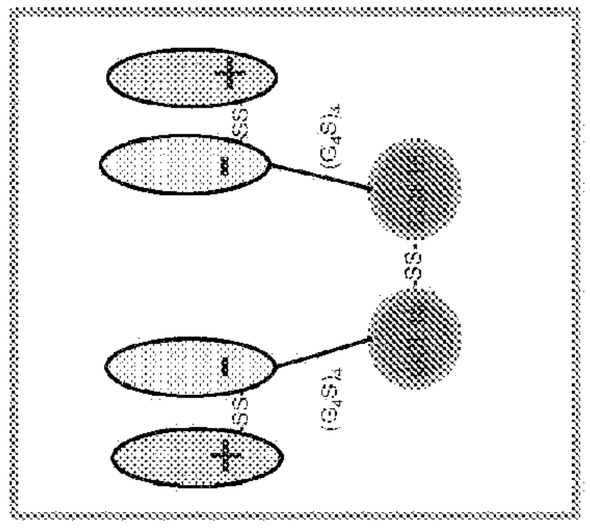

Figure 6

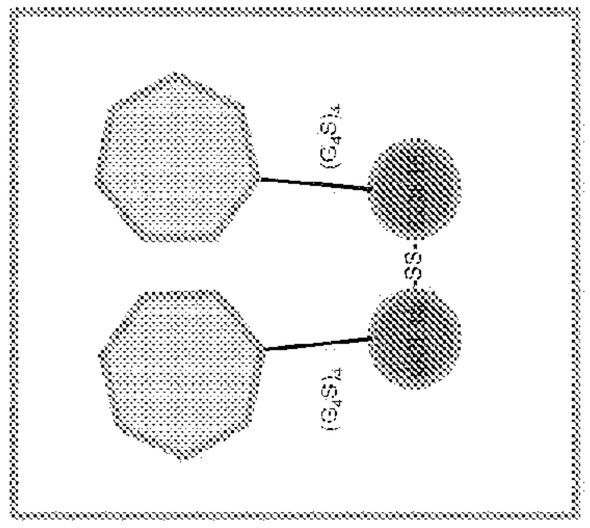

Figure 7

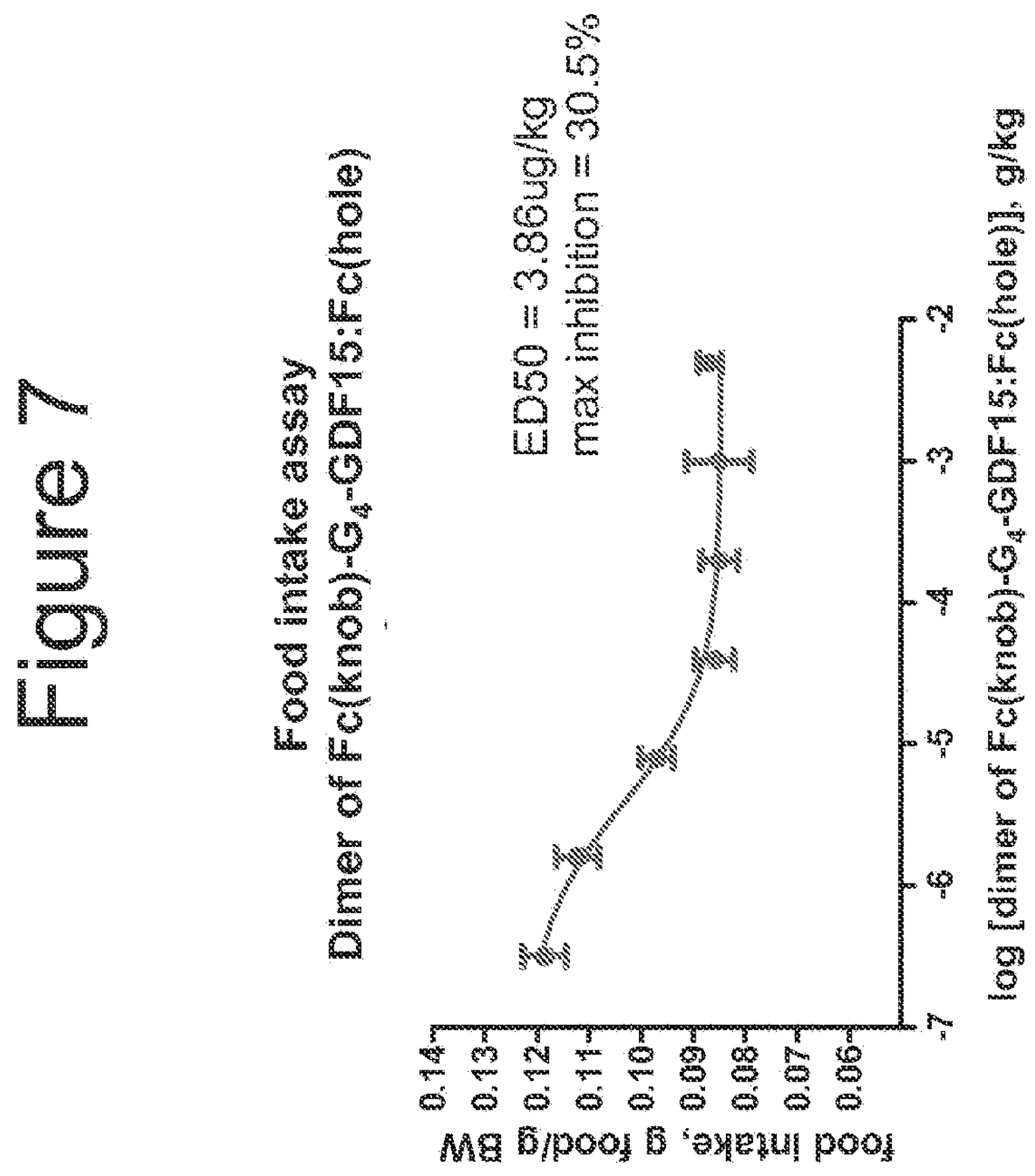
Food intake assay
Dimer of Fc(knob)-G4-GDF15:Fc(hole)
ED50 = 3.86ug/kg
max inhibition = 30.5%
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of Fc(knob)-G4-GDF15:Fc(hole)], g/kg

Figure 8

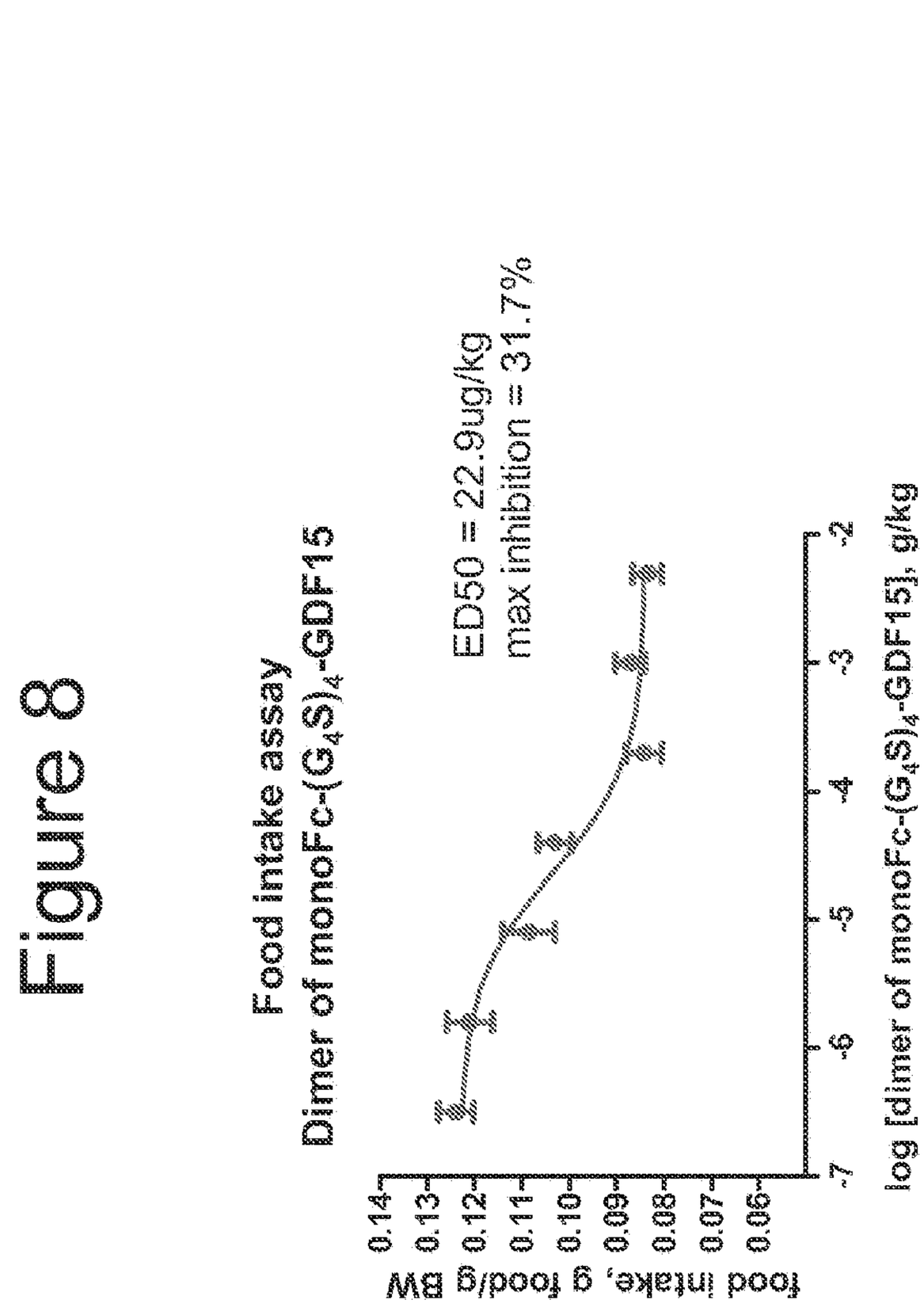
Food intake assay
Dimer of monoFc-(G4S)4-GDF15
ED50 = 22.9ug/kg
max inhibition = 31.7%
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of monoFc-(G4S)4-GDF15], g/kg

Figure 9

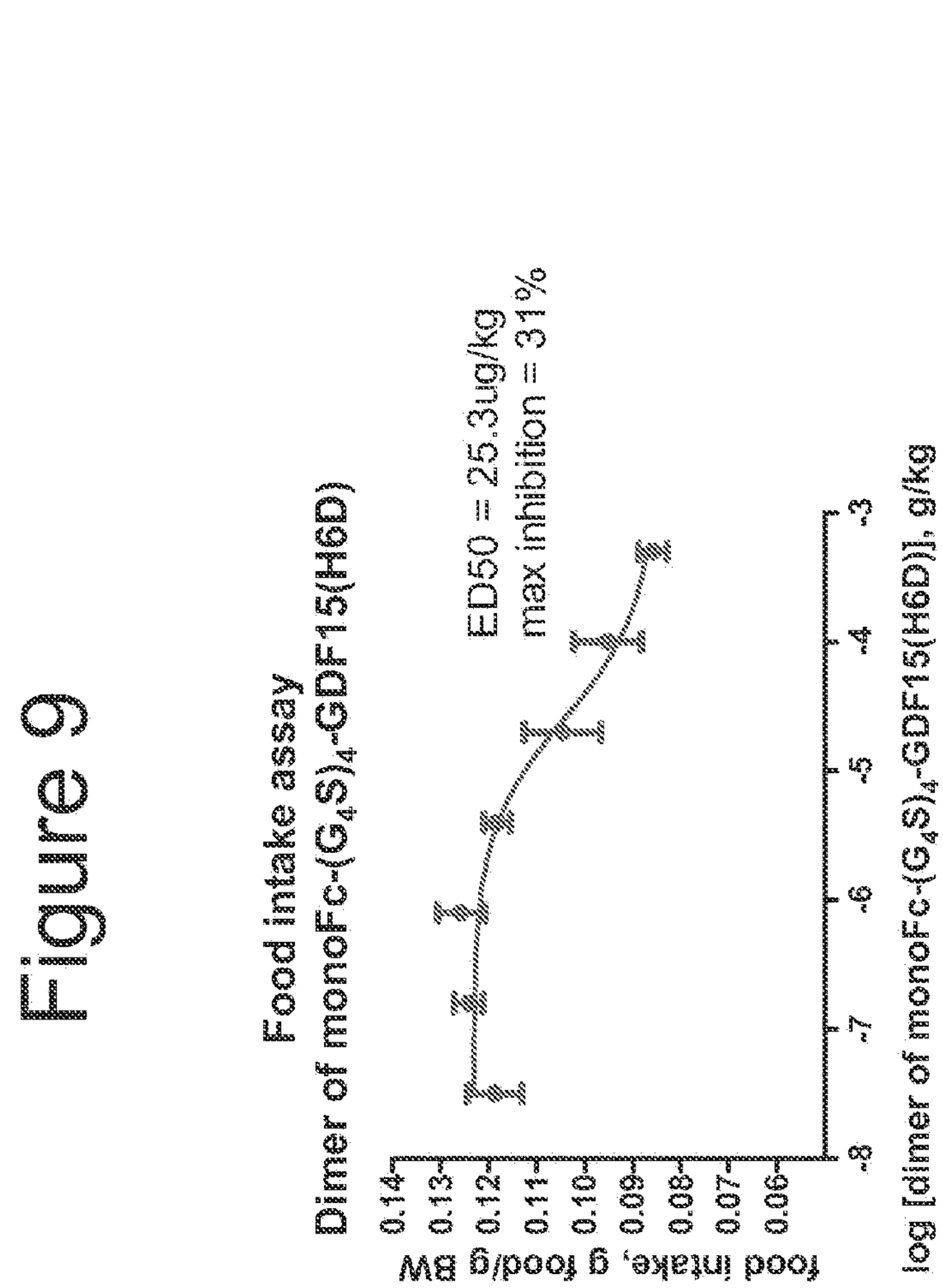
Food intake assay
Dimer of monoFc-(G4S)4-GDF15(H6D)
ED50 = 25.3ug/kg
max inhibition = 31%
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-8
-7
-6
-5
-4
-3
log [dimer of monoFc-(G4S)4-GDF15(H6D)], g/kg

Figure 10

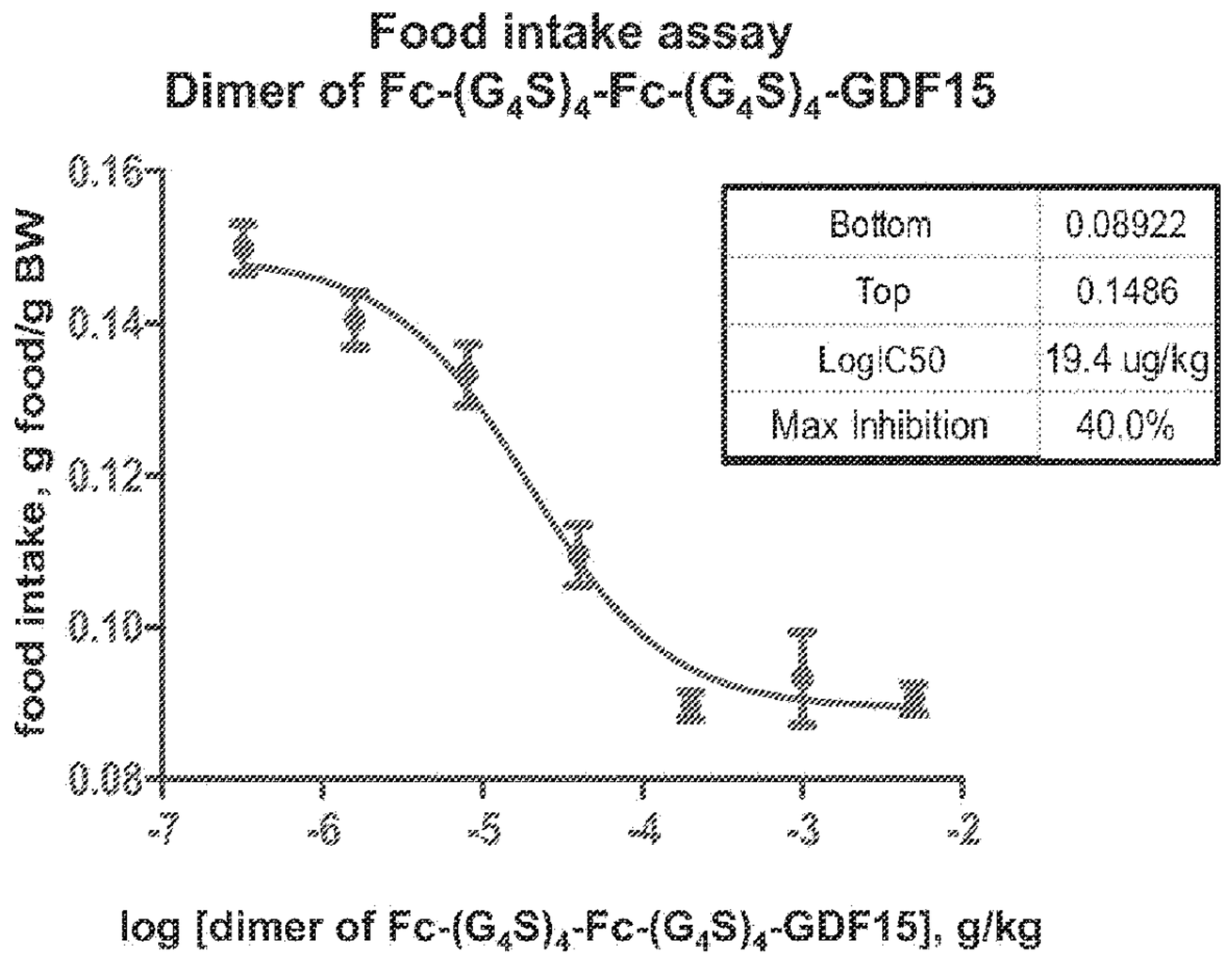
Food intake assay
Dimer of Fc-(G4S)4-Fc-(G4S)4-GDF15
food intake, g food/g BW
0.16
0.14
0.12
0.10
0.08
-7
-6
-5
-4
-3
-2
log [dimer of Fc-(G4S)4-Fc-(G4S)4-GDF15], g/kg
Bottom 0.08922
Top 0.1486
LogIC50 19.4 ug/kg
Max Inhibition 40.0%

Figure 11

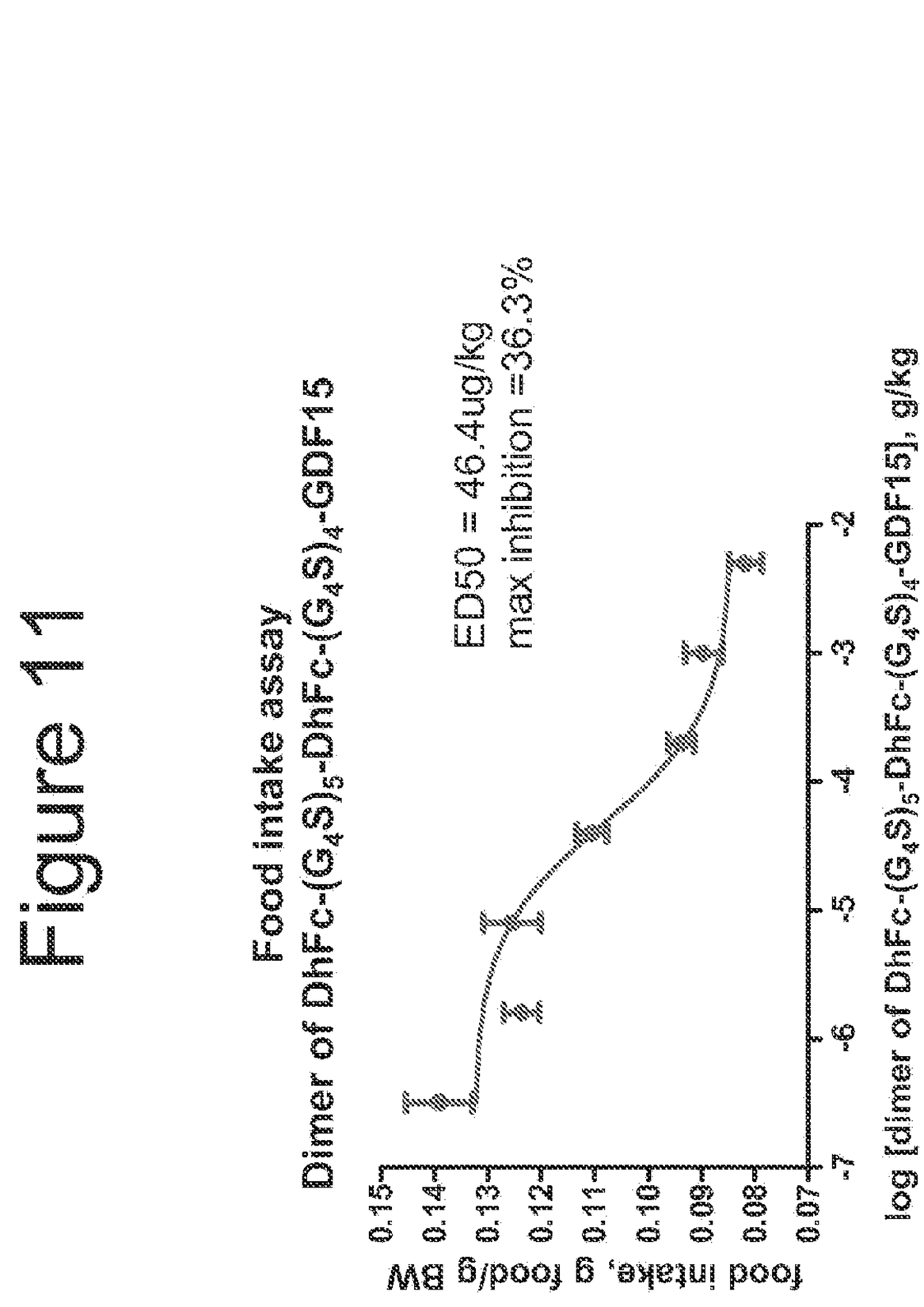
Food intake assay
Dimer of DhFc-(G4S)5-DhFc-(G4S)4-GDF15
ED50 = 46.4ug/kg
max inhibition =36.3%
food intake, g food/g BW
0.15
0.14
0.13
0.12
0.11
0.10
0.08
0.08
0.07
-7
-6
-5
-4
-3
-2
log [dimer of DhFc-(G4S)5-DhFc-(G4S)4-GDF15], g/kg

Figure 12

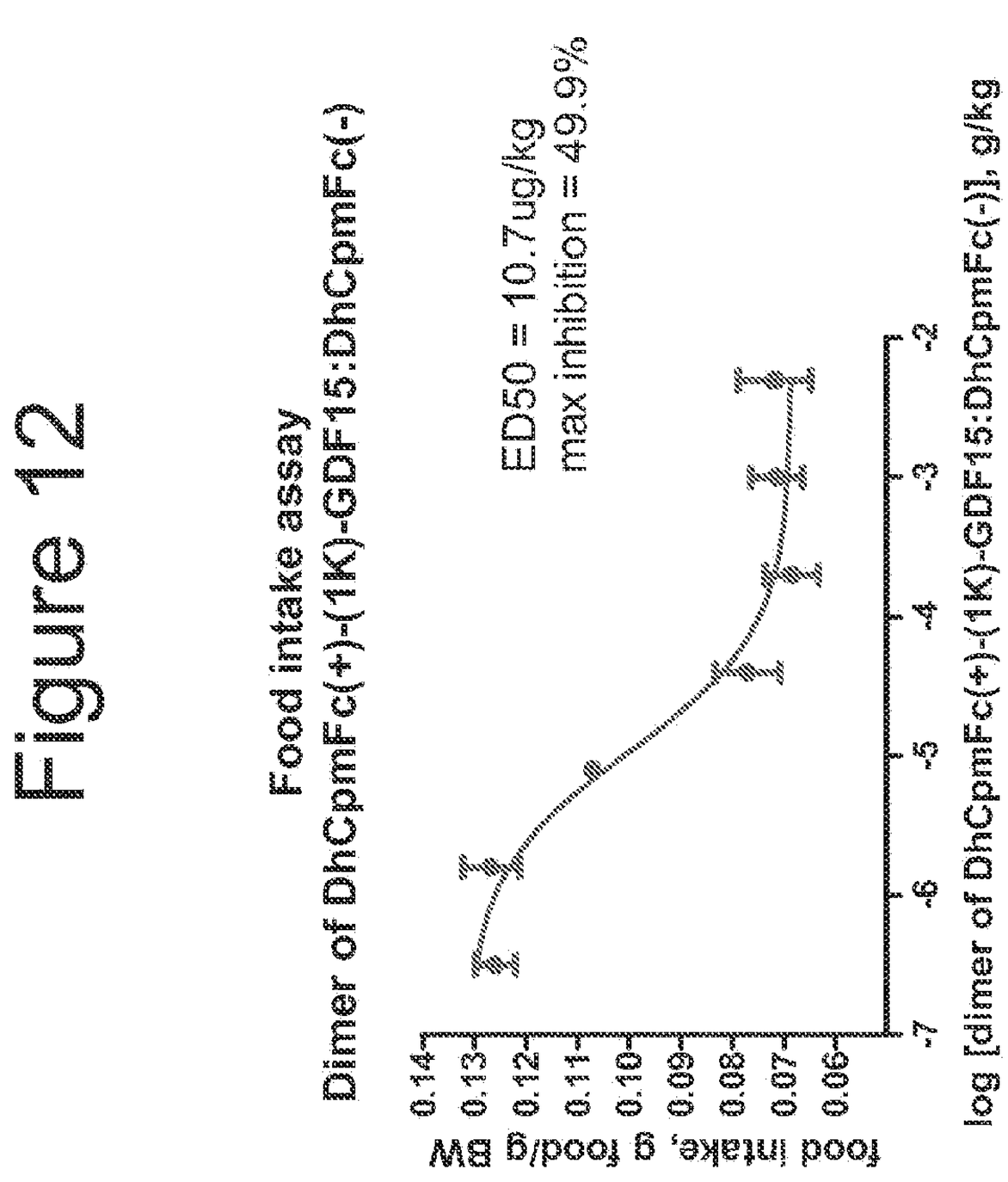
Food intake assay
Dimer of DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)
ED50 = 10.7ug/kg
max inhibition = 49.9%
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)], g/kg

Figure 13

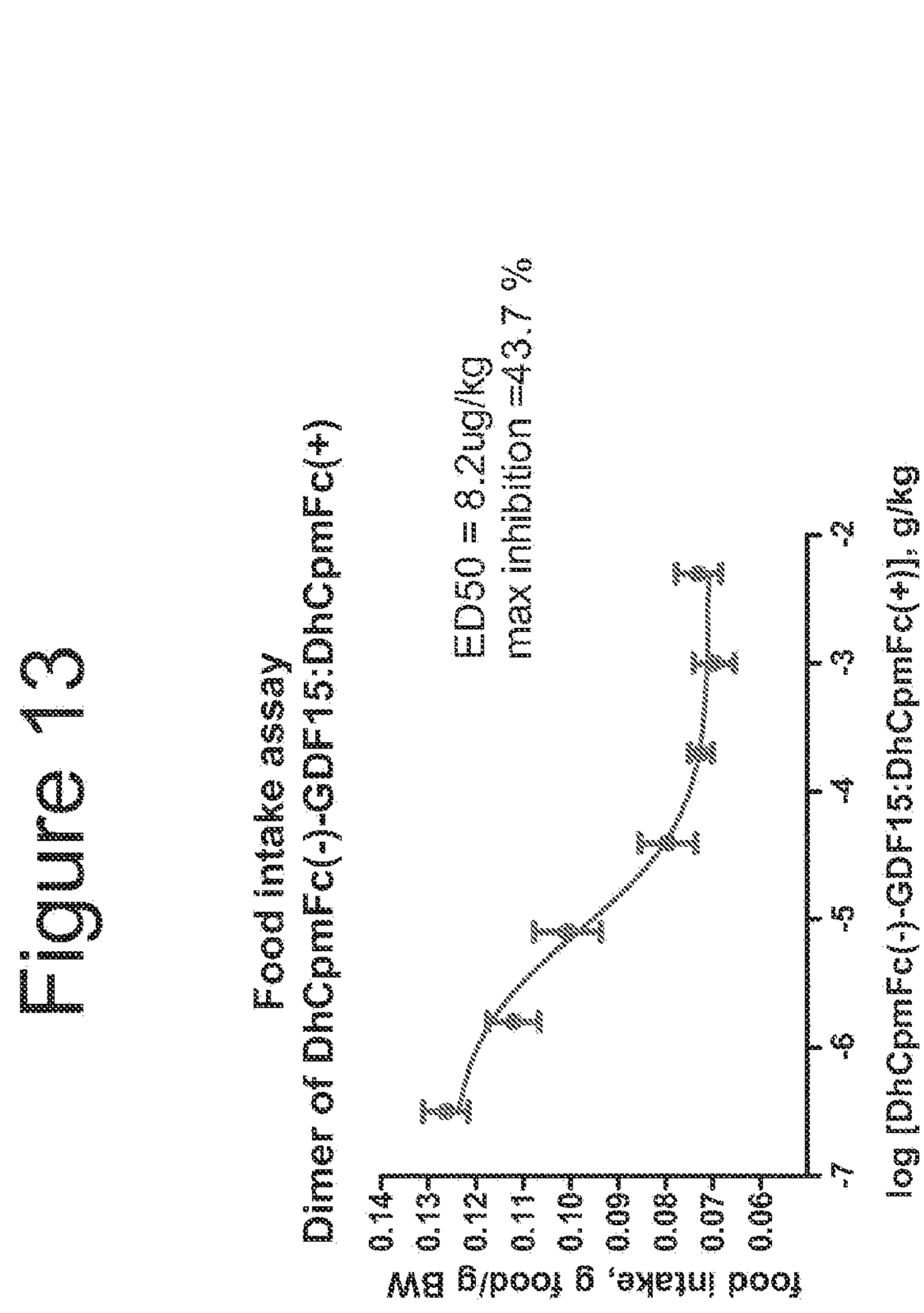
Food intake assay
Dimer of DhCpmFc(-)-GDF15:DhCpmFc(+)
ED50 = 8.2ug/kg
max inhibition =43.7 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(-)-GDF15:DhCpmFc(+)], g/kg

Figure 14

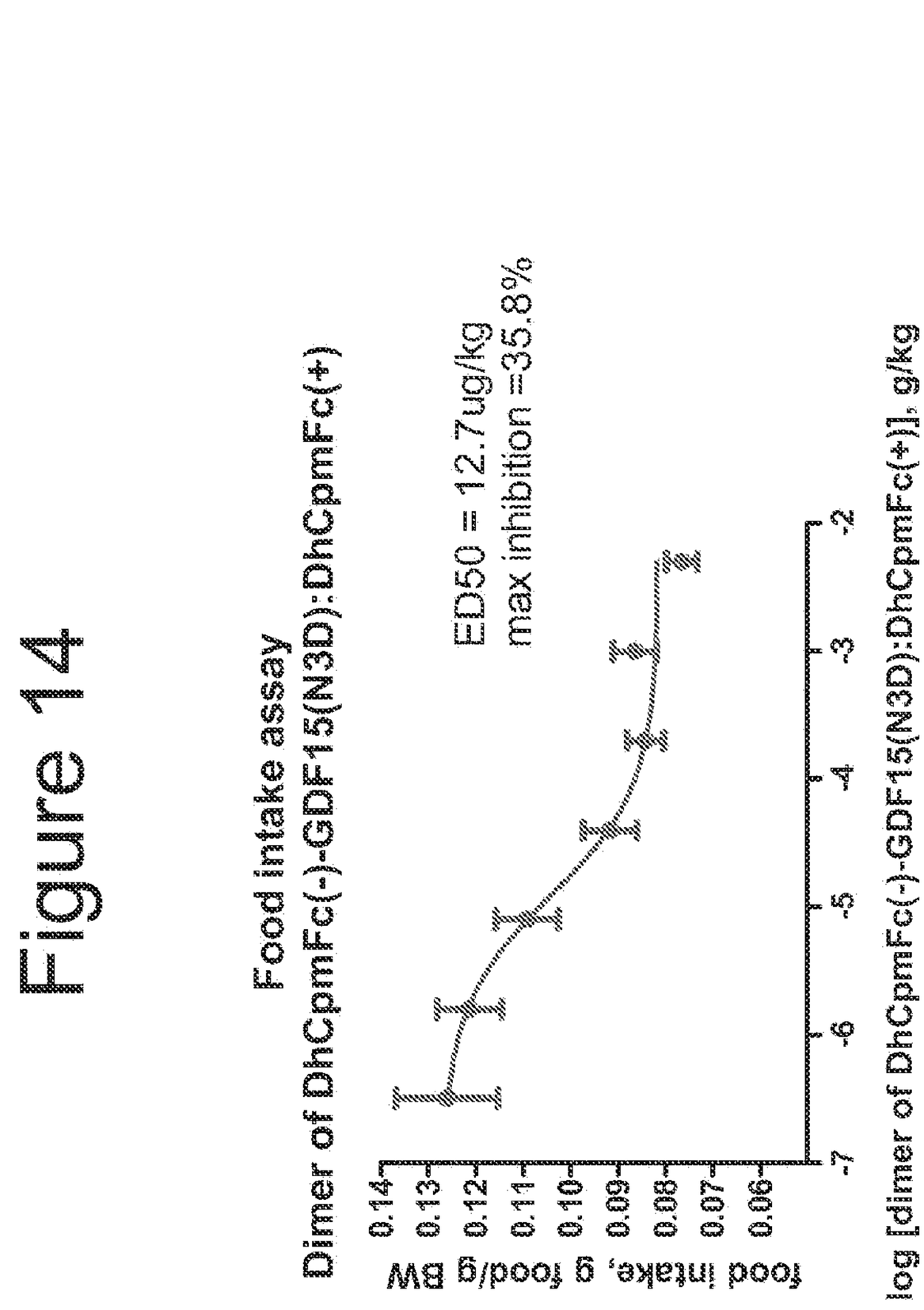
Food intake assay
Dimer of DhCpmFc(-)-GDF15(N3D):DhCpmFc(+)
ED50 = 12.7ug/kg
max inhibition =35.8%
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-GDF15(N3D):DhCpmFc(+)], g/kg

Figure 15

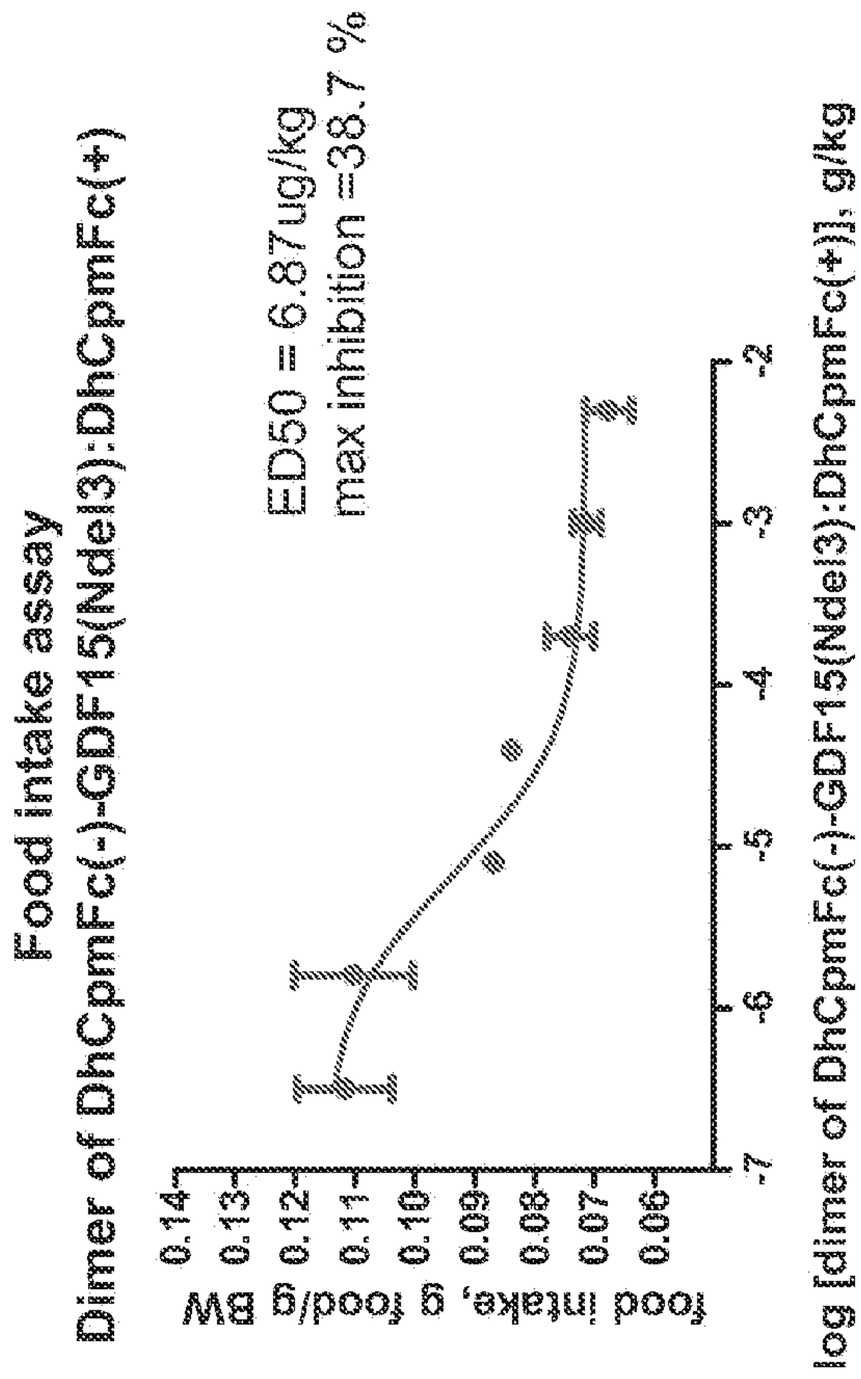
Food intake assay
Dimer of DhCpmFc(-)-GDF15(Ndel3):DhCpmFc(+)
ED50 = 6.87ug/kg
max inhibition =38.7 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-GDF15(Ndel3):DhCpmFc(+)], g/kg

Figure 16

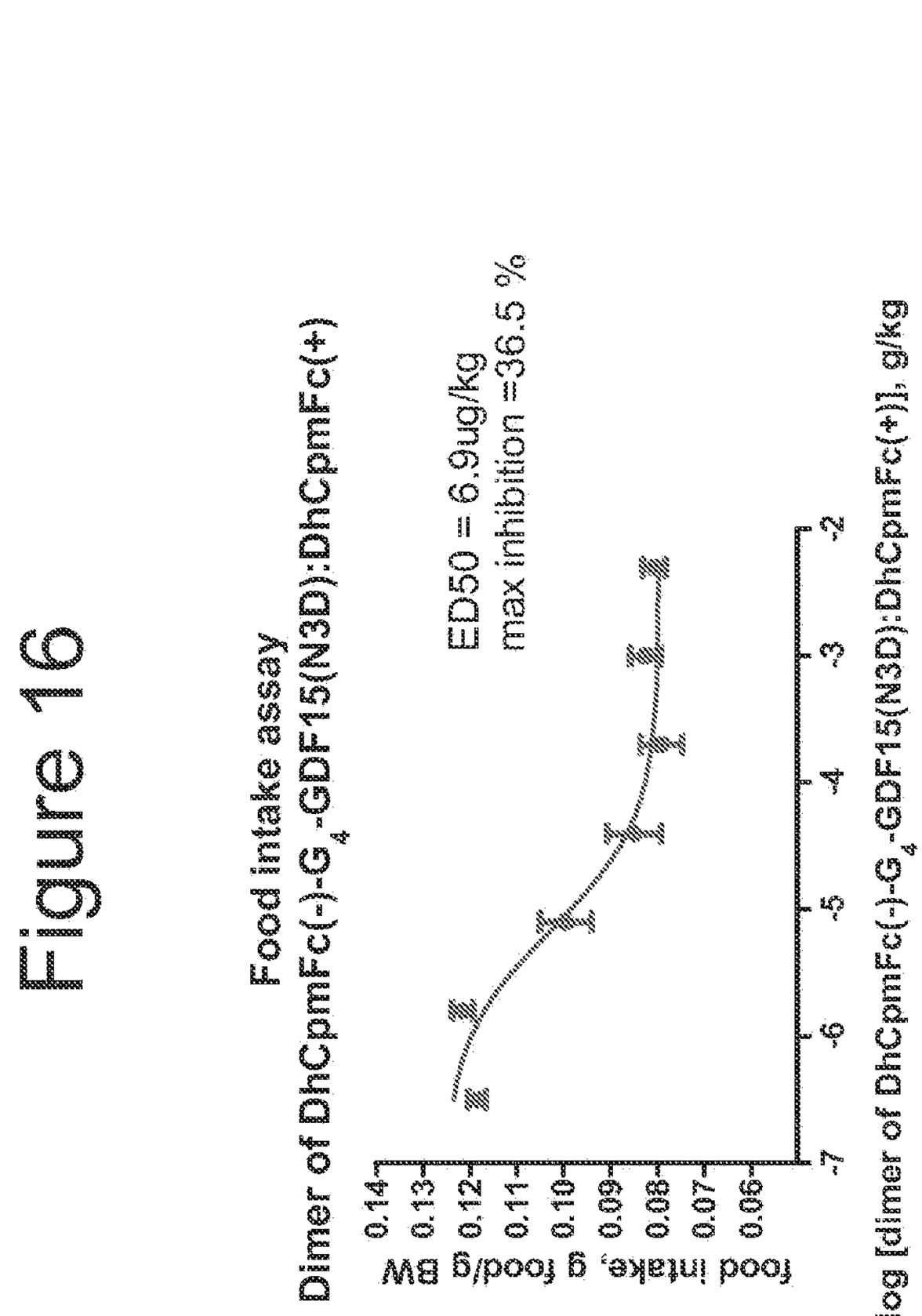
Food intake assay
Dimer of DhCpmFc(-)-G4-GDF15(N3D):DhCpmFc(+)
ED50 = 6.9ug/kg
max inhibition =36.5 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-G4-GDF15(N3D):DhCpmFc(+)], g/kg

Figure 17

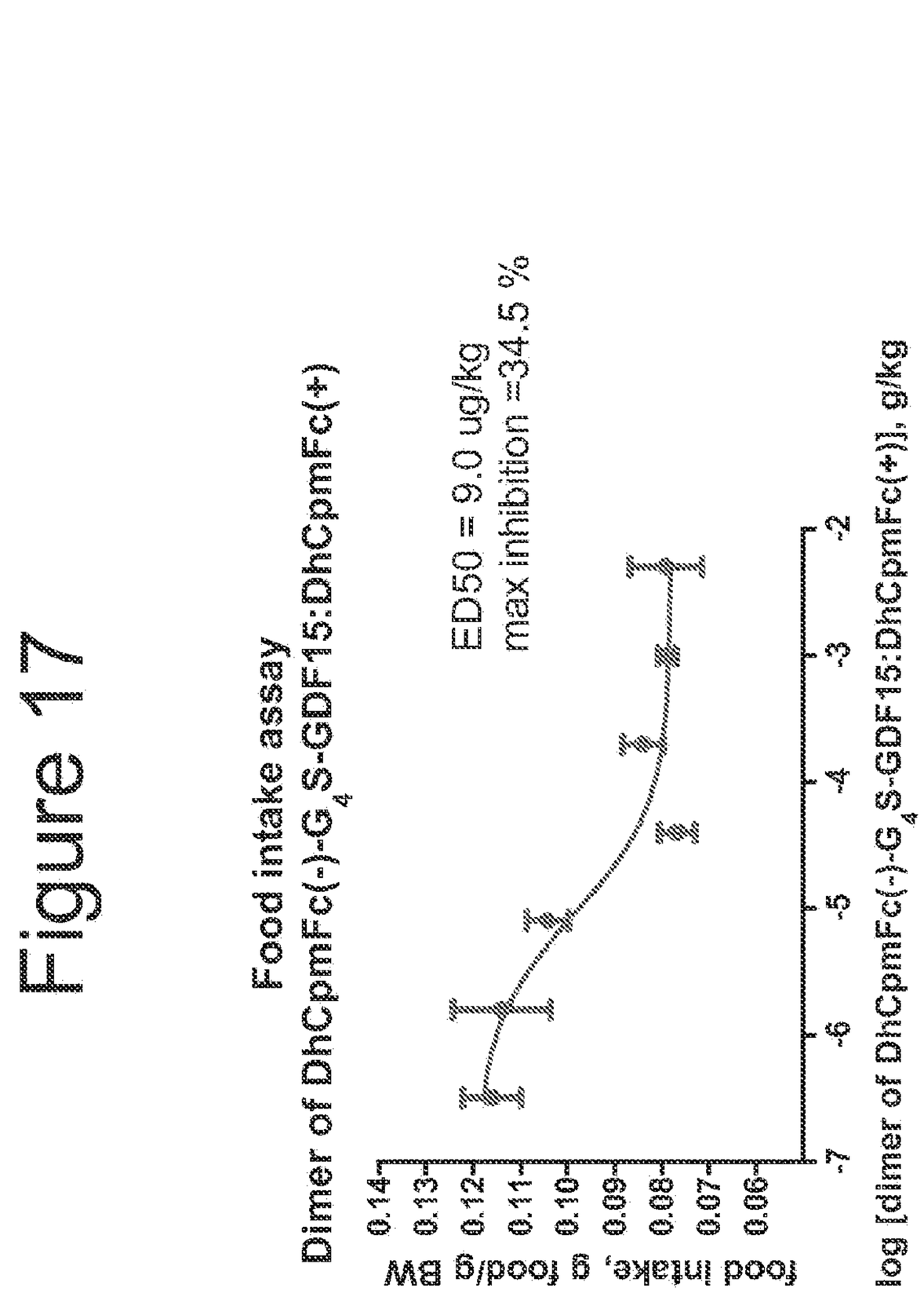
Food intake assay
Dimer of DhCpmFc(-)-G4S-GDF15:DhCpmFc(+)
ED50 = 9.0 ug/kg
max inhibition =34.5 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-G4S-GDF15:DhCpmFc(+)], g/kg

Figure 18

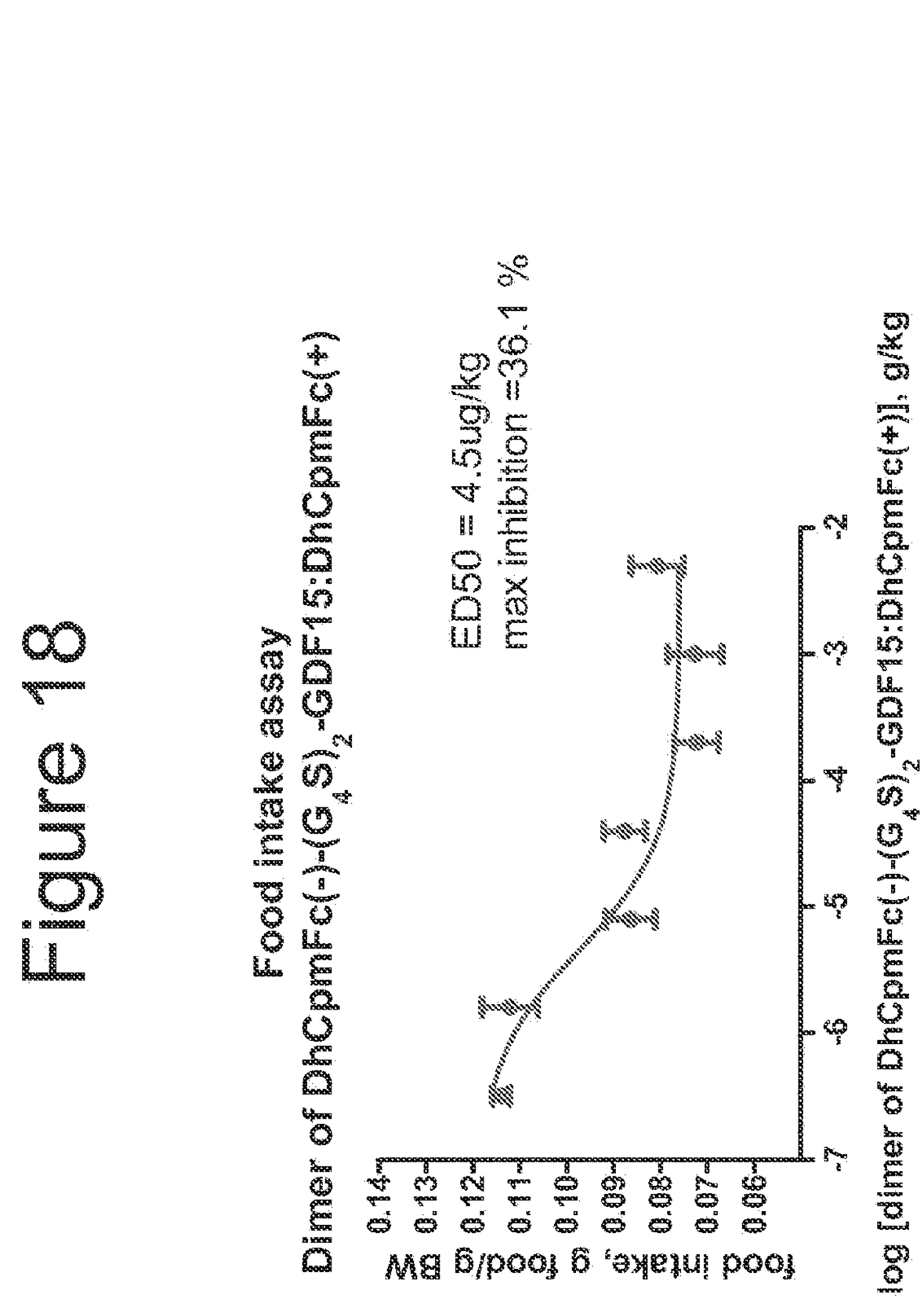
Food intake assay
Dimer of DhCpmFc(-)-(G4S)2-GDF15:DhCpmFc(+)
ED50 = 4.5ug/kg
max inhibition =36.1 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-(G4S)2-GDF15:DhCpmFc(+)], g/kg

Figure 19

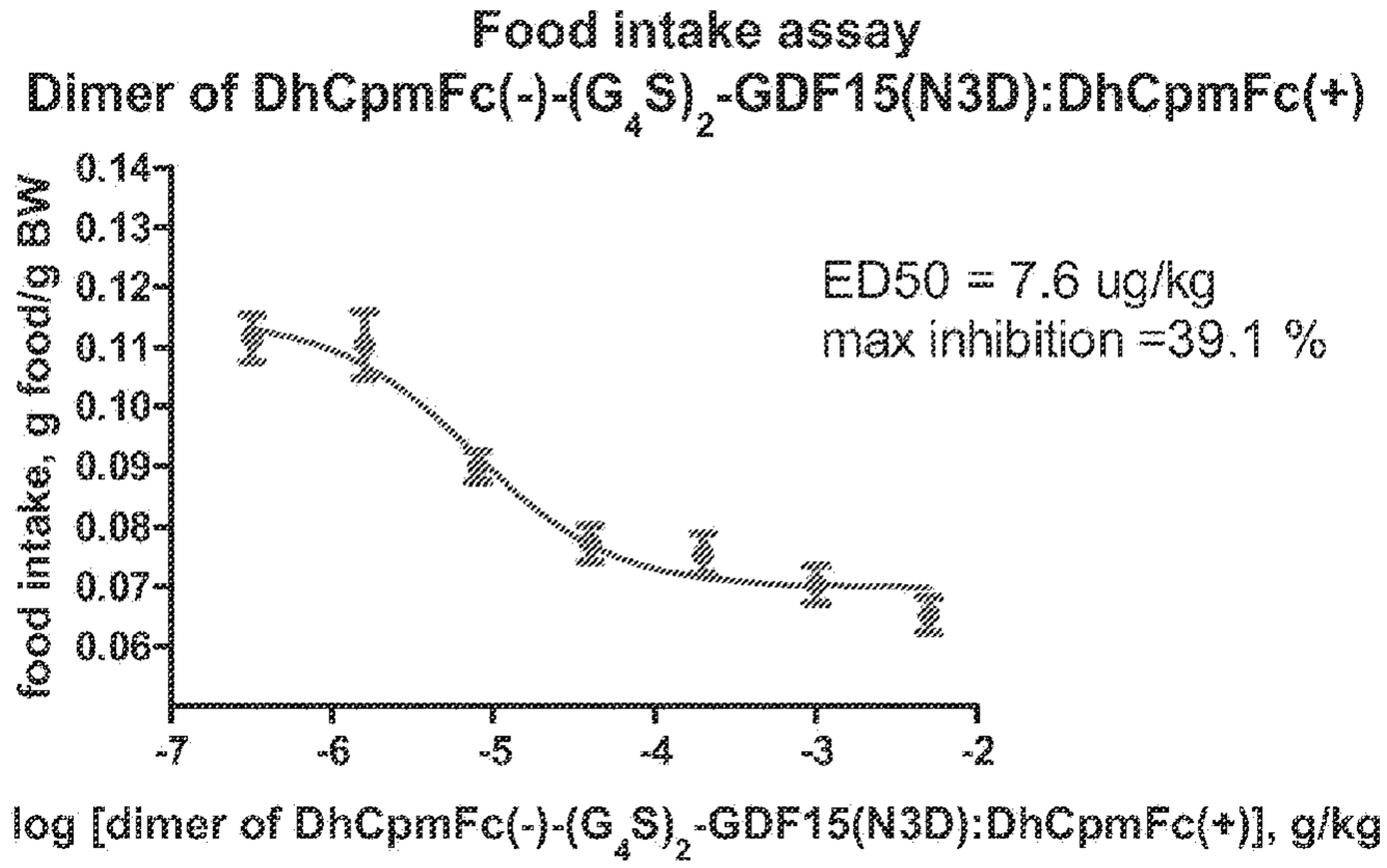

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Figure 20

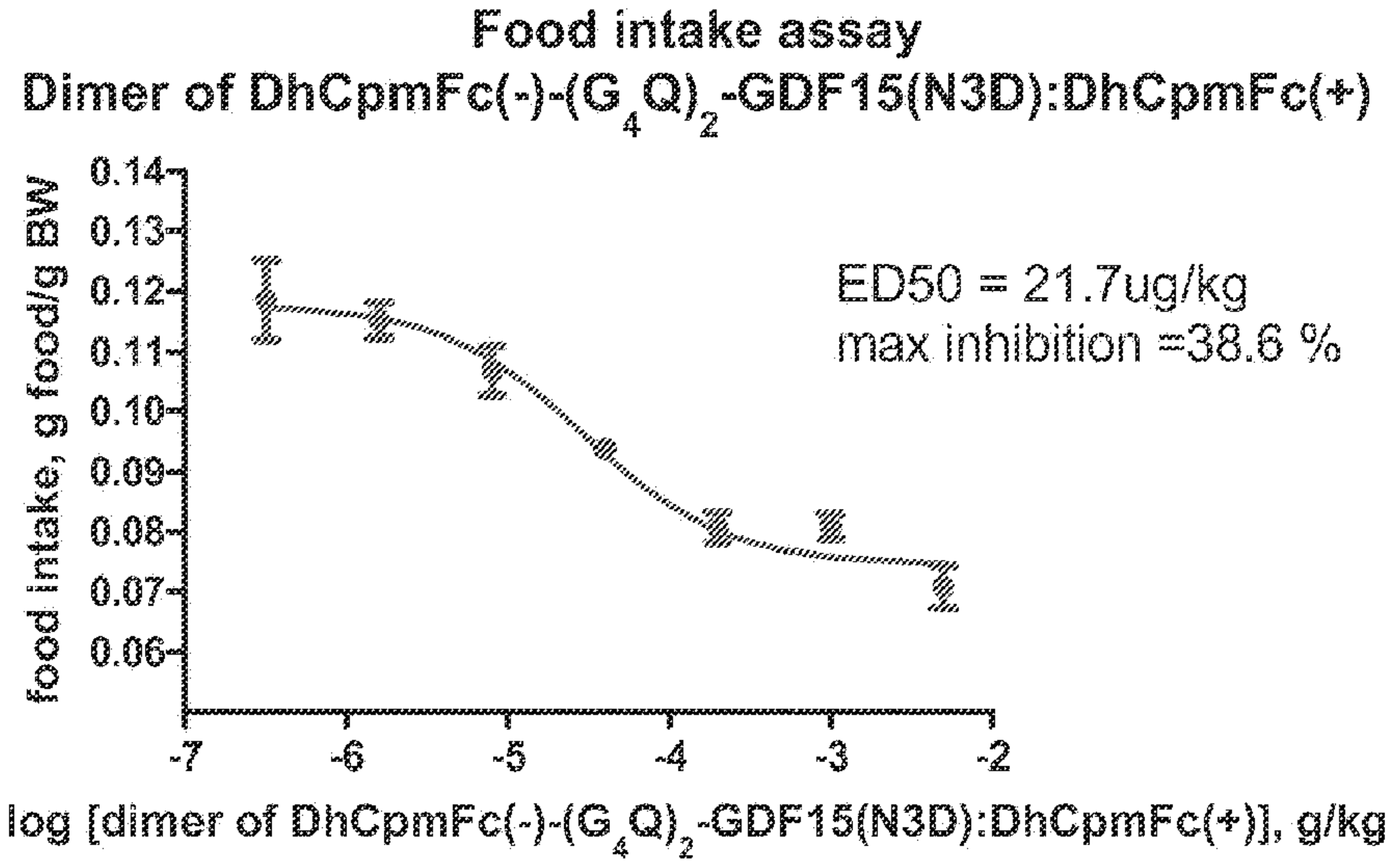

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Figure 21

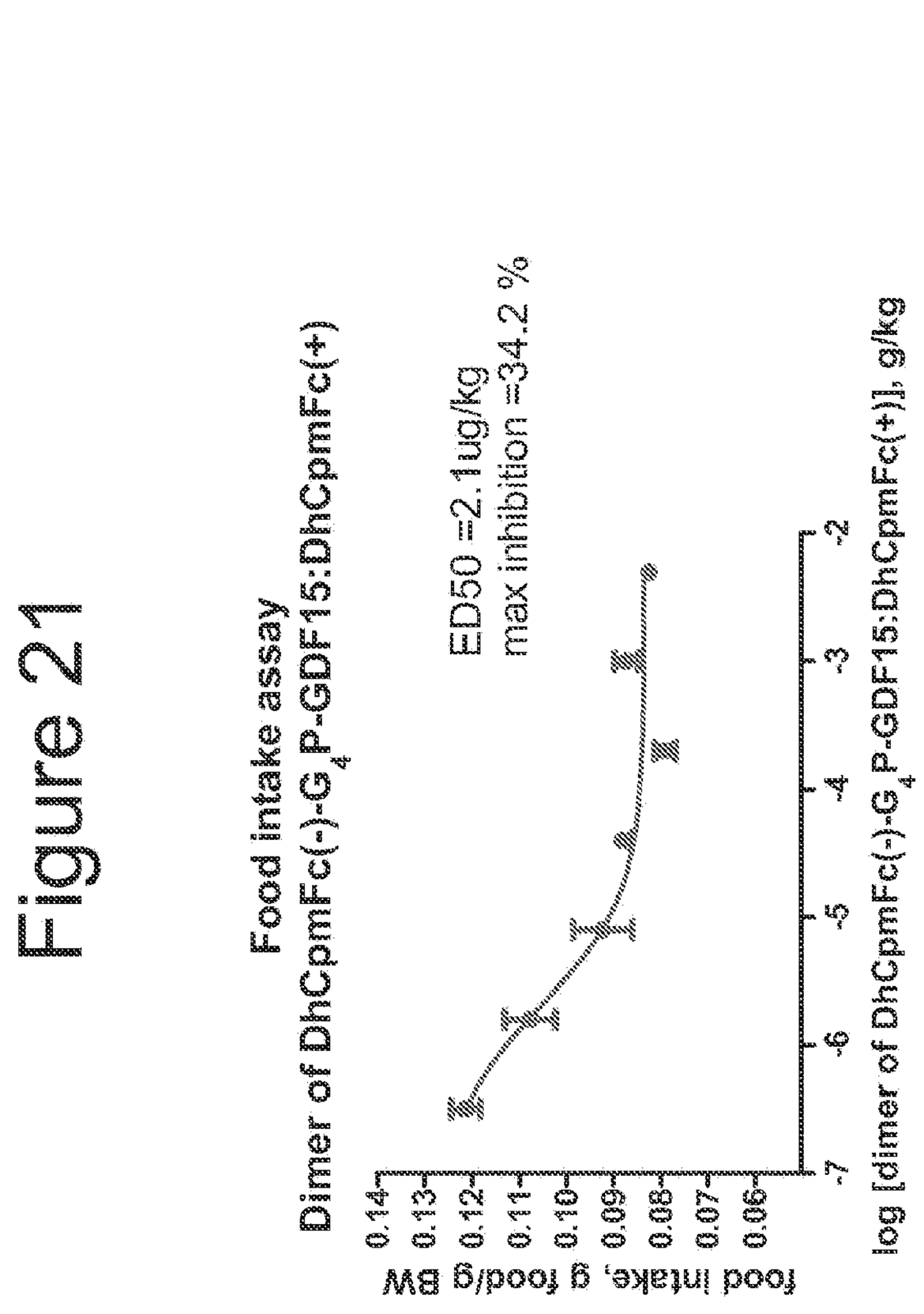
Food intake assay
Dimer of DhCpmFc(-)-G4P-GDF15:DhCpmFc(+)
ED50 =2.1ug/kg
max inhibition =34.2 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-G4P-GDF15:DhCpmFc(+)], g/kg

Figure 22

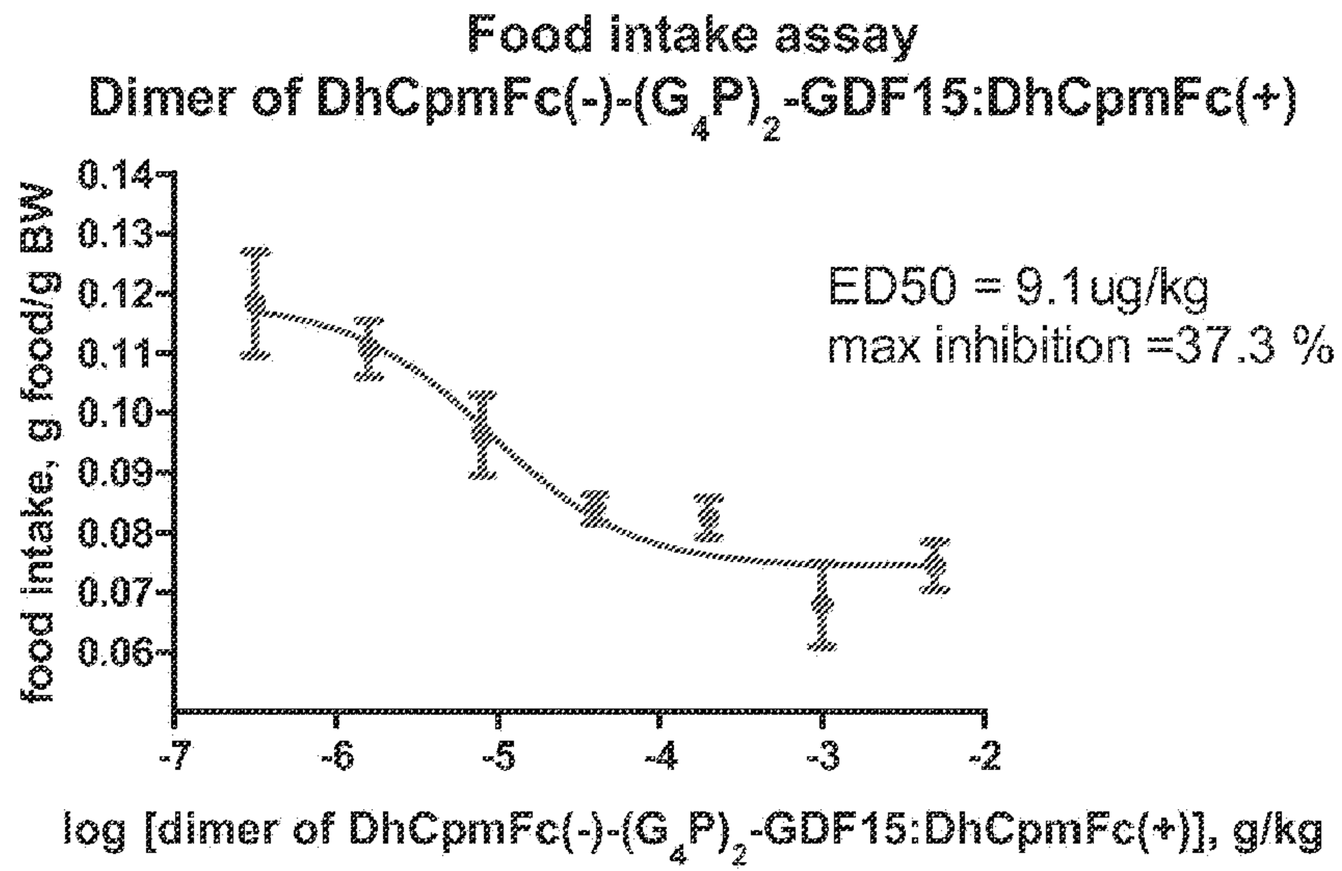

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Figure 23

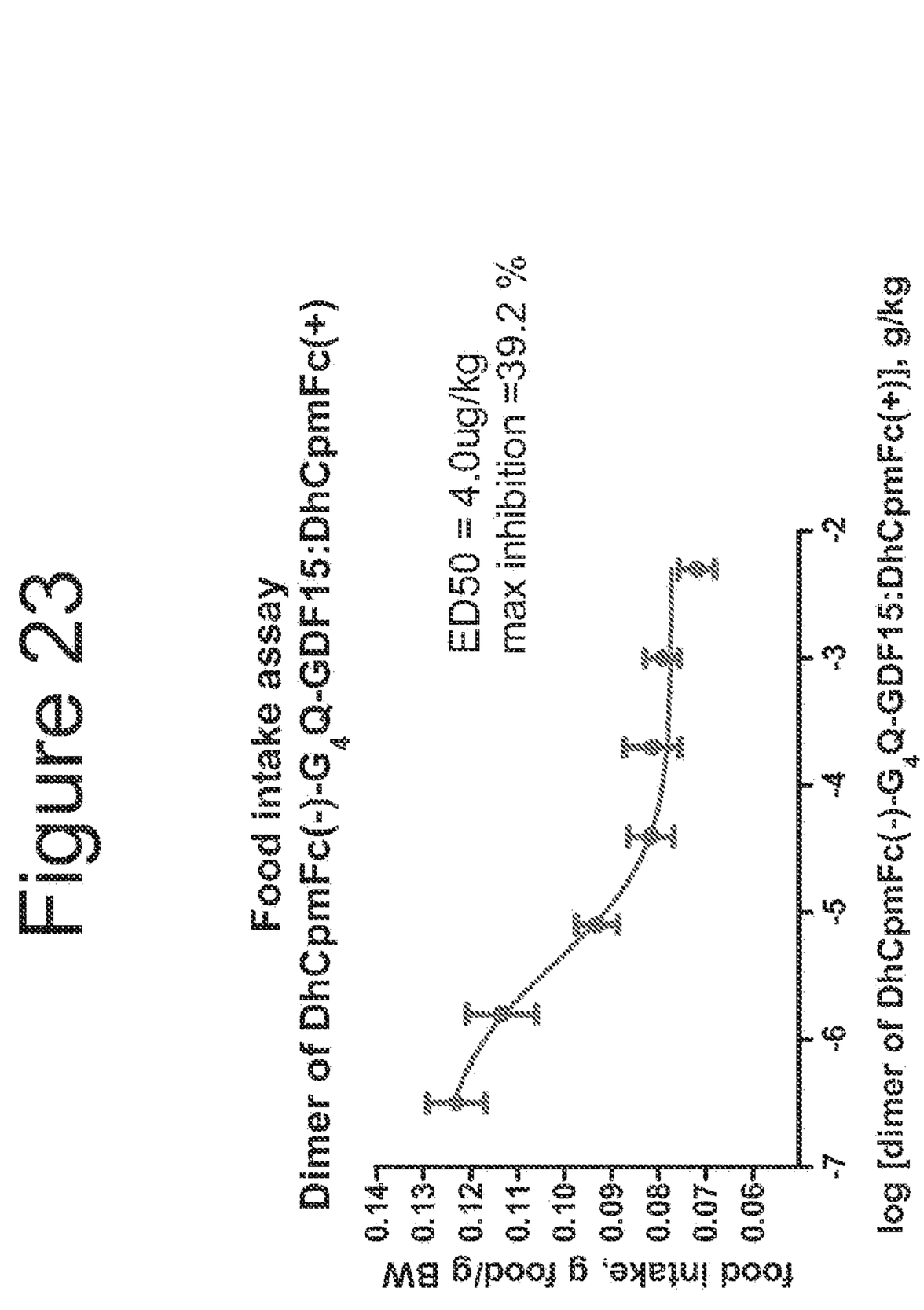
Food intake assay
Dimer of DhCpmFc(-)-G4Q-GDF15:DhCpmFc(+)
ED50 = 4.0ug/kg
max inhibition =39.2 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-G4Q-GDF15:DhCpmFc(+)], g/kg

Figure 24

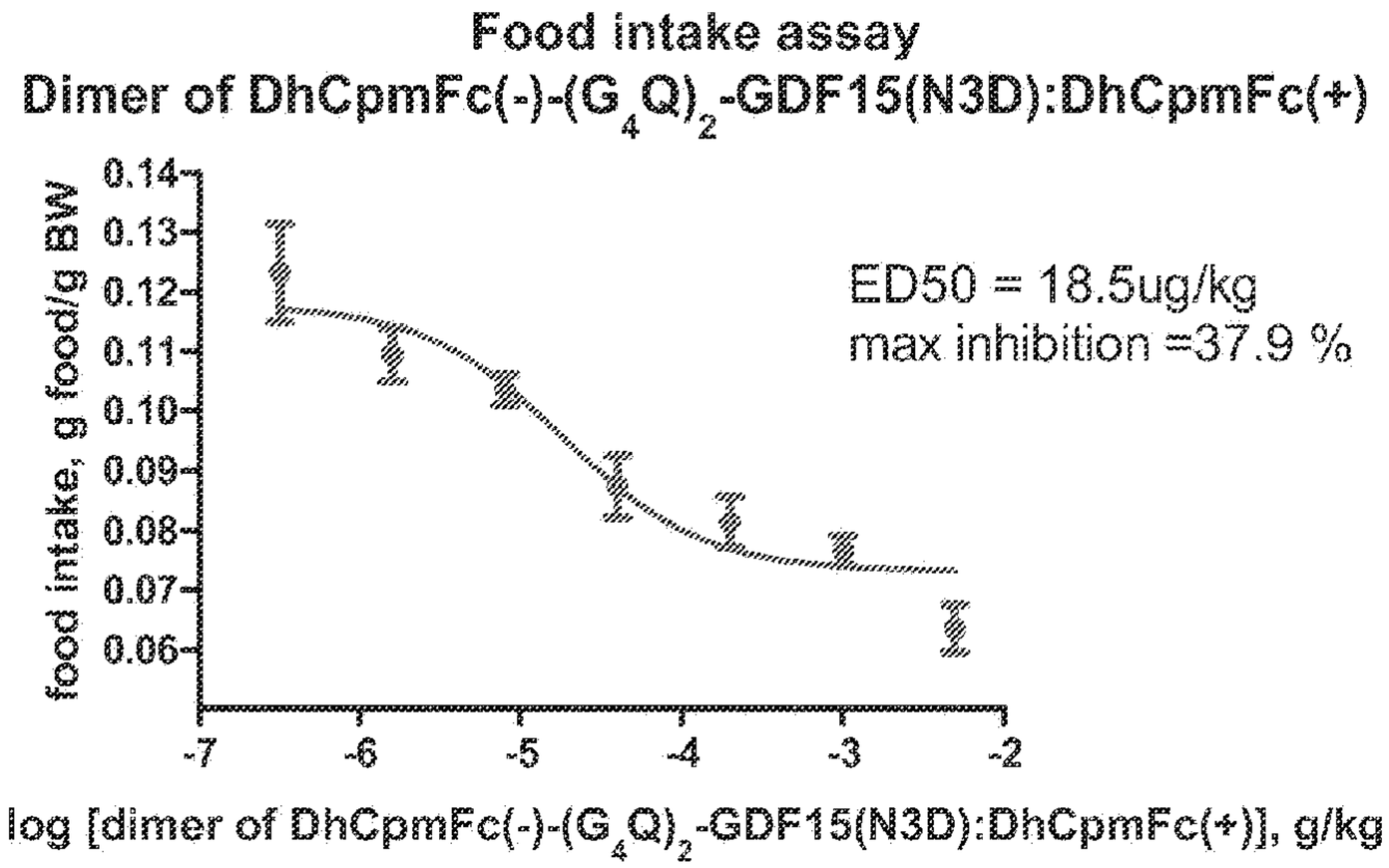

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Figure 25

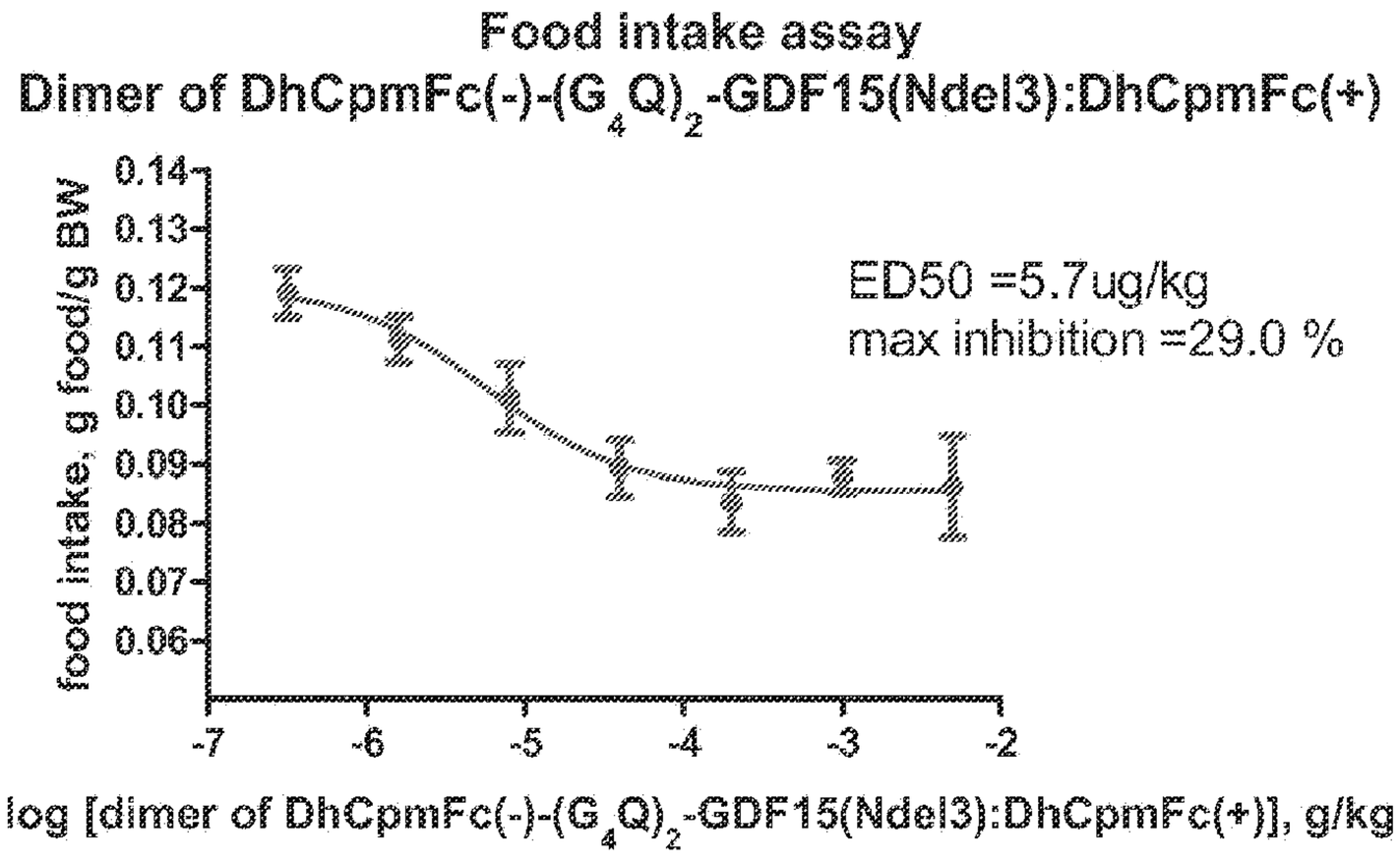
Food intake assay
Dimer of DhCpmFc(-)-(G4Q)2-GDF15(Ndel3):DhCpmFc(+)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
ED50 =5.7ug/kg
max inhibition =29.0 %
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)-(G4Q)2-GDF15(Ndel3):DhCpmFc(+)], g/kg

Figure 26

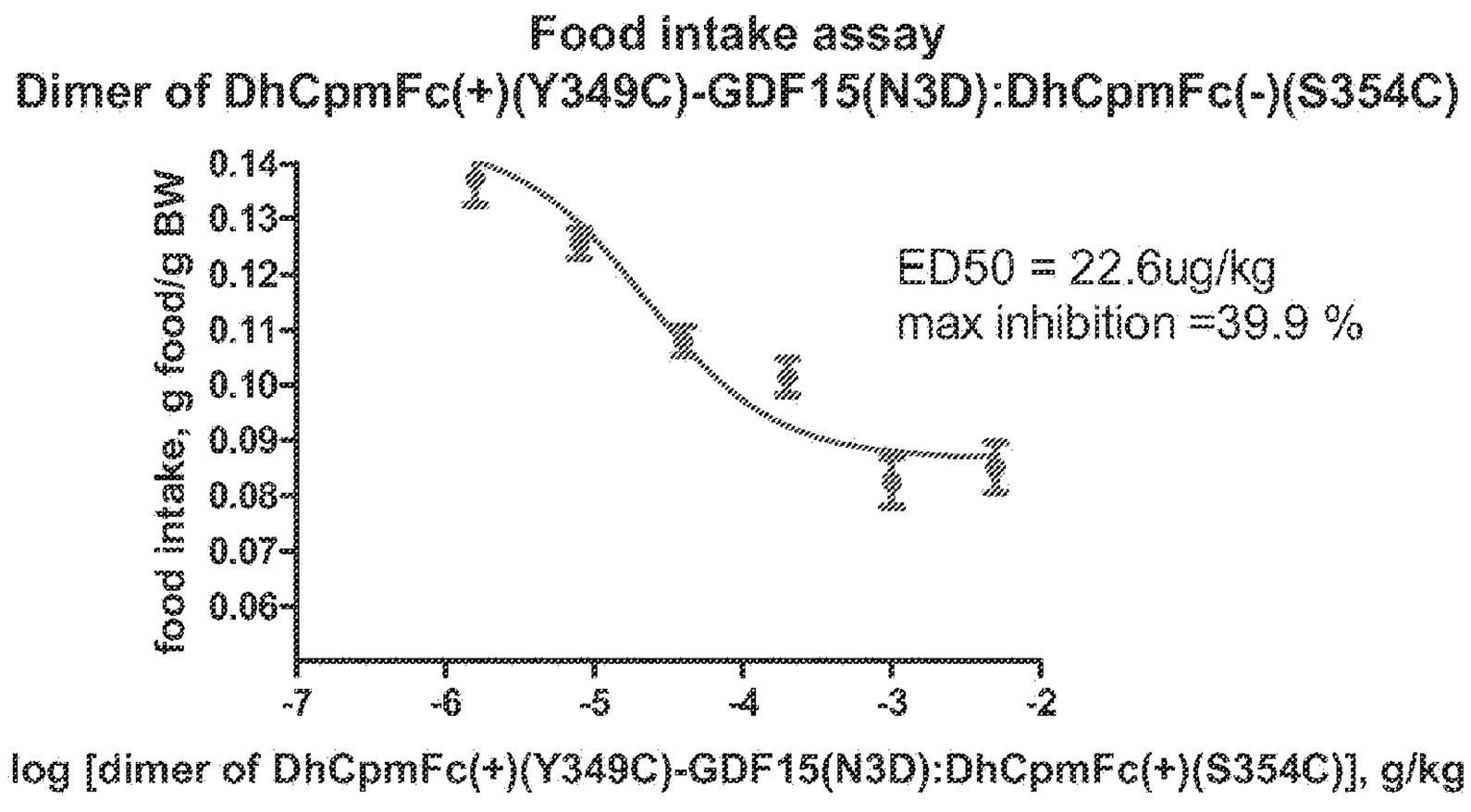

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Figure 27

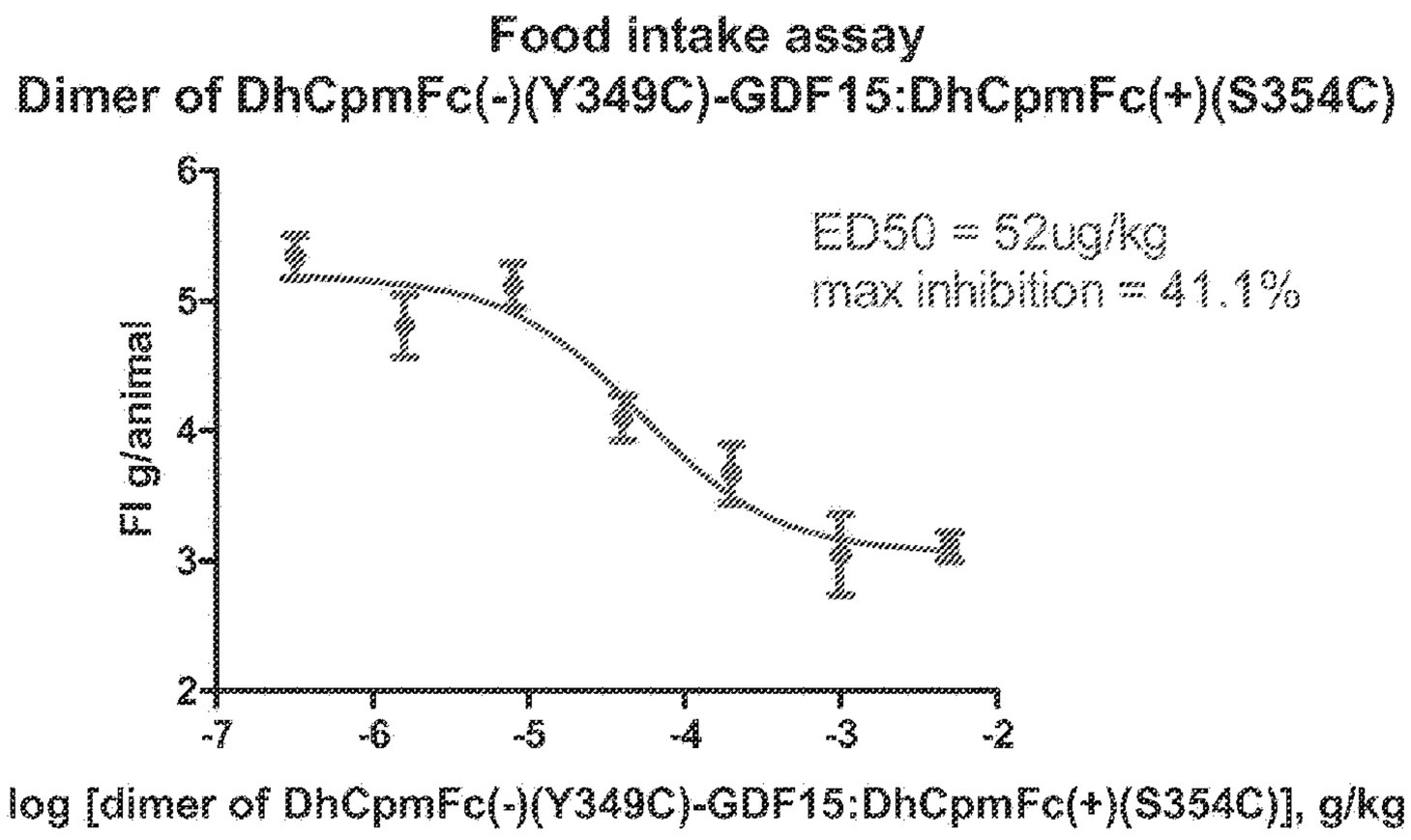
Food intake assay
Dimer of DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C)
ED50 = 52ug/kg
max inhibition = 41.1%
FI g/animal
6
5
4
3
2
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)(Y349C)-GDF15:DhCpmFc(+)(S354C)], g/kg

Figure 28

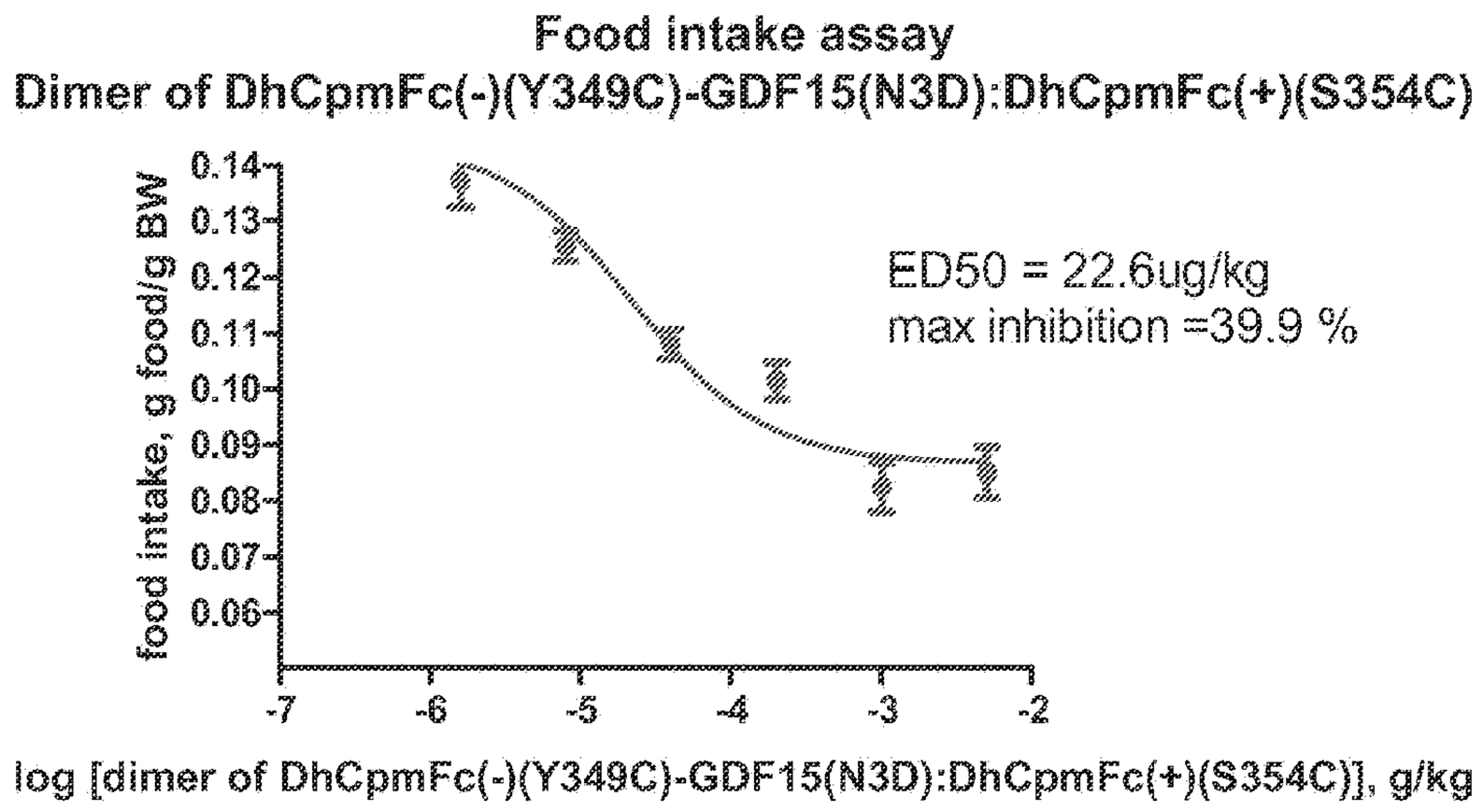
Food intake assay
Dimer of DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
ED50 = 22.6ug/kg
max inhibition =39.9 %
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)(Y349C)-GDF15(N3D):DhCpmFc(+)(S354C)], g/kg

Figure 29

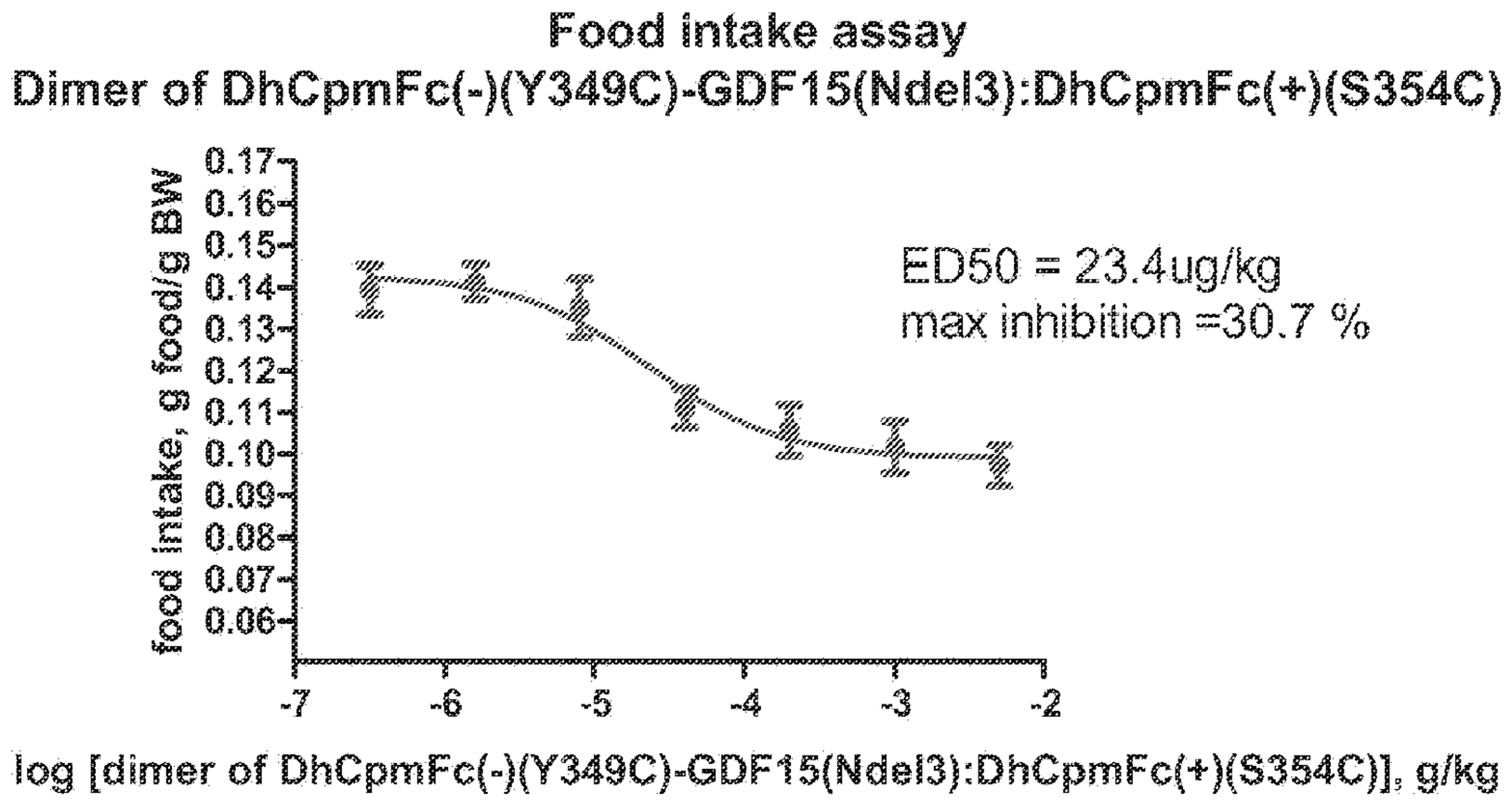
Food intake assay
Dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C)
food intake, g food/g BW
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
ED50 = 23.4ug/kg
max inhibition =30.7 %
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C)], g/kg

Figure 30

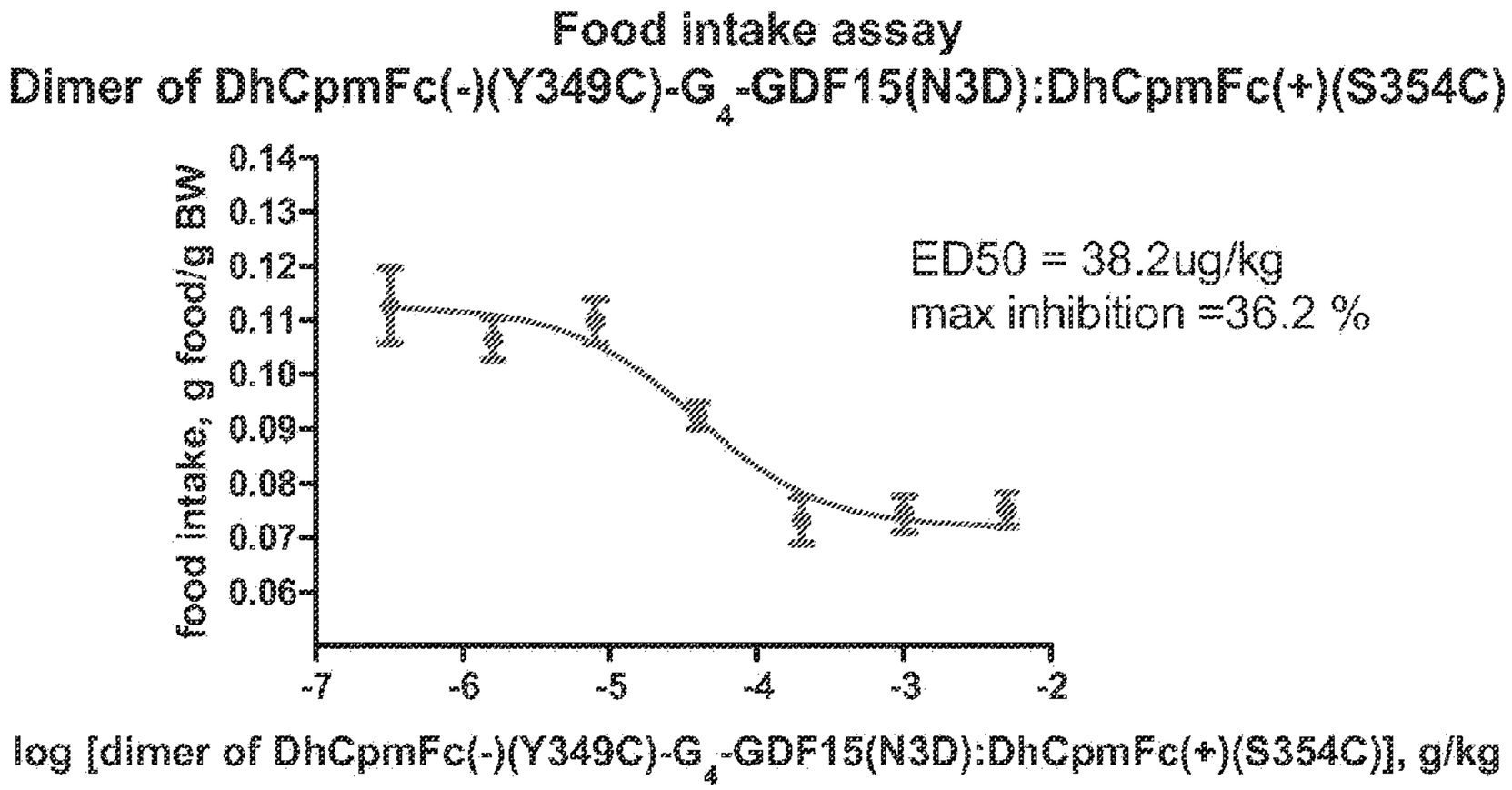

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Figure 31

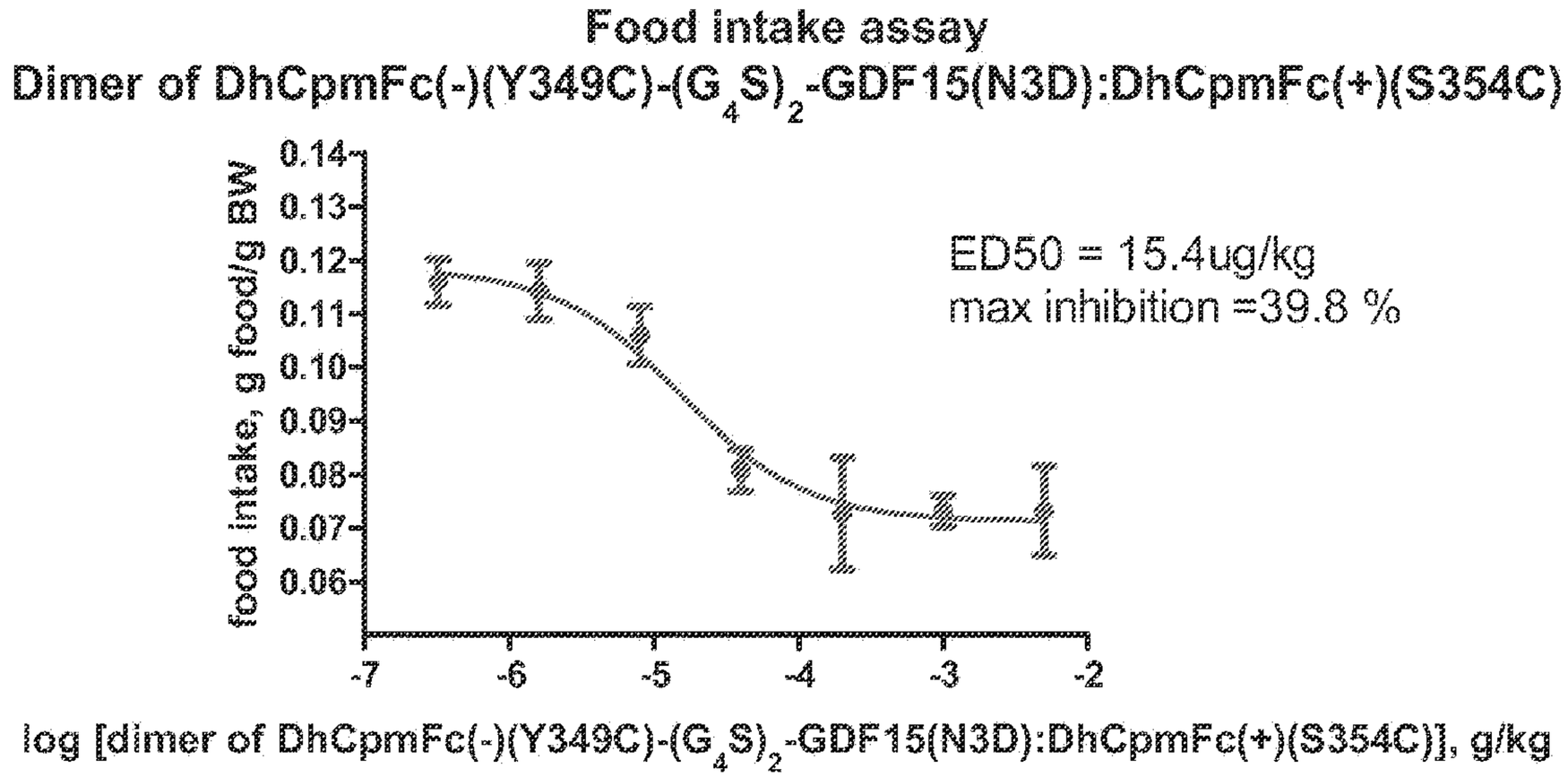

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Figure 32

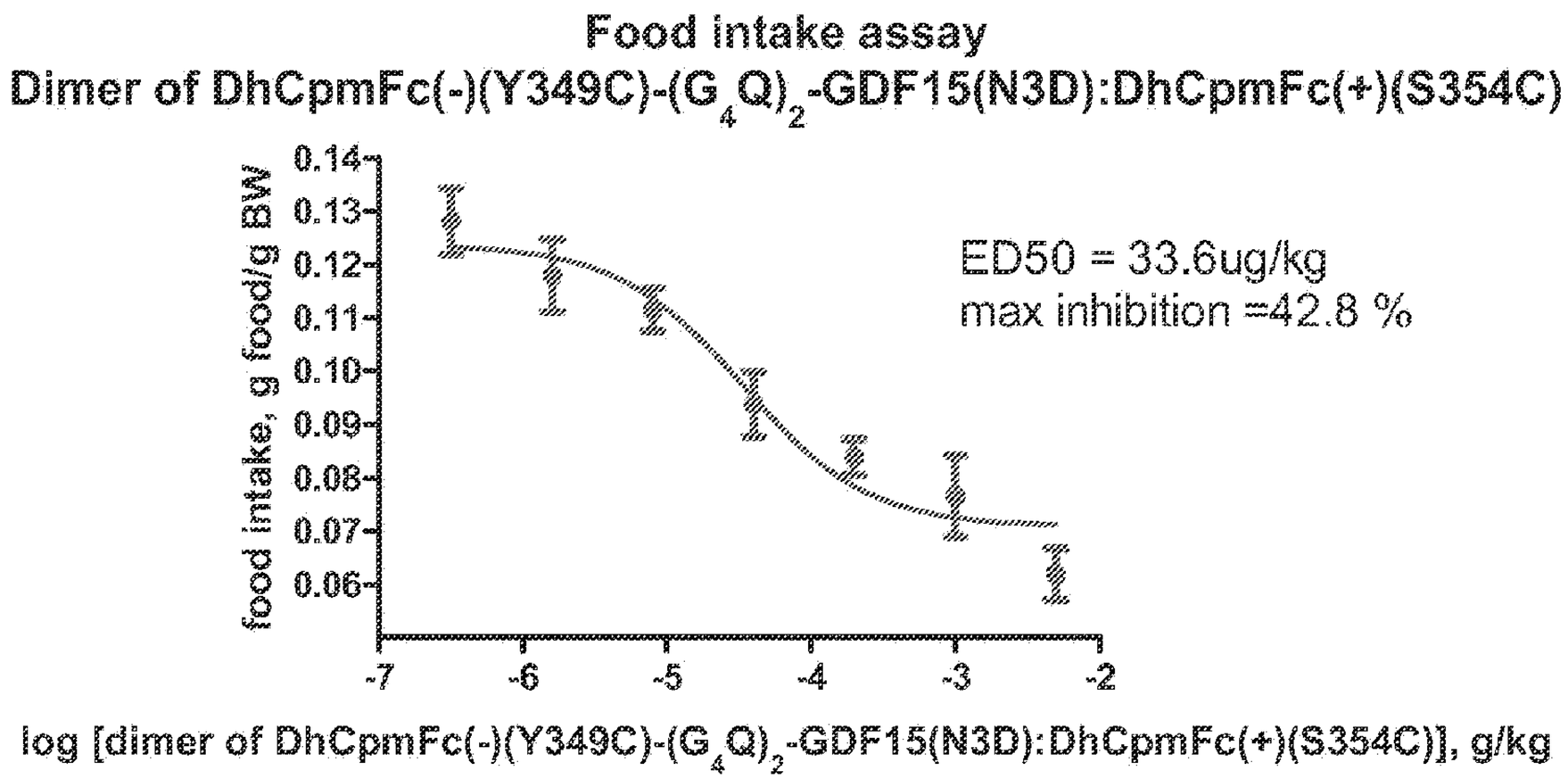

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Figure 33

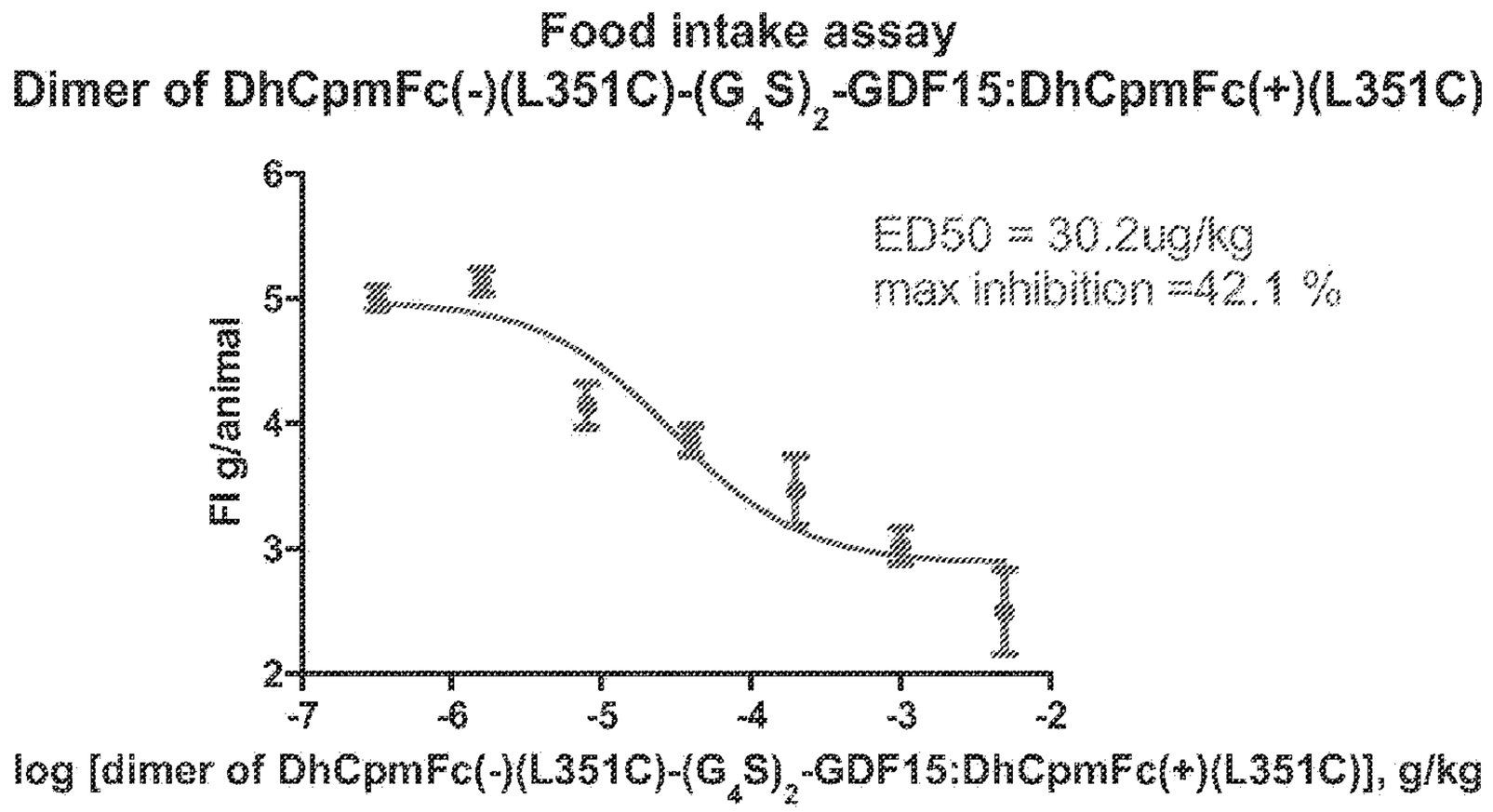

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Figure 34

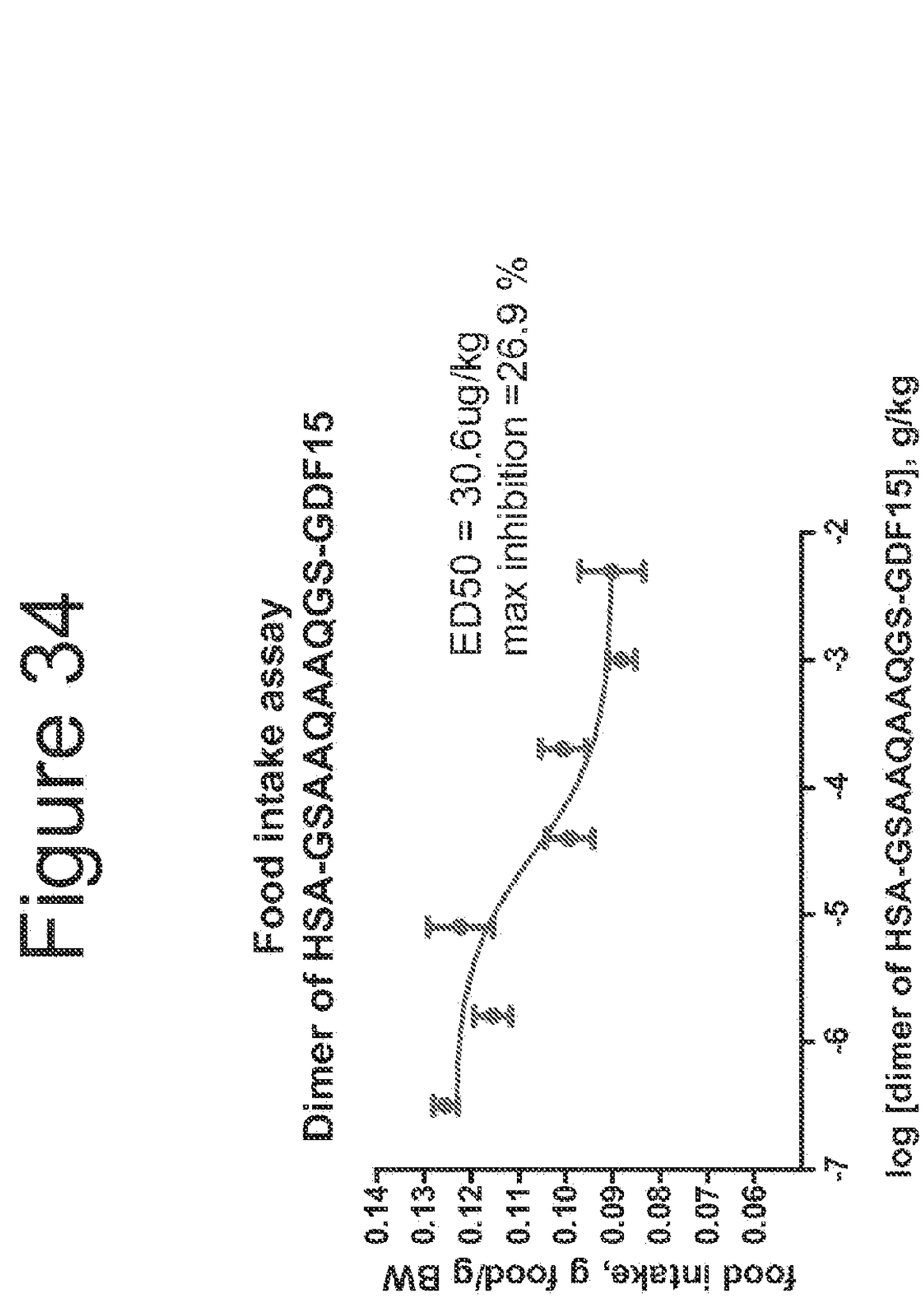
Food intake assay
Dimer of HSA-GSAAQAAQGS-GDF15
ED50 = 30.6ug/kg
max inhibition =26.9 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GSAAQAAQGS-GDF15], g/kg

Figure 35

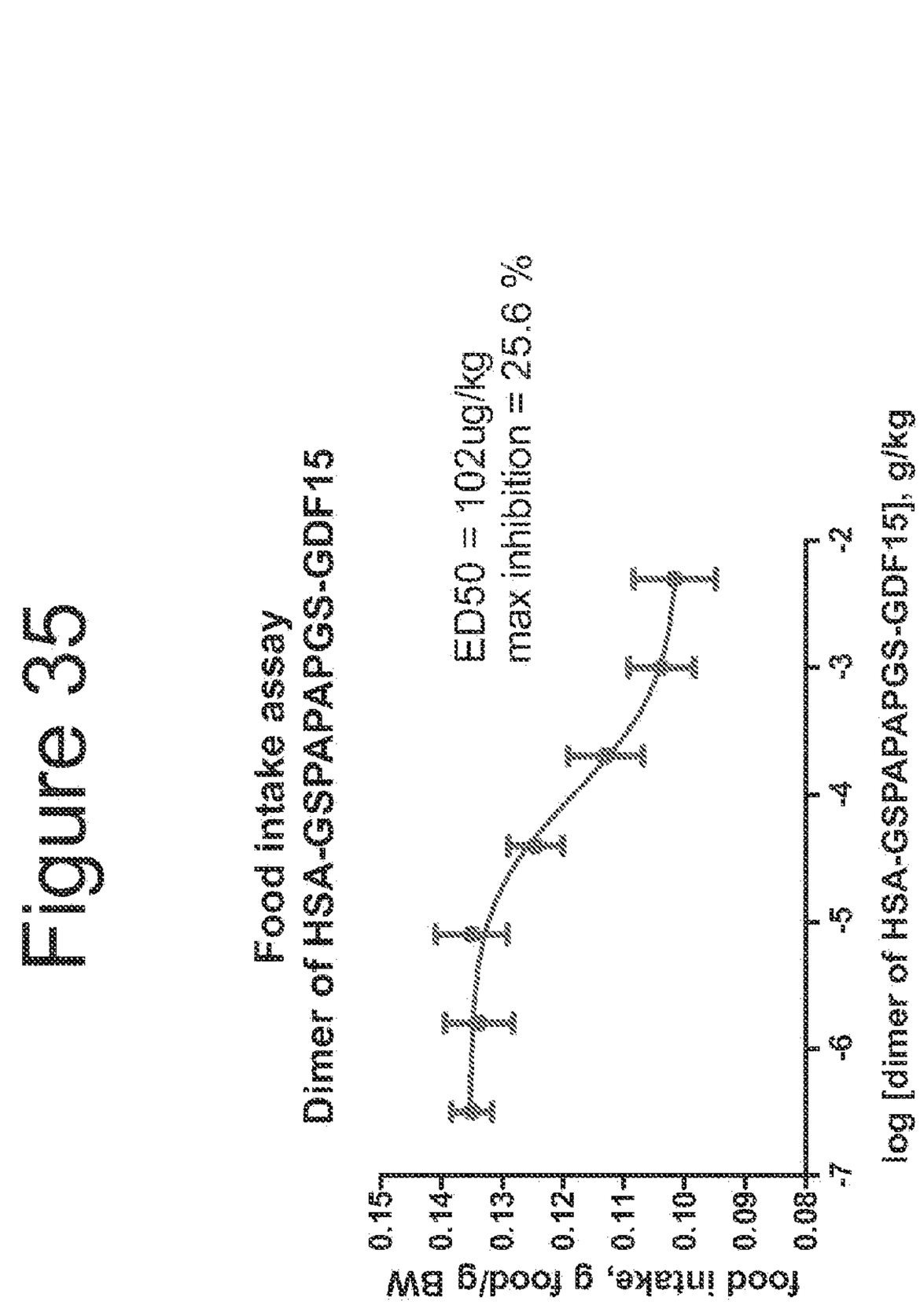
Food intake assay
Dimer of HSA-GSPAPAPGS-GDF15
ED50 = 102ug/kg
max inhibition = 25.6 %
food intake, g food/g BW
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GSPAPAPGS-GDF15], g/kg

Figure 36

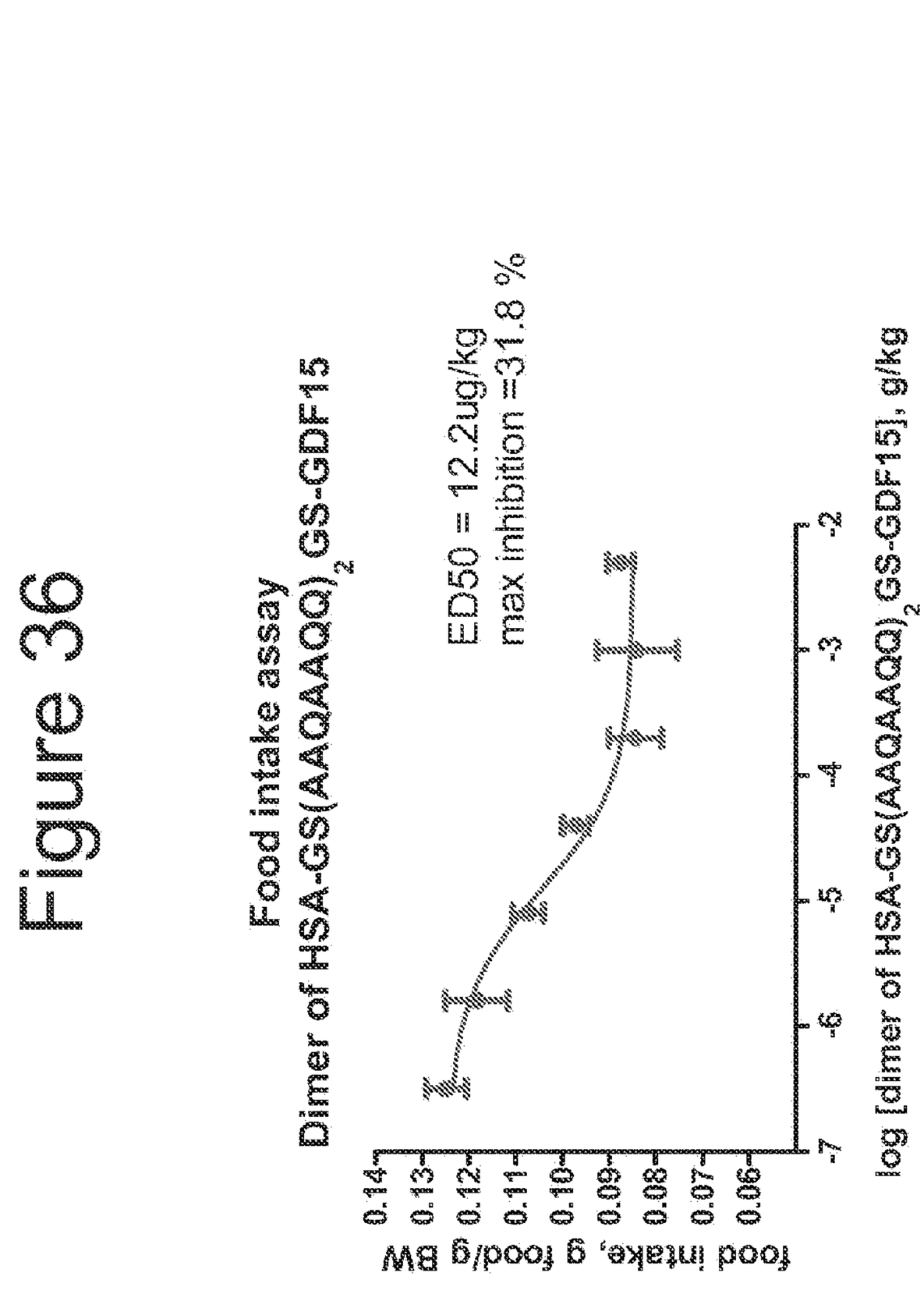
Food intake assay
Dimer of HSA-GS(AAQAAAQQ)2 GS-GDF15
ED50 = 12.2ug/kg
max inhibition =31.8 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GS(AAQAAAQQ)2 GS-GDF15], g/kg

Figure 37

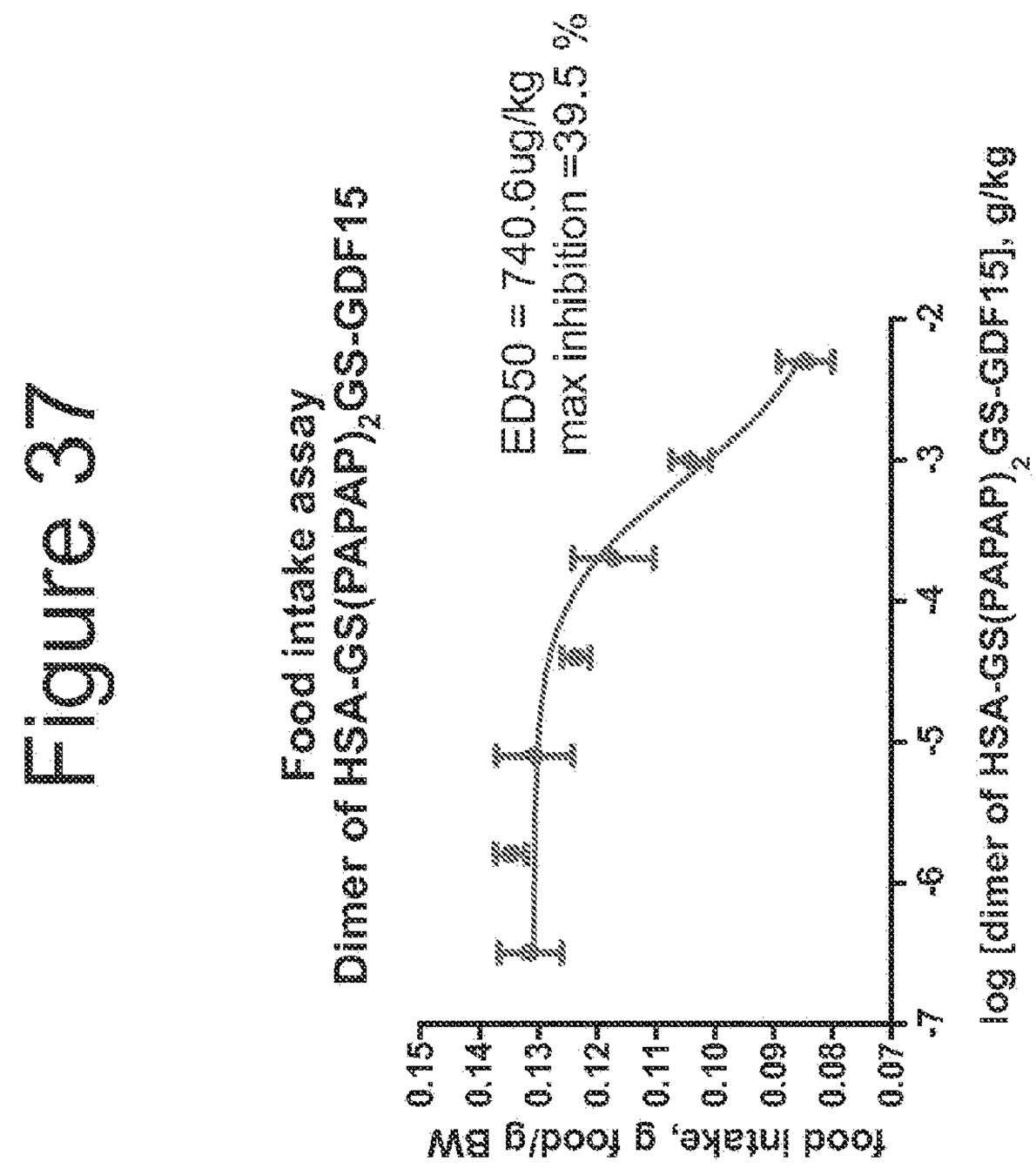
Food intake assay
Dimer of HSA-GS(PAPAP)2GS-GDF15
ED50 = 740.6ug/kg
max inhibition =39.5 %
food intake, g food/g BW
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GS(PAPAP)2 GS-GDF15], g/kg

Figure 38

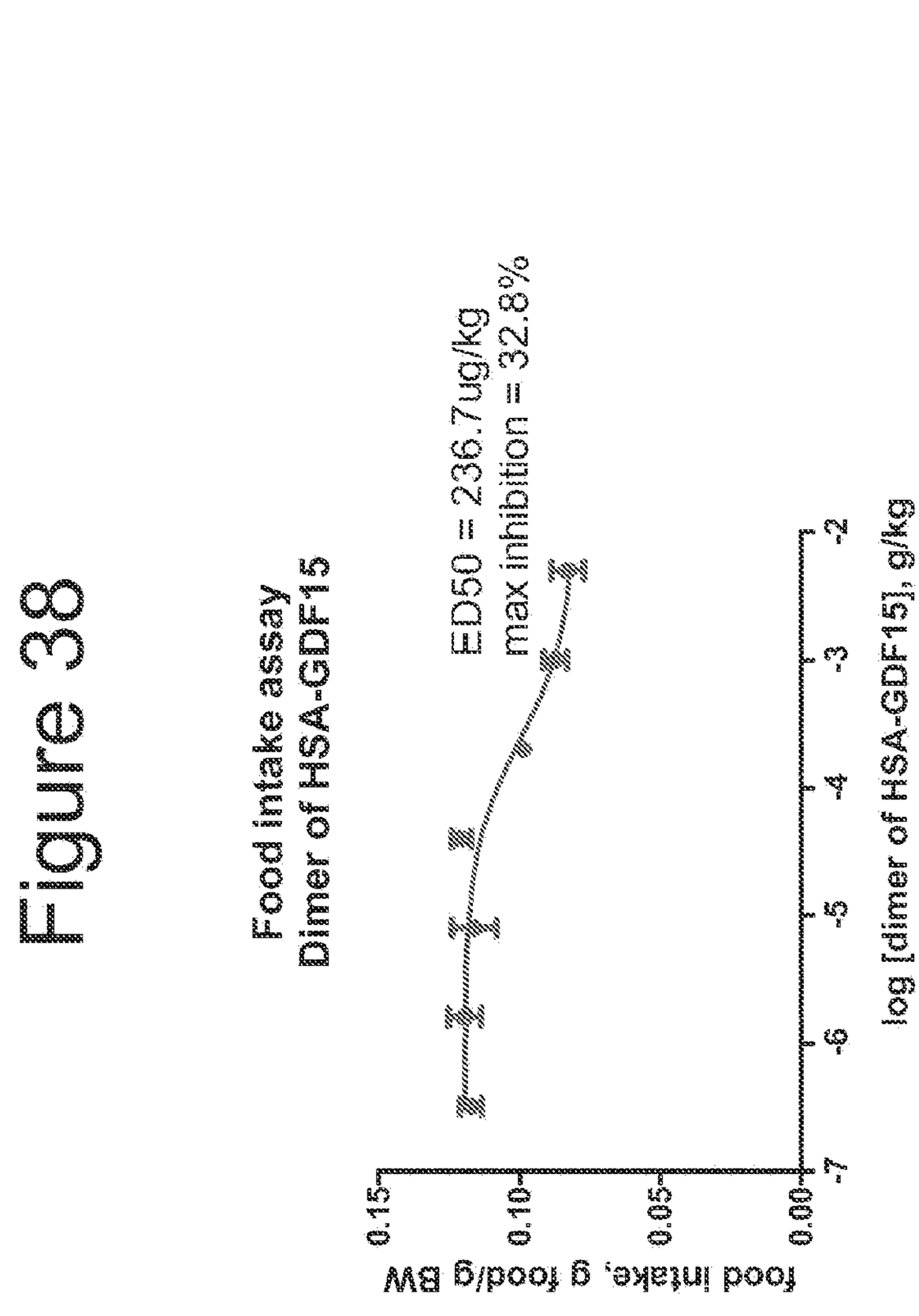
Food intake assay
Dimer of HSA-GDF15
ED50 = 236.7ug/kg
max inhibition = 32.8%
food intake, g food/g BW
0.15
0.10
0.05
0.00
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GDF15], g/kg

Figure 39

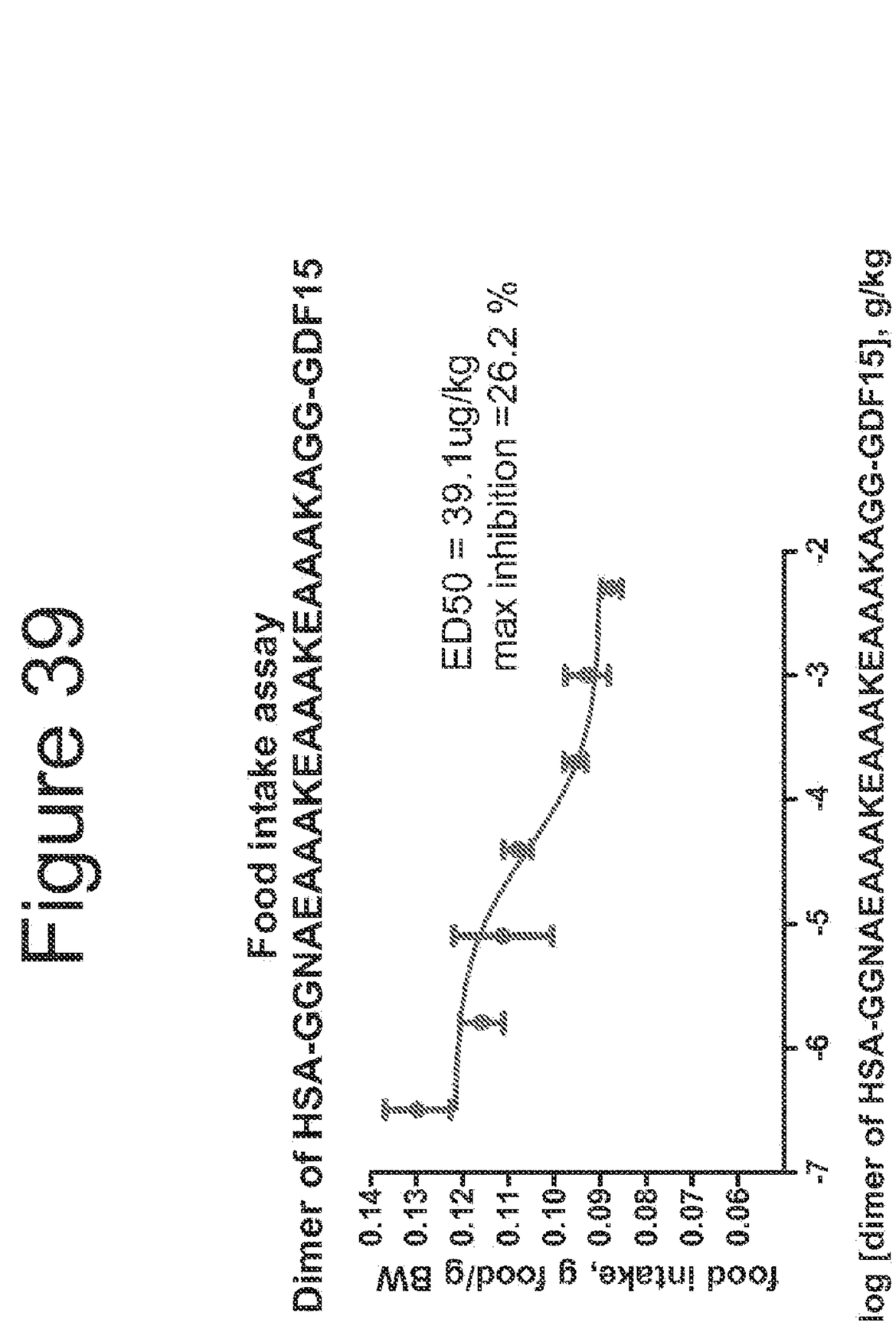
Food intake assay
Dimer of HSA-GGNAEAAAKEAAAAKAGG-GDF15
ED50 = 39.1ug/kg
max inhibition =26.2 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of HSA-GGNAEAAAKEAAAAKAGG-GDF15], g/kg

Figure 40

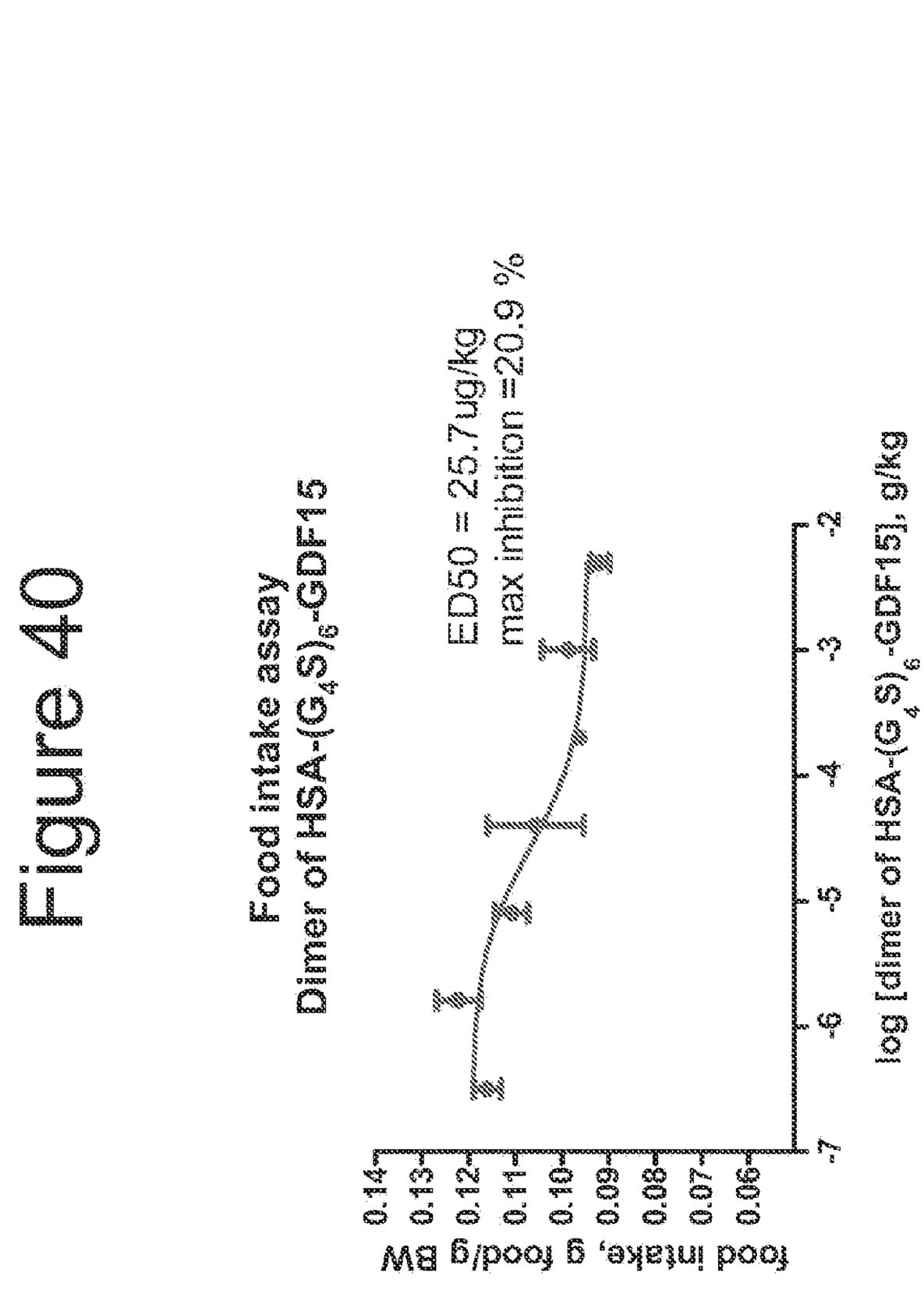
Food intake assay
Dimer of HSA-(G4S)6-GDF15
ED50 = 25.7ug/kg
max inhibition =20.9 %
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of HSA-(G4S)6-GDF15], g/kg

Figure 41

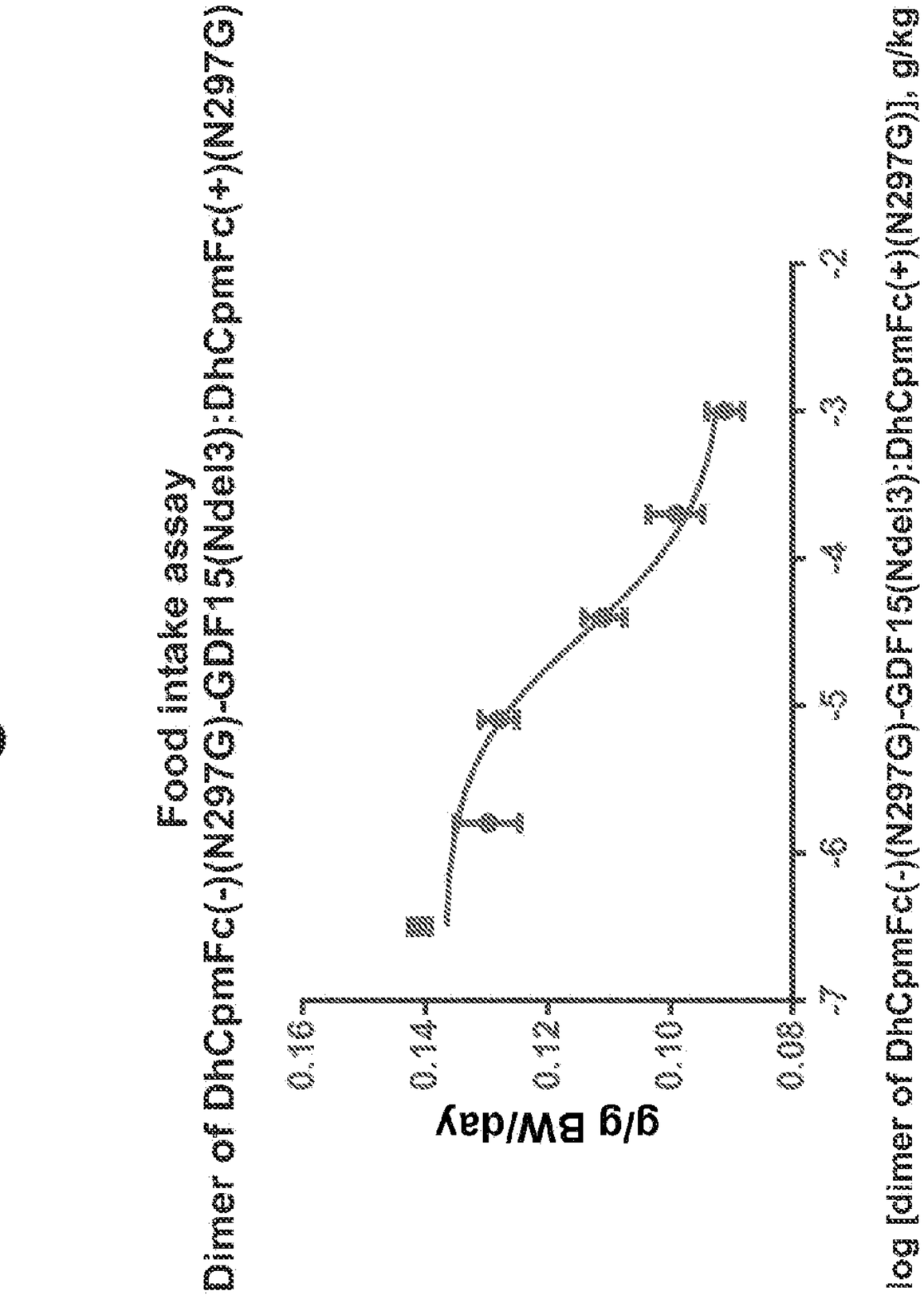
Dimer of DhCpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G)
Food intake assay
g/g BW/day
0.16
0.14
0.12
0.10
0.08
-7
-6
-5
-4
-3
log rd
Dimer of DhCpmFc(-)(N297G)-GDF15(Ndel3):DhCpmFc(+)(N297G)], g/kg

Figure 42

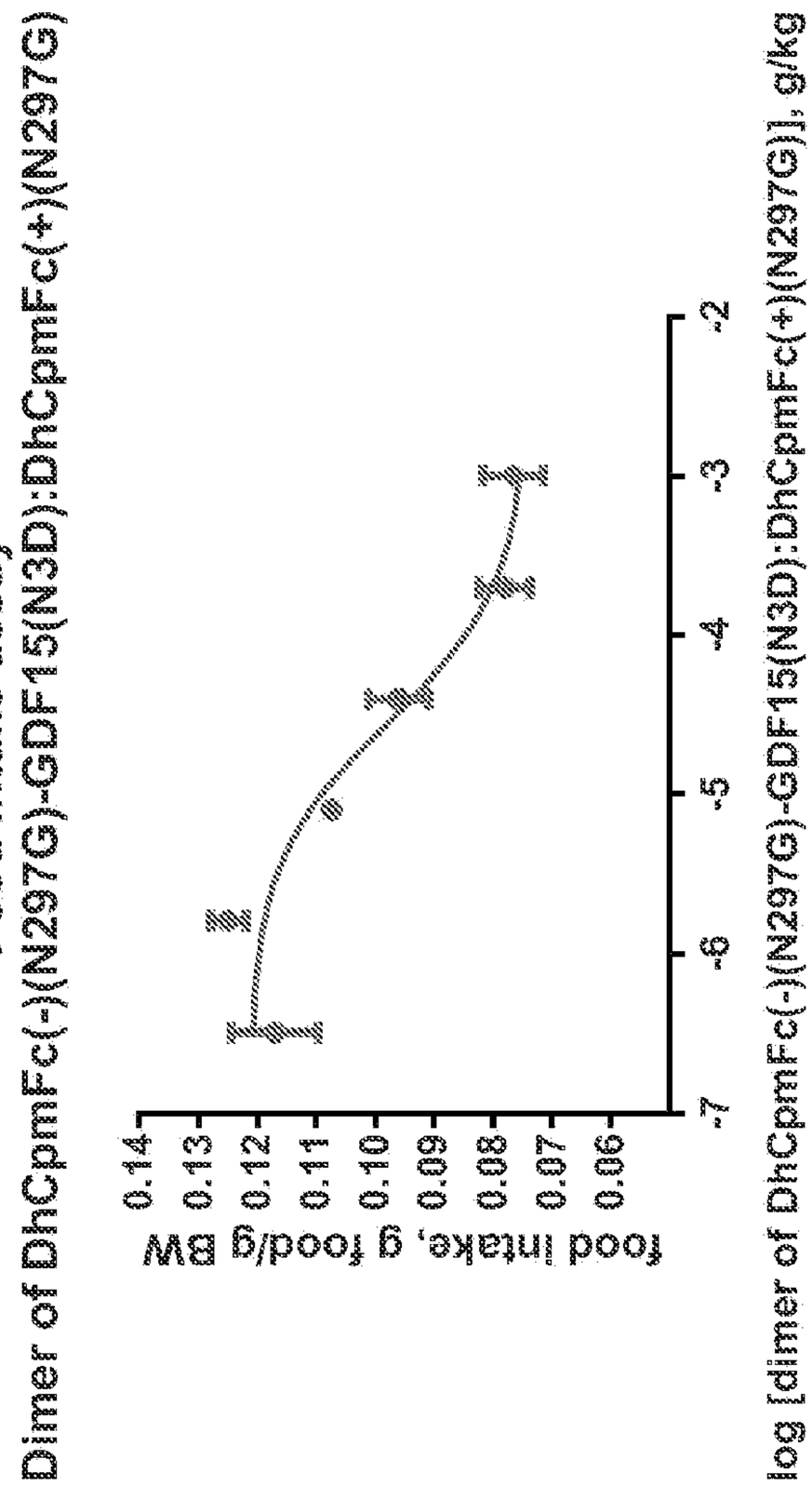
Food intake assay
dimer of DhCpmFc(-)/(N297G)-GDF15(N3D):DhCpmFc(+)/(N297G)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)/(N297G)-GDF15(N3D):DhCpmFc(+)/(N297G)], g/kg

Figure 43

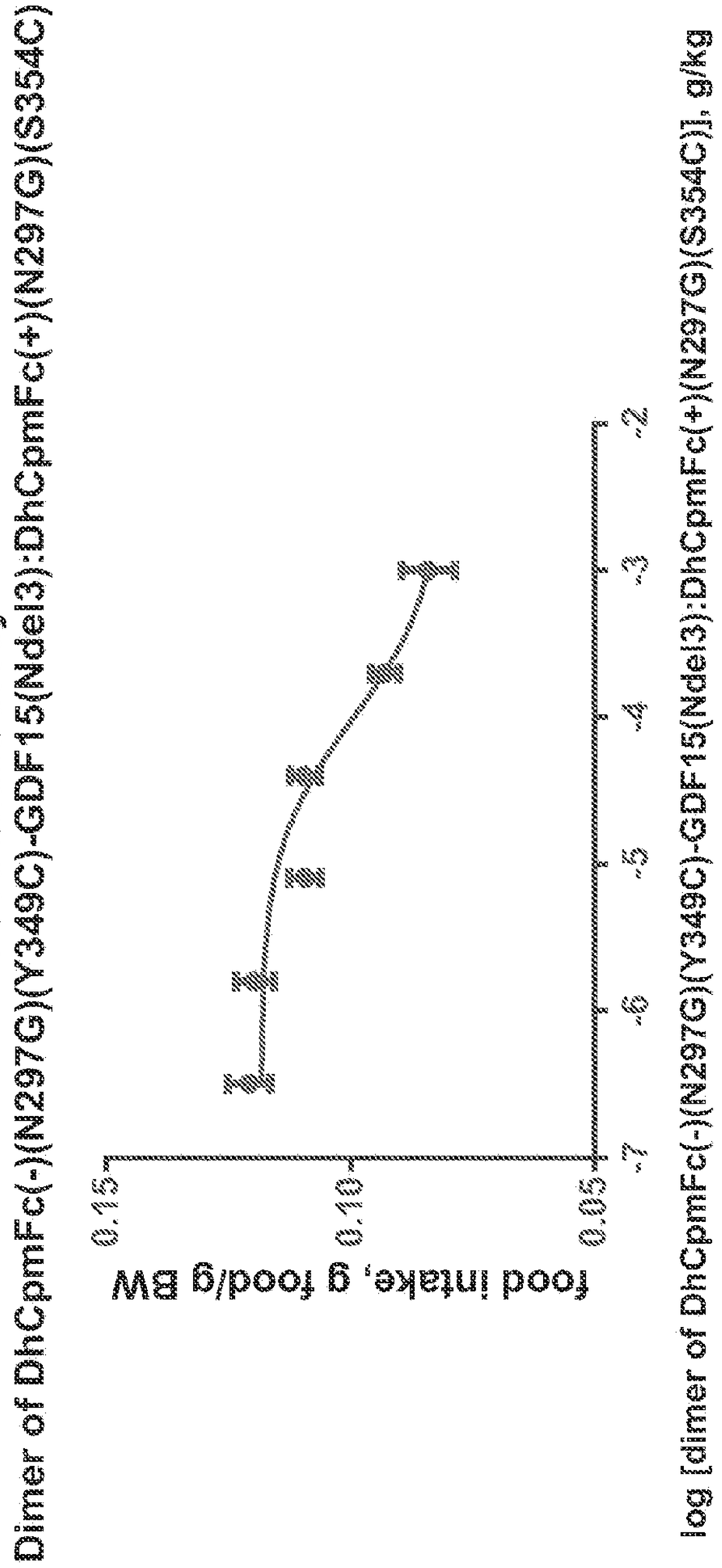
Food intake assay
Dimer of DhCpmFc(-)/(N297G)(Y349C)-GDF15(Ndel3):DhCpmFc(+)/(N297G)(S354C)
food intake, g food/g BW
0,15
0,10
0,05
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)/(N297G)(Y349C)-GDF15(Ndel3):DhCpmFc(+)/(N297G)(S354C)], g/kg

Figure 44

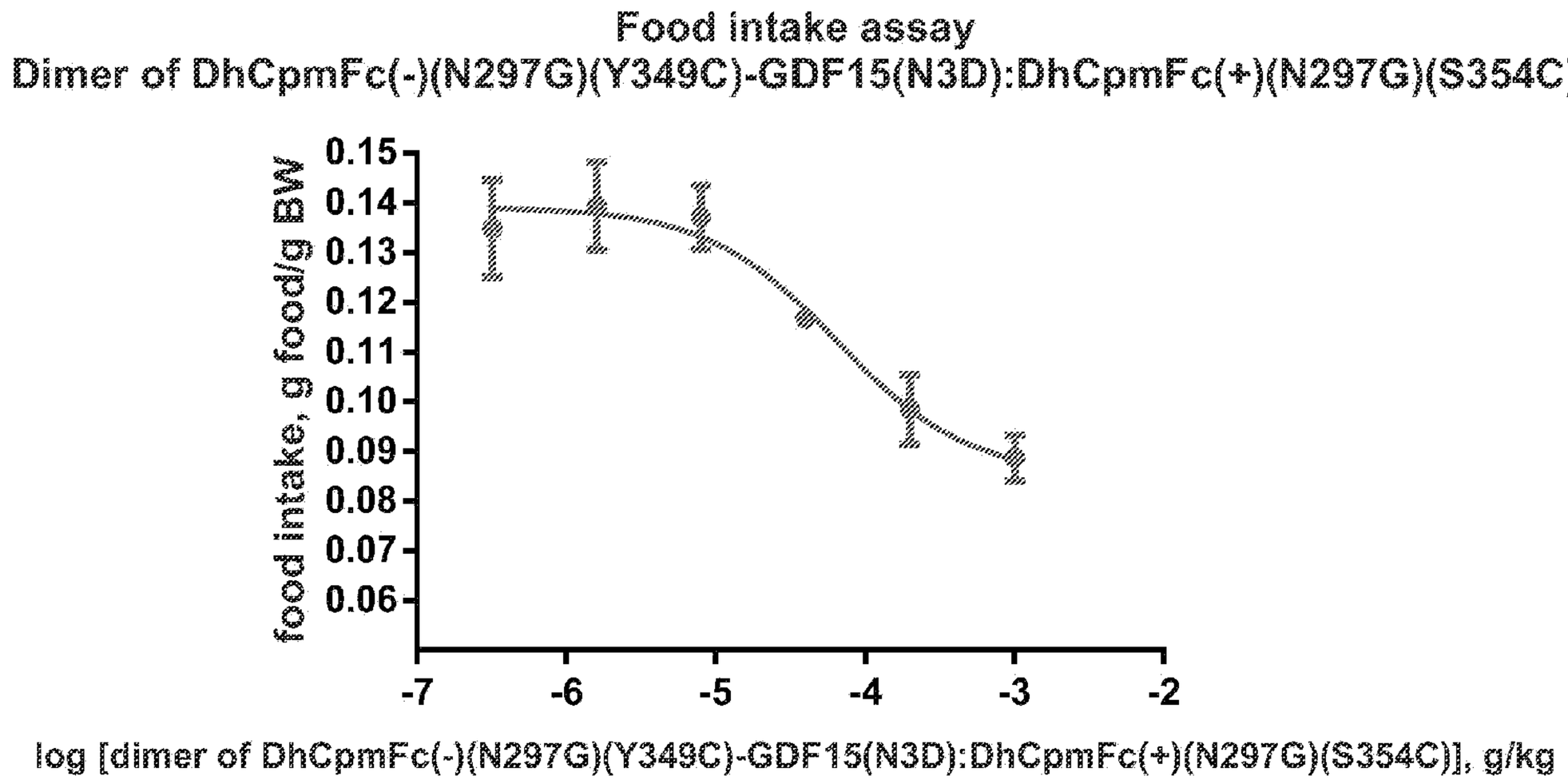

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Figure 45

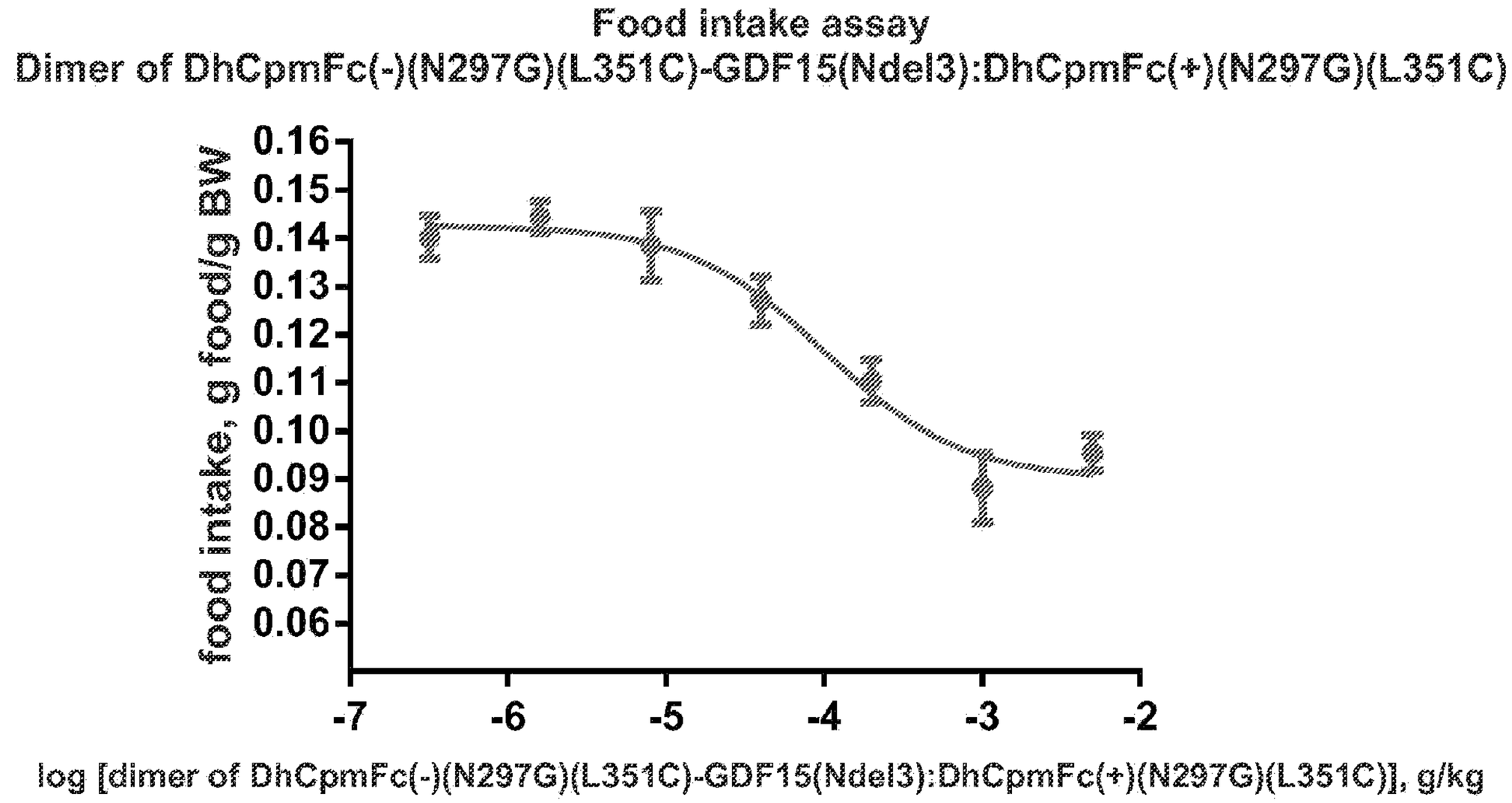

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Figure 46

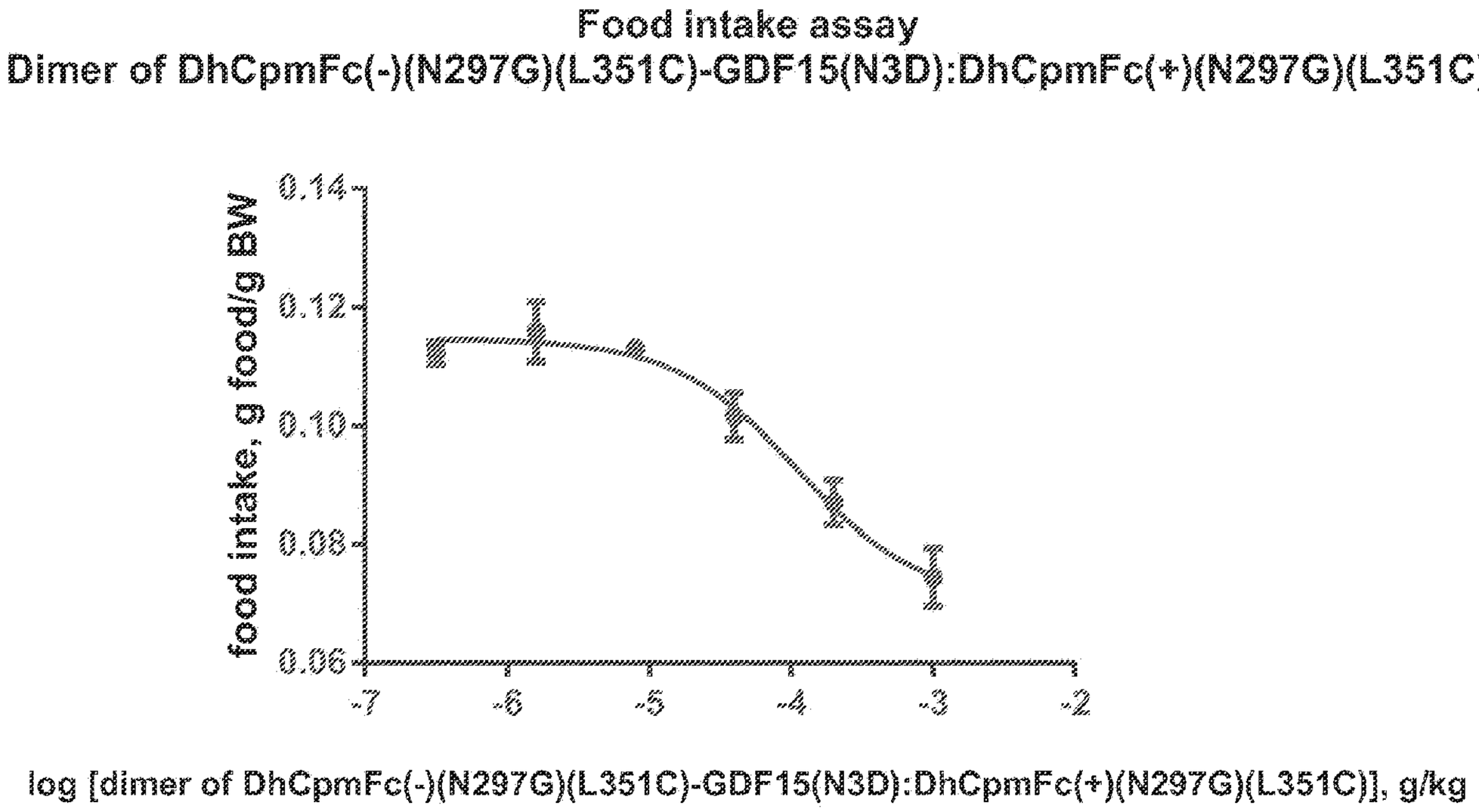

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Figure 47

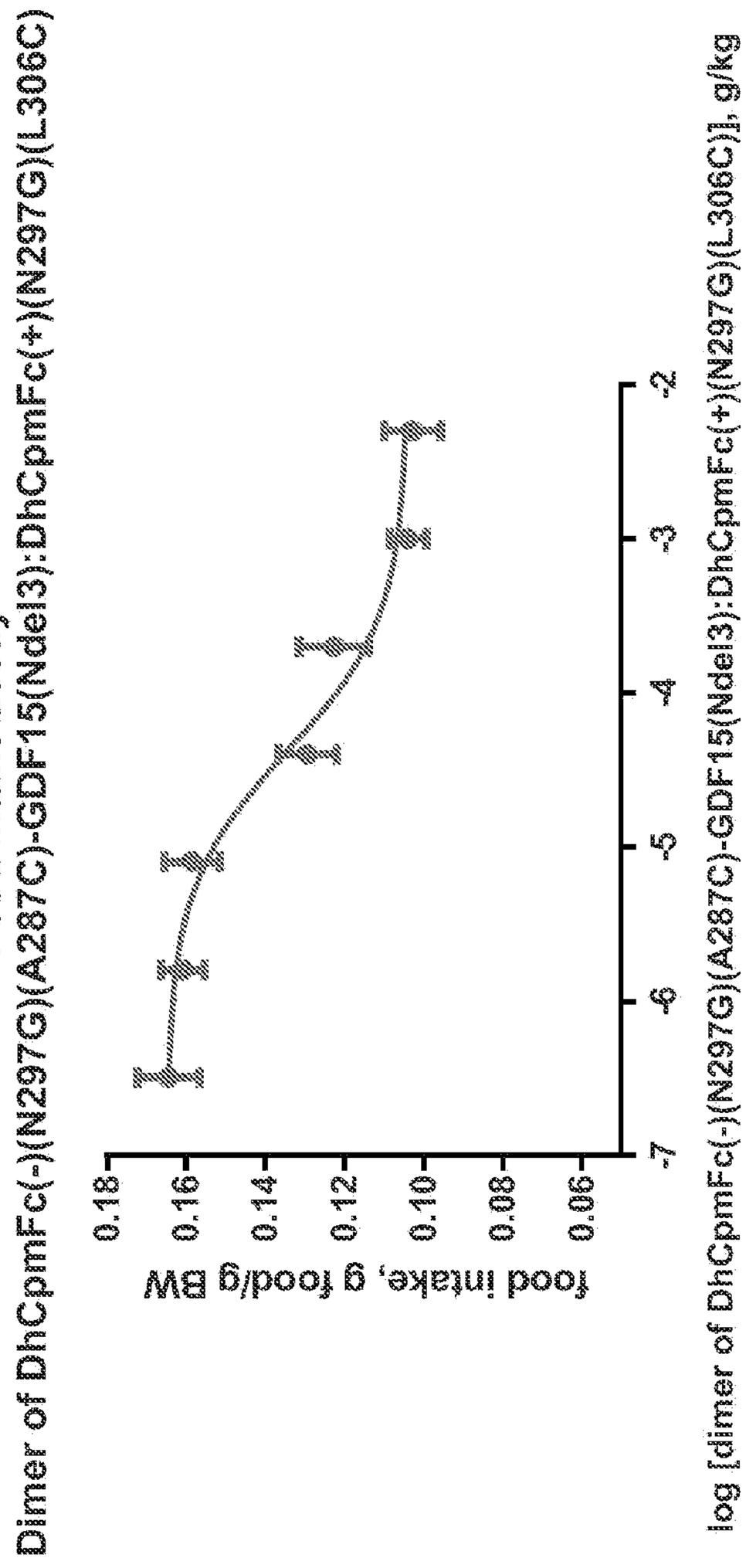
Food intake assay
Dimer of DhCpmFc(-)/(N297G)/(A287C)-GDF15(NdeI3):DhCpmFc(+)/(N297G)/(L306C)
food intake, g food/g BW
0.18
0.16
0.14
0.12
0.10
0.08
0.06
-7
-6
-5
-4
-3
-2
log [dimer of DhCpmFc(-)/(N297G)/(A287C)-GDF15(NdeI3):DhCpmFc(+)/(N297G)/(L306C)], g/kg

Figure 48

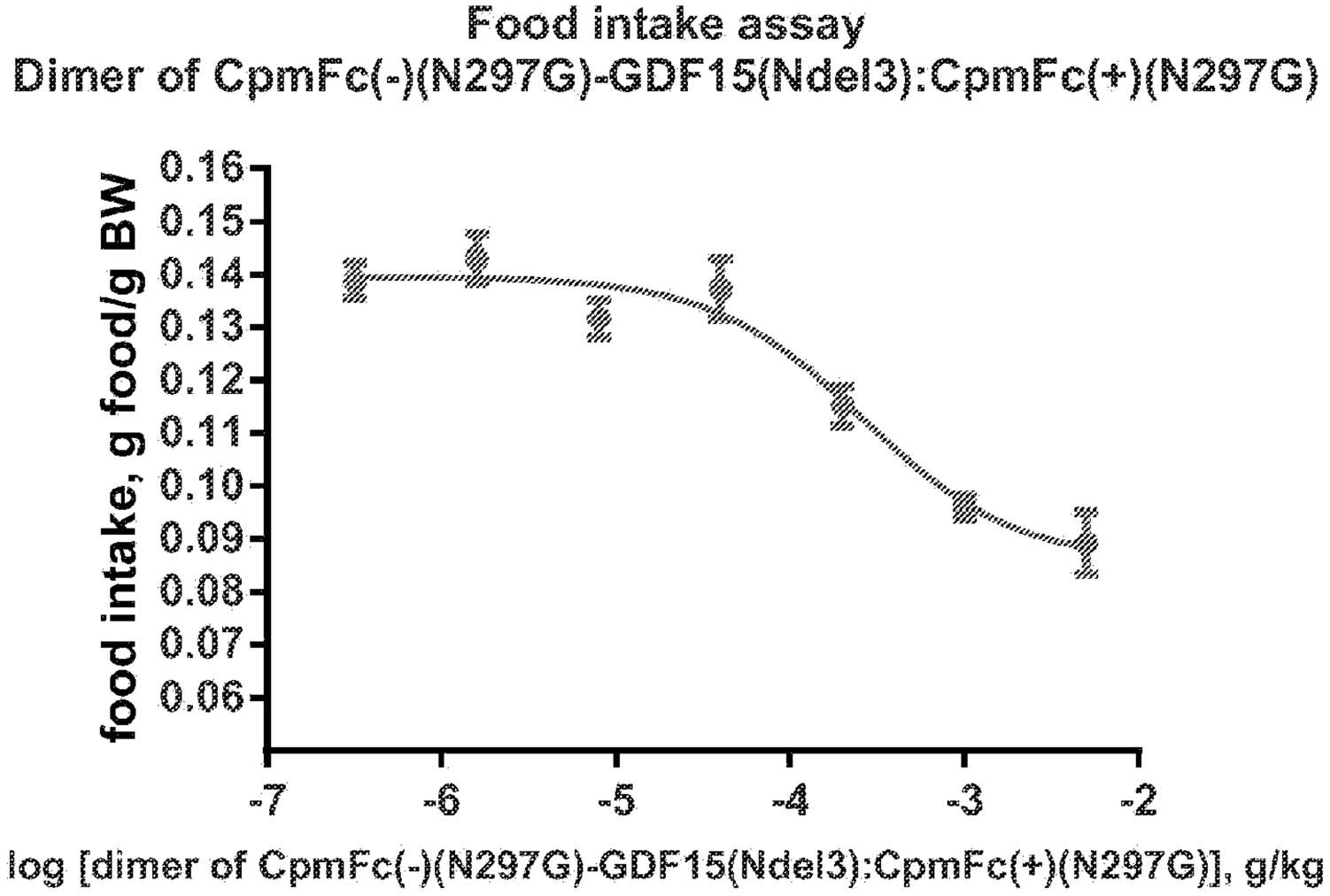

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Figure 49

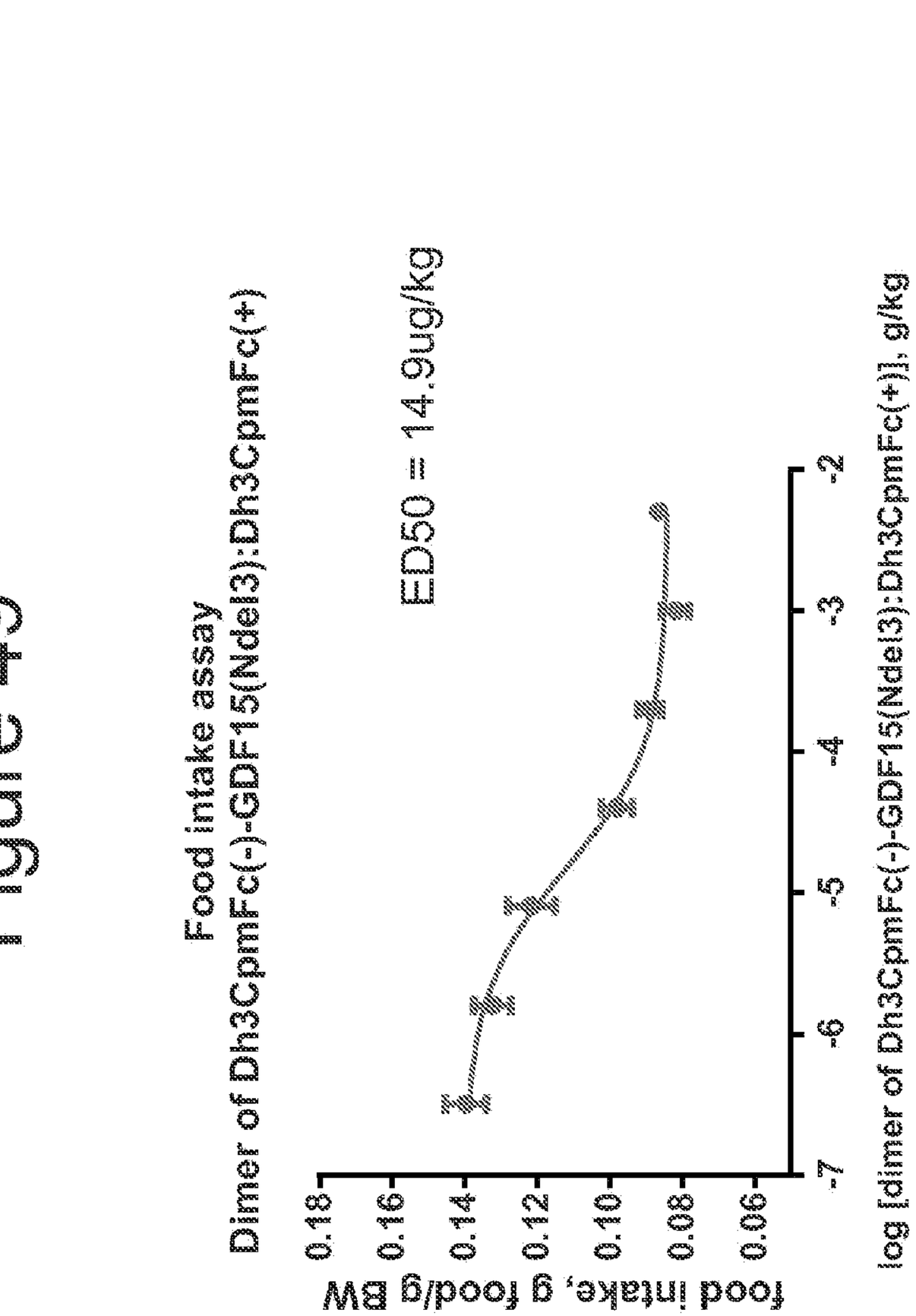
Food intake assay
Dimer of Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+)
ED50 = 14.9ug/kg
food intake, g food/g BW
0.18
0.16
0.14
0.12
0.10
0.08
0.06
-7
-6
-5
-4
-3
-2
log [dimer of Dh3CpmFc(-)-GDF15(Nde13):Dh3CpmFc(+)], g/kg

Figure 50

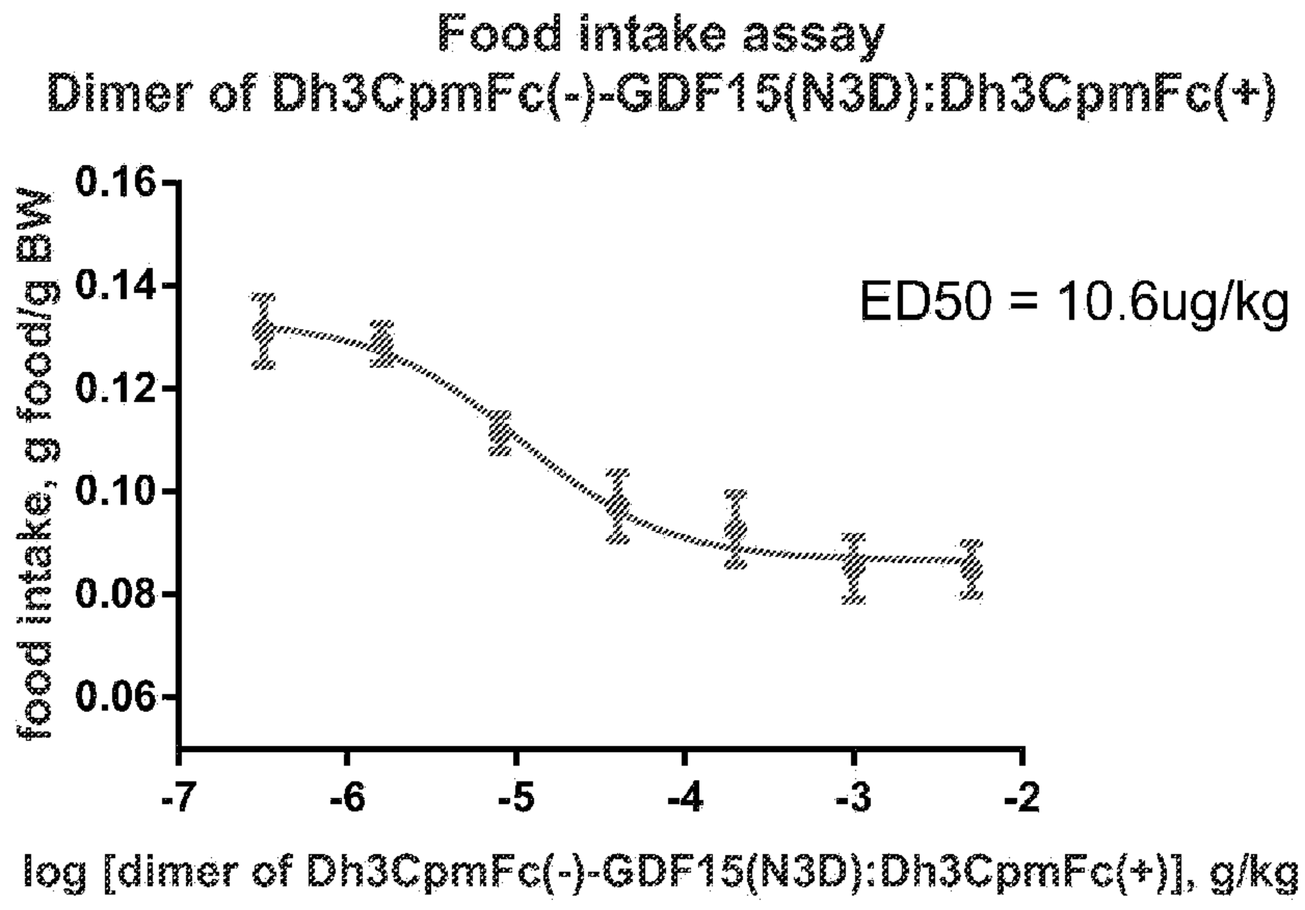

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Figure 51

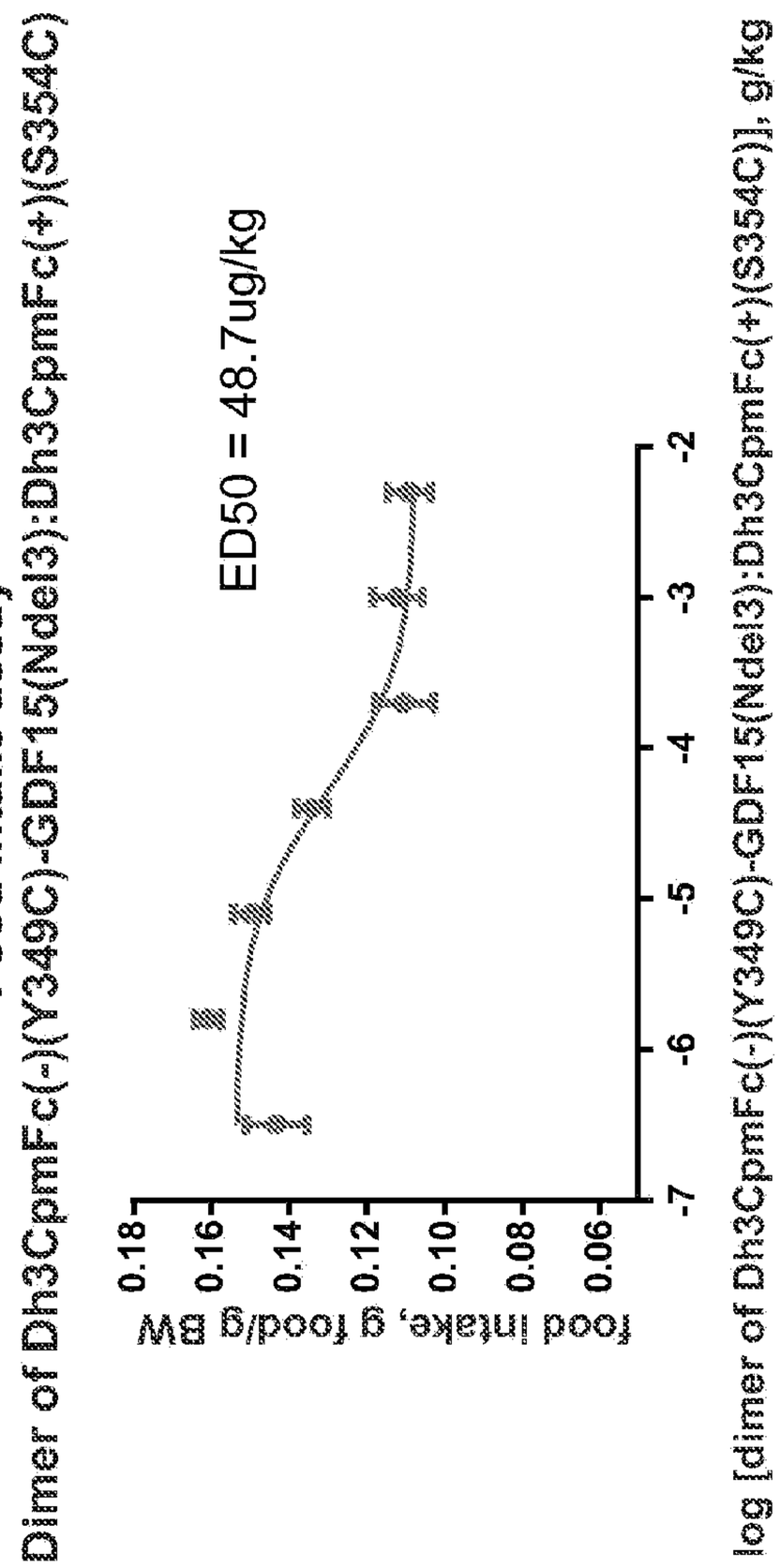

Dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):Dh3CpmFc(+)(S354C)
Food intake assay
ED50 = 48.7ug/kg
food intake, g food/g BW
0.18
0.16
0.14
0.12
0.10
0.08
0.06
-7
-6
-5
-4
-3
-2
log [Dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):Dh3CpmFc(+)(S354C)], g/kg

Figure 52

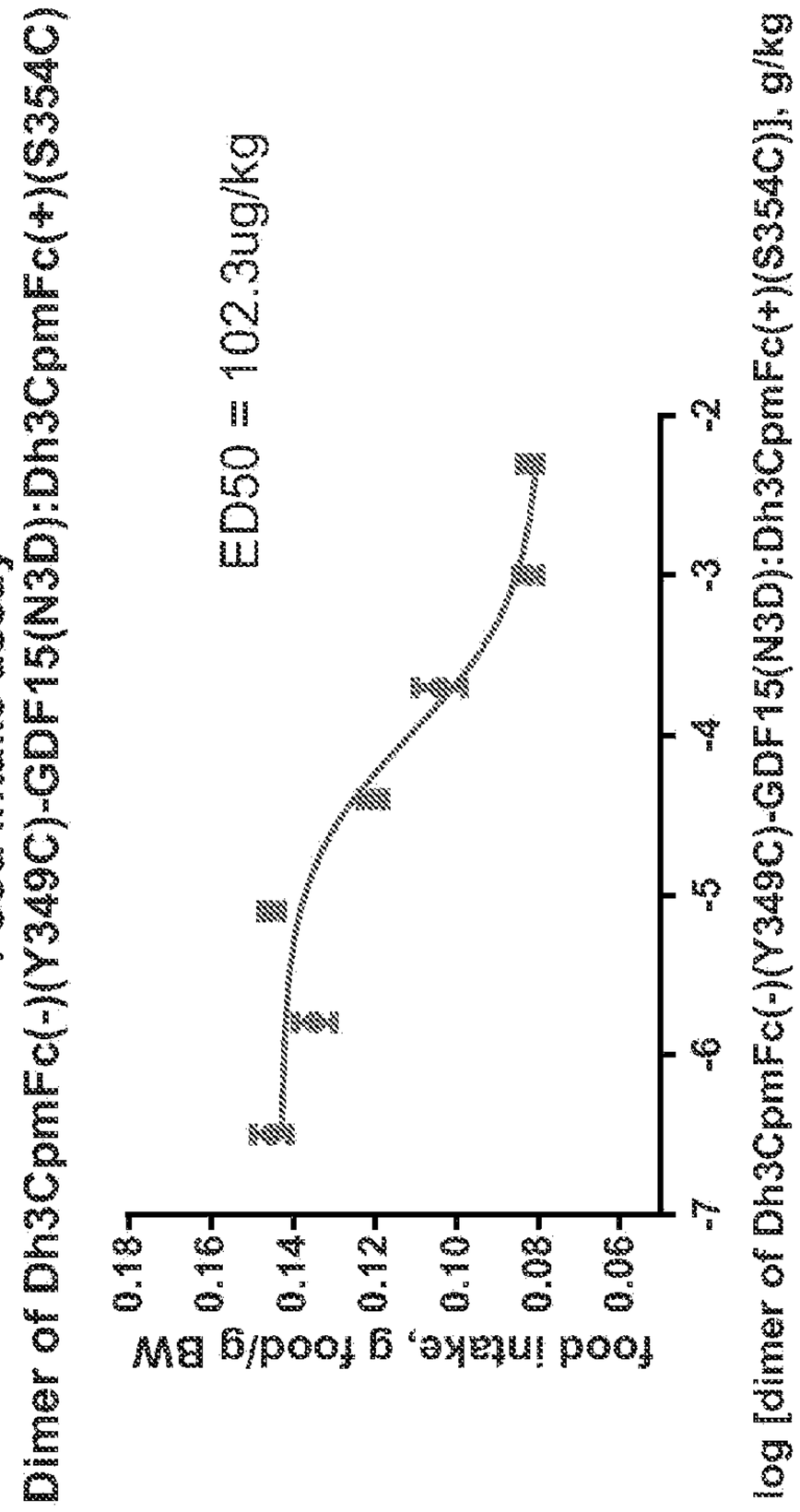

Food intake assay
Dimer of Dh3CpmFc(-)/(Y349C)-GDF15(N3D):Dh3CpmFc(+)/(S354C)
ED50 = 102.3ug/kg
food intake, g food/g BW
0.18
0.16
0.14
0.12
0.10
0.08
0.06
-7
-6
-5
-4
-3
-2
log [dimer of Dh3CpmFc(-)/(Y349C)-GDF15(N3D):Dh3CpmFc(+)/(S354C)], g/kg

Figure 53

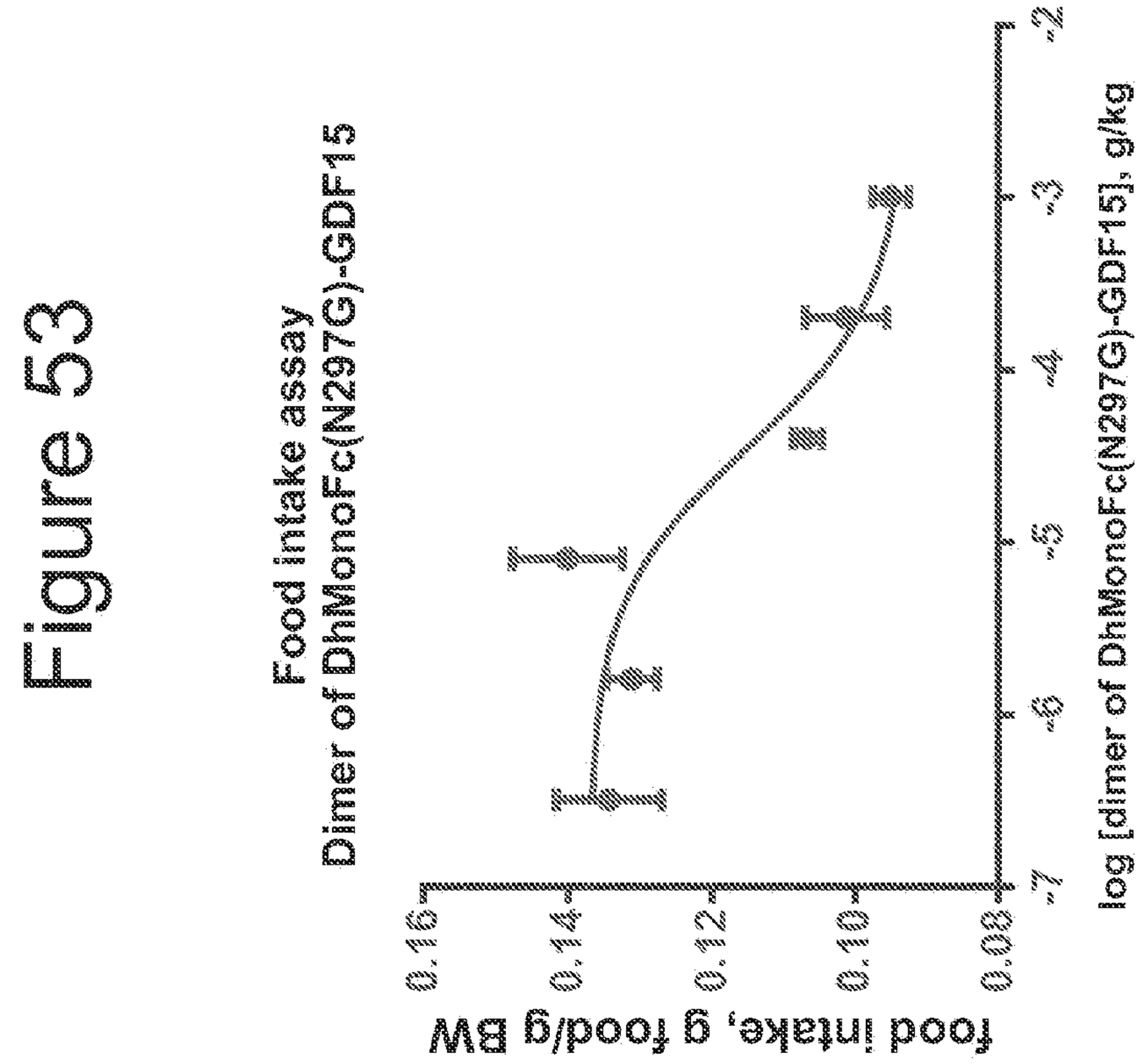

Food intake assay
Dimer of DhMonoFc(N297G)-GDF15
food intake, g food/g BW
0.16
0.14
0.12
0.10
0.08
log [dimer of DhMonoFc(N297G)-GDF15], g/kg
-5
-4
-3
-2
-7
-6

Figure 54

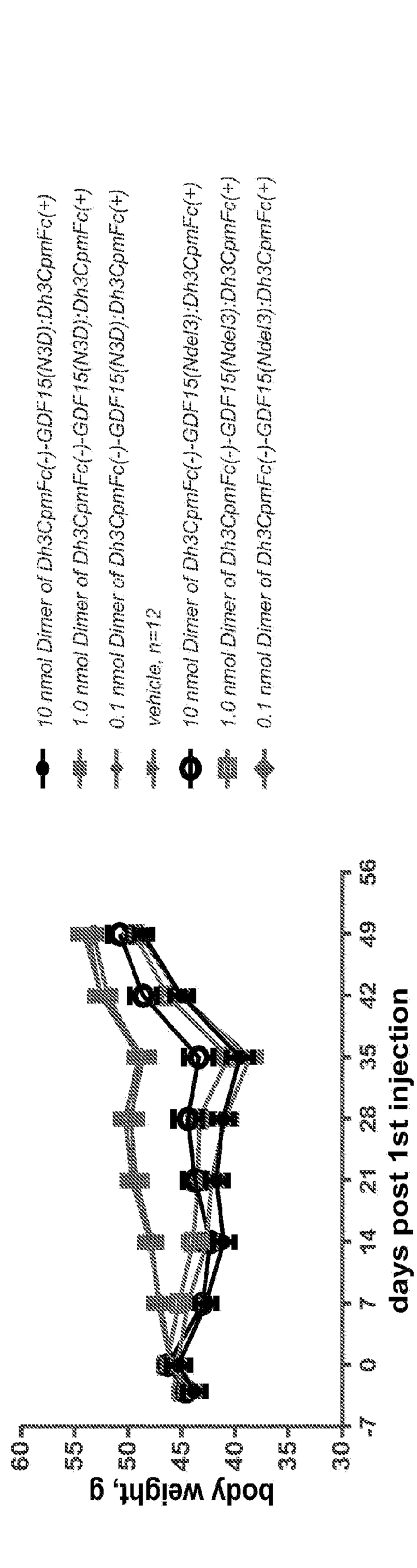

10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
Body weight
body weight, g
60
55
50
45
40
35
30
-7
0
7
14
21
28
35
42
49
days post 1st injection

Figure 55

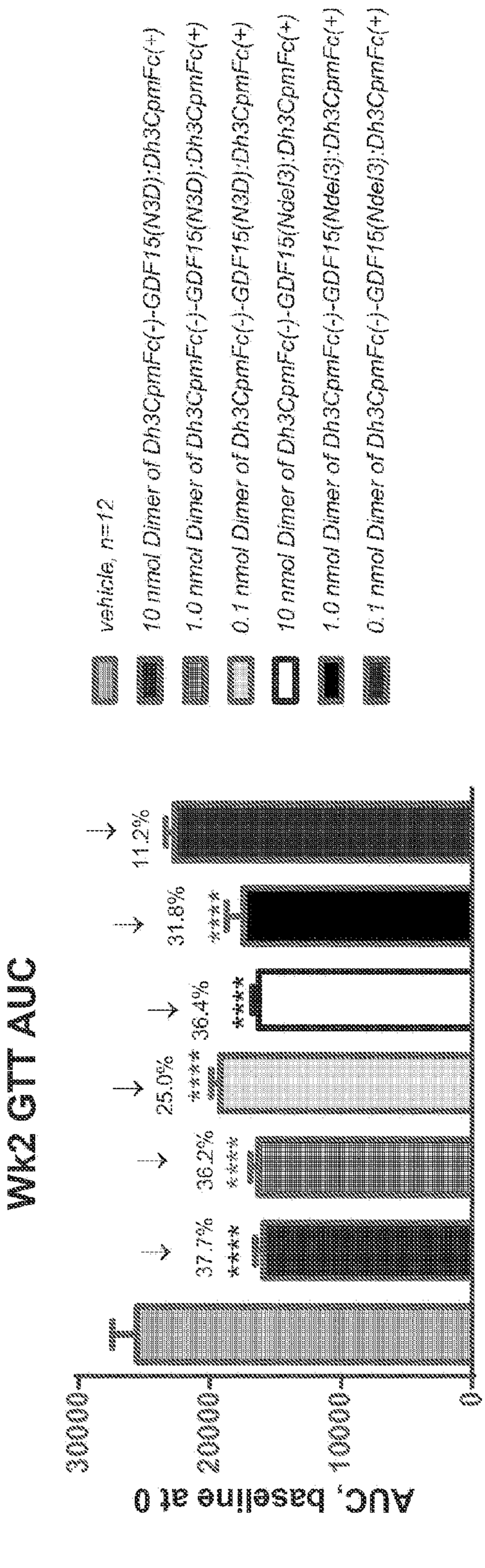

Wk2 GTT AUC
AUC, baseline at 0
30000
20000
10000
0
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
10 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
11.2%
31.8%
****
37.7%
****
36.2%
****
25.0%
****
36.4%
****

Figure 56

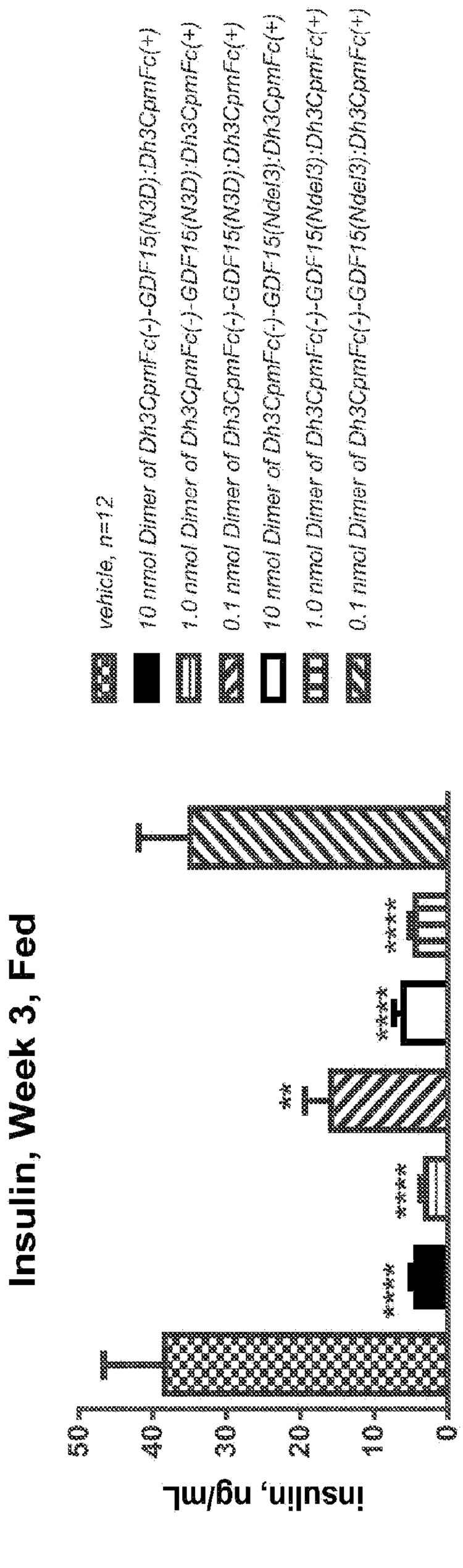

Insulin, Week 3, Fed
insulin, ng/mL
0
10
20
30
40
50
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
10 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
****
**
****
****
****
****

Figure 57

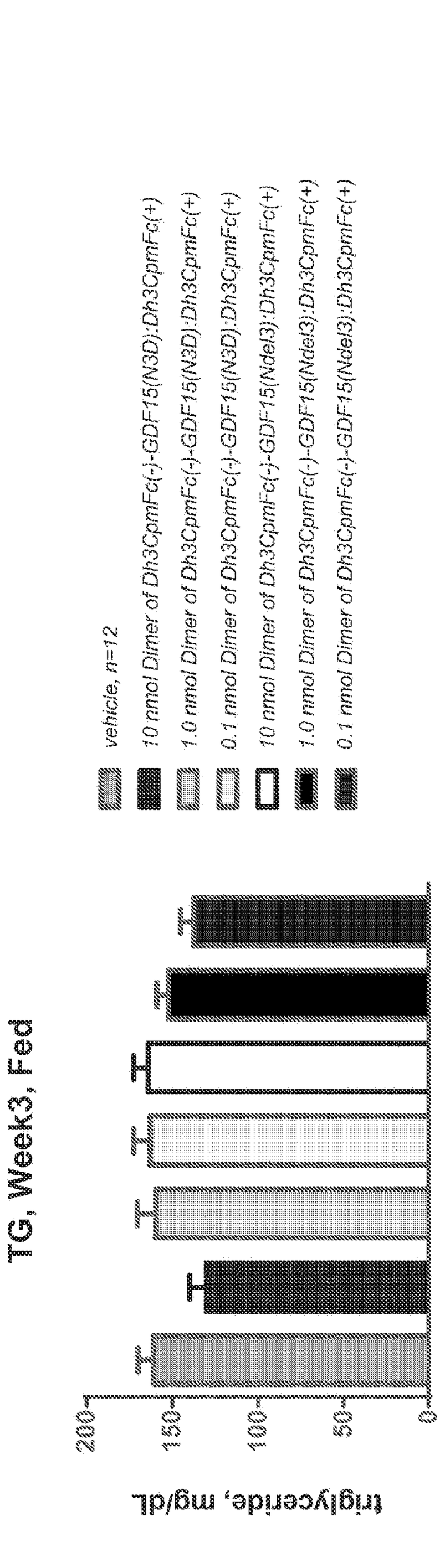

TG, Week3, Fed
triglyceride, mg/dL
200
150
100
50
0
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
10 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)

Figure 58

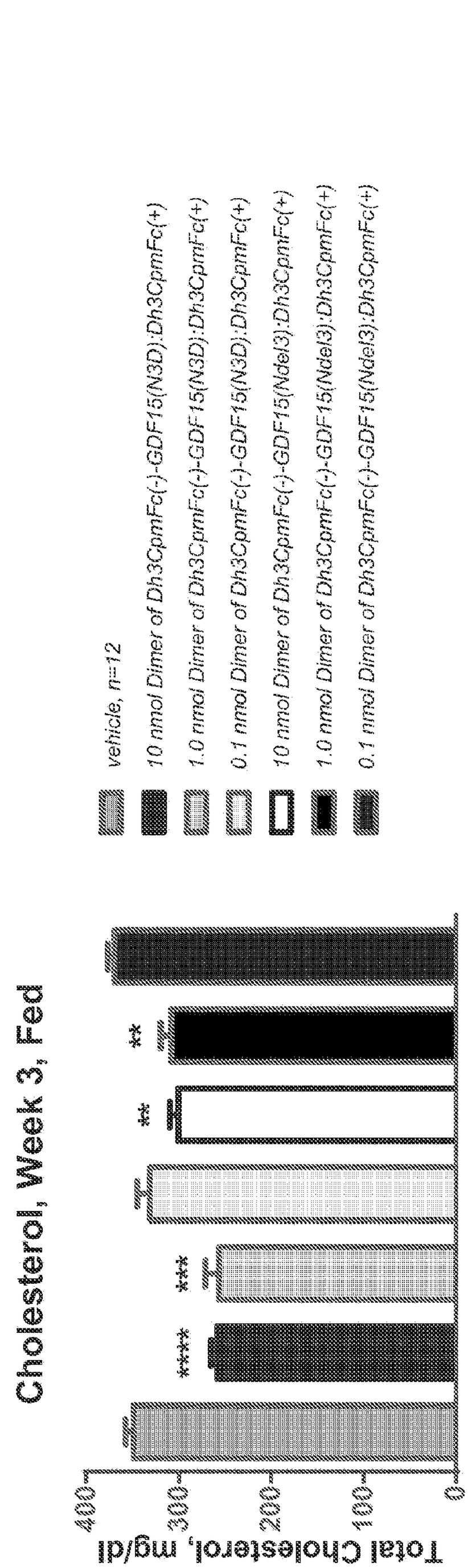

Cholesterol, Week 3, Fed
Total Cholesterol, mg/dl
400
300
200
100
0
****
***
**
**
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
10 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)

Figure 59

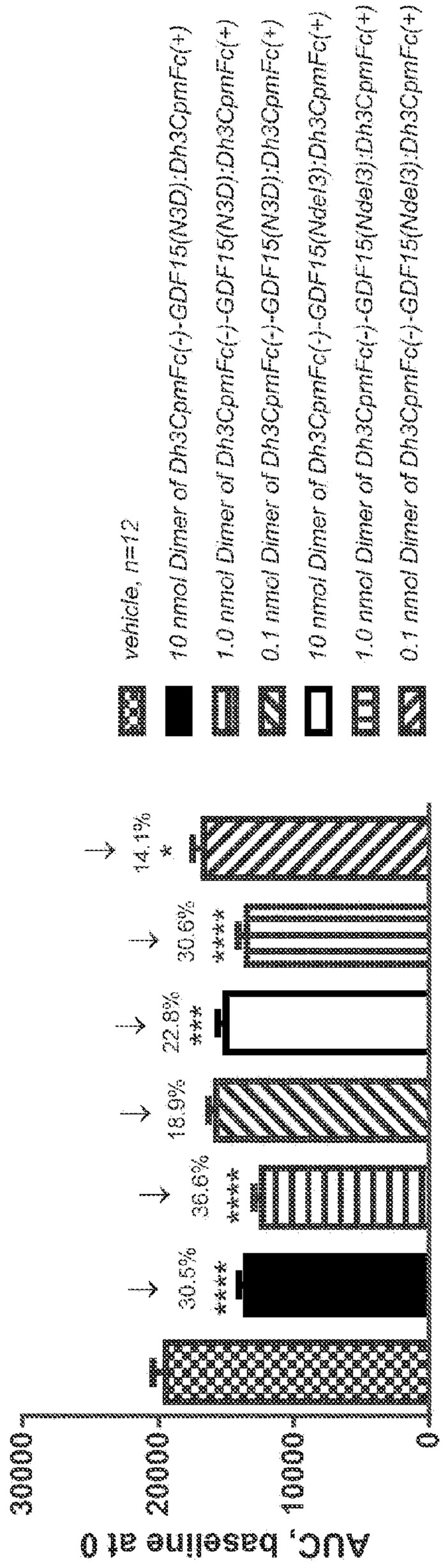

Wk5 GTT AUC
AUC, baseline at 0
30000
20000
10000
0
30.5%
****
36.6%
****
18.9%
22.8%
***
14.1%
*
30.6%
****
vehicle, n=12
10 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
10 nmol Dimer of Dh3CpmFc(-)-GDF15(NdeI3):Dh3CpmFc(+)
1.0 nmol Dimer of Dh3CpmFc(-)-GDF15(NdeI3):Dh3CpmFc(+)
0.1 nmol Dimer of Dh3CpmFc(-)-GDF15(NdeI3):Dh3CpmFc(+)

Figure 60

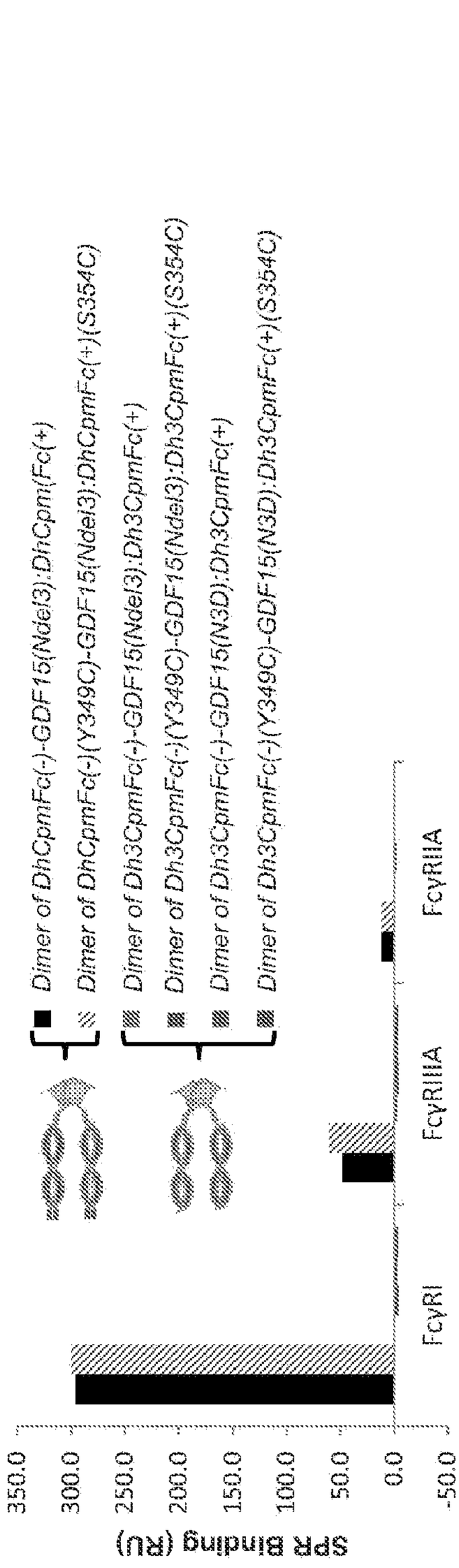
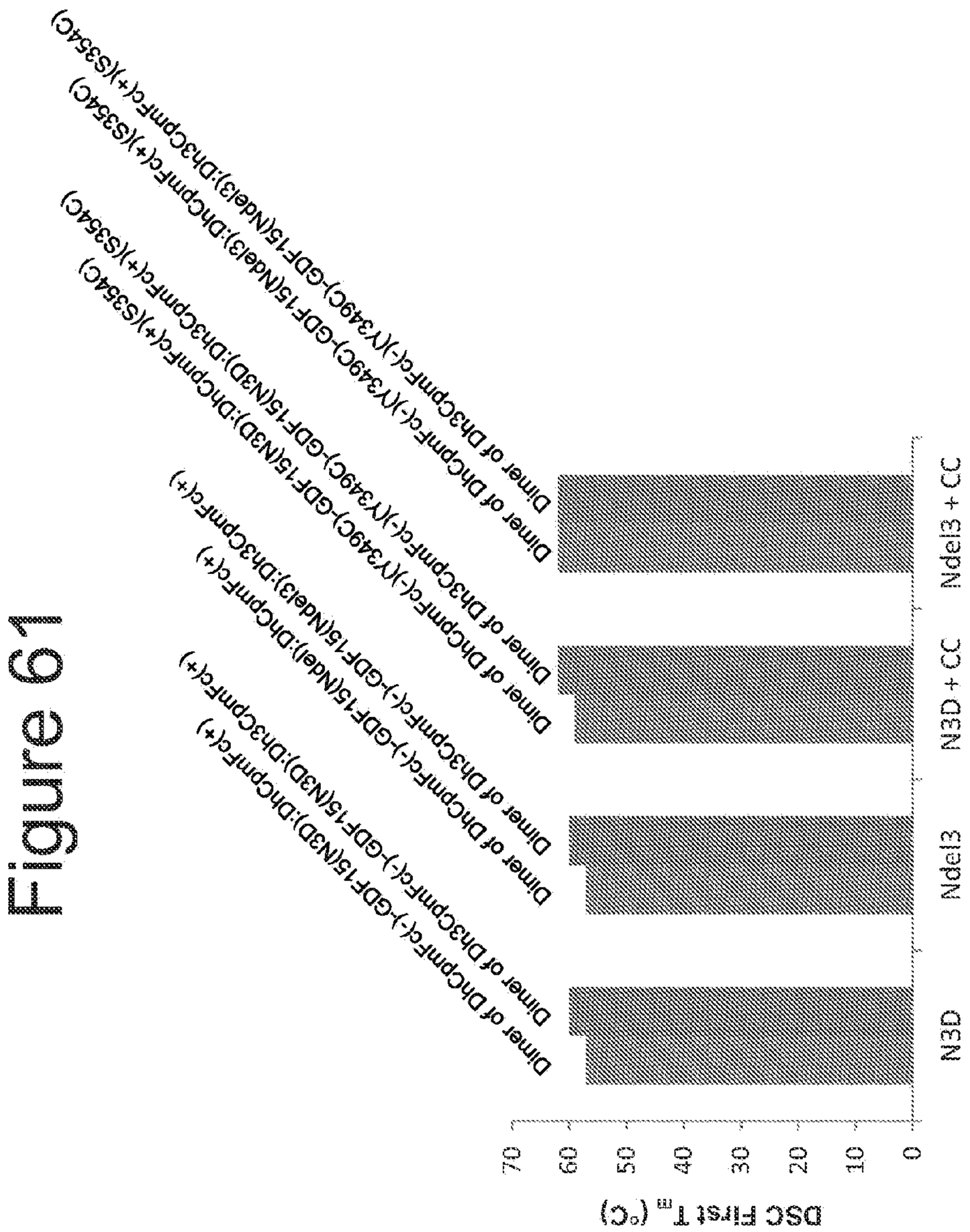

Dimer of DhCpmFc(-)-GDF15(Ndel3):DhCpm(Fc(+)
Dimer of DhCpmFc(-)(Y349C)-GDF15(Ndel3):DhCpmFc(+)(S354C)
Dimer of Dh3CpmFc(-)-GDF15(Ndel3):Dh3CpmFc(+)
Dimer of Dh3CpmFc(-)(Y349C)-GDF15(Ndel3):Dh3CpmFc(+)(S354C)
Dimer of Dh3CpmFc(-)-GDF15(N3D):Dh3CpmFc(+)
Dimer of Dh3CpmFc(-)(Y349C)-GDF15(N3D):Dh3CpmFc(+)(S354C)
FcγRIIIA
FcγRIIA
FcγRI
SPR binding (RU)
350.0
300.0
250.0
200.0
150.0
100.0
50.0
0.0
-50.0

Figure 61


DSC First T_m (°C)
0
10
20
30
40
50
60
70
N3D
Ndel3
N3D + CC
Ndel3 + CC
Dimer of Dhcpmfc(-)-GDF-15(N3D):Dhcpmfc(+)
Dimer of Dhcpmfc(-)-GDF-15(Ndel):Dhcpmfc(+)
Dimer of Dhcpmfc(-)-GDF-15(N3D):Dh3Cpmfc(+)(S354C)
Dimer of Dhcpmfc(-)(Y349C)-GDF-15(Ndel3):Dhcpmfc(+)(S354C)
Dimer of Dhcpmfc(-)(Y349C)-GDF-15(N3D):Dh3Cpmfc(+)(S354C)