pharmacological administration of FGF21 for the treatment of type 2 diabetes, obesity, dyslipidemia, and other metabolic conditions or disorders in humans.

Human FGF21 has a short half-life *in vivo*. In mice, the half-life of human FGF21 is 1 to 2 hours, and in cynomolgus monkeys, the half-life is 2.5 to 3 hours. In developing an FGF21 protein for use as a therapeutic in the treatment of type 2 diabetes, an increase in half-life would be desirable. FGF21 proteins having an enhanced half-life would allow for less frequent dosing of patients being administered the protein. Such proteins are described herein.

SUMMARY ~~OF THE INVENTION~~

The present disclosure provides an isolated polypeptide comprising an amino acid sequence of SEQ ID NO:4, further comprising the substitution of any amino acid for: the alanine residue at position 45, the leucine residue at position 86, the leucine residue at position 98, the alanine residue at position 111, the alanine residue at position 129, the glycine residue at position 170, the proline residue at position 171 or the serine residue at position 172, and combinations thereof. In one embodiment the isolated polypeptide comprises the substitution of any amino acid for: the leucine residue at position 98, the proline residue at 171 or both the leucine residue at position 98 and the proline residue at position 171. In another embodiment the isolated polypeptide comprises the substitution of any amino acid for both the leucine residue at position 98 and the proline residue at position 171.

The present disclosure also provides an isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 4 having: (a) at least one amino acid substitution that is: (i) a glutamine, isoleucine, or lysine residue at position 19; (ii) a histidine, leucine, or phenylalanine residue at position 20; (iii) an isoleucine, phenylalanine, tyrosine, or valine residue at position 21; (iv) an isoleucine, phenylalanine, or valine residue at position 22; (v) an alanine or arginine residue at position 150; (vi) an alanine or valine residue at position 151; (vii) a histidine, leucine, phenylalanine, or valine residue at position 152; (viii) an alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, proline, or serine residue at position 170; (ix) an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, serine, threonine,

acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal.

In some embodiments, the polypeptides disclosed herein can be covalently linked to one or more polymers, such as PEG. In other embodiments, the polypeptides of the present invention can be fused to a heterologous amino acid sequence, optionally via a linker, such as GGGGGSGGGSGGGGS (SEQ ID NO: 23). The heterologous amino acid sequence can be an IgG constant domain or fragment thereof, such as the amino acid sequence of SEQ ID NO:13. Such fusion polypeptides disclosed herein can also form multimers.

The present disclosure also provides pharmaceutical compositions comprising the polypeptides disclosed herein and a pharmaceutically acceptable formulation agent. Such pharmaceutical compositions can be used in a method for treating a metabolic disorder, and the method comprises administering to a human patient in need thereof a pharmaceutical composition of the present invention. Metabolic disorders that can be treated include diabetes and obesity.

Also provided are isolated nucleic acid molecules encoding the polypeptides of disclosed herein, as well as vectors comprising such nucleic acid molecules and host cells comprising such nucleic acid molecules.

Truncated forms of the polypeptide of SEQ ID NO:4 are also disclosed. In various embodiments the polypeptide can comprise: (a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; (b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or (c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal.

In one aspect, there is provided an isolated fusion protein comprising:

(a) an IgG constant domain;

(b) a linker sequence fused to the IgG constant domain; and

(c) an FGF21 mutant fused to the linker sequence and wherein the FGF21 mutant comprises the amino acid sequence of SEQ ID NO: 4, wherein an arginine residue has been substituted for the leucine residue at position 98, and wherein a glutamic acid residue has been substituted for the glycine at position 170.

The present disclosure additionally provides an isolated fusion protein that can comprise: (a) an IgG constant domain; (b) a linker sequence fused to the IgG constant domain; and (c) an FGF21 mutant fused to the linker sequence and comprising the amino acid sequence of SEQ ID NO: 4 wherein the an arginine residue has been substituted for the leucine residue at position 98 and a glycine residue has been substituted for the

proline residue at position 171. In one embodiment, the linker sequence can comprise GGGGGSGGGSGGGGS (SEQ ID NO:23) and in another the IgG constant domain can comprise SEQ ID NO: 13. In another embodiment, the linker sequence comprises GGGGGSGGGSGGGGS (SEQ ID NO:23) and the IgG constant domain comprises the amino acid sequence of SEQ ID NO: 13. In still another embodiment the N terminus of the linker is fused to the C terminus of the IgG constant domain and the N terminus of the FGF21 mutant is fused to the C terminus of the linker. The disclosed fusion proteins can form multimers.

In various embodiments of the fusion protein, the FGF21 mutant component can comprise at least one amino acid substitution that is: (a) a phenylalanine, proline, alanine, serine or glycine at position 179; (b) a glutamic acid, glycine, proline, or serine at position 180; or (c) a lysine, glycine, threonine, alanine, leucine, or proline at position 181 and can further comprise 1 to 10 amino acid residues fused to the C-terminus of the FGF21 mutant, and the 1 to 10 amino acid residues, and can be any amino acid, for example, one or more residues selected from the group consisting of glycine, proline and combinations thereof.

In still other embodiments of the fusion protein, the FGF21 mutant component can comprise: (a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; (b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or (c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal. In another embodiment, the FGF21 mutant component of a fusion protein can comprise an amino acid sequence that is at least 85 percent identical to the amino acid sequence of SEQ ID NO: 4, but wherein the arginine and glycine residues are not further modified.

In one aspect, there is provided a ~~The present disclosure also provides~~ pharmaceutical compositions comprising the isolated fusion protein disclosed herein and a pharmaceutically acceptable formulation agent. Such pharmaceutical compositions can be used in a method for treating a metabolic disorder, the method comprising administering to a human patient in need thereof a

pharmaceutical composition of the present invention. Metabolic disorders that can be treated include diabetes and obesity.

Also provided are isolated nucleic acid molecules encoding the fusion protein disclosed herein, as well as vectors comprising such nucleic acid molecules and host cells comprising such nucleic acid molecules.

In one aspect, there is provided an isolated nucleic acid encoding a fusion protein comprising:

(a) an IgG constant domain;

(b) a linker sequence fused to the IgG constant domain; and

(c) an FGF21 mutant fused to the linker sequence and wherein the FGF21 mutant comprises the amino acid sequence of SEQ ID NO: 4, wherein an arginine residue has been substituted for the leucine residue at position 98, and wherein a glutamic acid residue has been substituted for the glycine at position 170.

In one aspect, there is provided a vector comprising the nucleic acid molecule as defined herein.

In one aspect, there is provided a host cell comprising the nucleic acid molecule as defined herein.

Specific embodiments of the present invention will become evident from the following more detailed description of certain embodiments and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1B show the results of an ELK-luciferase activity assay performed on the FGF21 truncation mutants 7-181 and 8-181 (Figure 1A) and the FGF21 truncation mutants 1-172, 1-171, 1-169, and 1-164 (Figure 1B); each panel shows the results obtained for a human FGF21 control.

Figure 2 shows the results of an ELK-luciferase activity assay performed on a human FGF21 control and the FGF21 truncation mutants 3-181, 4-181, 5-181, 7-181, 8-181, 1-180, 1-178, 1-177, 1-176, 1-175, 1-174, 1-173, 1-172, 9-181, and 1-149.

Figure 3 shows the blood glucose levels measured in mice injected with PBS (solid bar), human FGF21 control (open bar), or the FGF21 truncation mutants 8-181 (gray bar) and 9-181 (stippled bar).

Figure 4 shows the percent change in blood glucose levels measured in mice injected with PBS (solid circles), an Fc-FGF21 control (WT) (open circles), or truncated Fc-FGF21 fusion proteins comprising amino acid residues 5-181 (solid triangles) or 7-181 (open triangles).

Figure 5 shows the percent change in blood glucose levels measured in mice injected with PBS (solid circles), an FGF21-Fc control (WT) (open circles), a truncated FGF21-Fc fusion protein comprising residues 1-175 (solid triangles), or a truncated Fc-FGF21 protein comprising amino acid residues 1-171 (open triangles).

Figures 6A-6D show the results of liquid chromatography-mass spectrometry (LC-MS) analysis of a human Fc(5)FGF21 control sample (Figure 6A) and samples of Fc(5)FGF21 drawn from mice at 6 hours (Sample D6; Figure 6B), 24 hours (Sample D24; Figure 6C), and 48 hours (Sample D48; Figure 6D) after injection.

CLAIMS

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO:4, further comprising the substitution of any amino acid for: the alanine residue at position 45, the leucine residue at position 86, the leucine residue at position 98, the alanine residue at position 111, the alanine residue at position 129, the glycine residue at position 170, the proline residue at position 171 or the serine residue at position 172, and combinations thereof.

2. The isolated polypeptide of claim 1, wherein the isolated polypeptide comprises the substitution of any amino acid for: the leucine residue at position 98, the proline residue at 171 or both the leucine residue at position 98 and the proline residue at position 171.

3. The isolated polypeptide of claim 2, wherein the isolated polypeptide comprises the substitution of any amino acid for both the leucine residue at position 98 and the proline residue at position 171.

4. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 4 having:

(a) at least one amino acid substitution that is:

(i) a glutamine, isoleucine, or lysine residue at position 19;

(ii) a histidine, leucine, or phenylalanine residue at position 20;

(iii) an isoleucine, phenylalanine, tyrosine, or valine residue at position 21;

(iv) an isoleucine, phenylalanine, or valine residue at position 22;

(v) an alanine or arginine residue at position 150;

(vi) an alanine or valine residue at position 151;

(vii) a histidine, leucine, phenylalanine, or valine residue at position 152;

(viii) an alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, proline, or serine residue at position 170;

(ix) an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, serine, threonine, tryptophan, or tyrosine residue at position 171;

(x) a leucine or threonine residue at position 172; or

(xi) an arginine or glutamic acid residue at position 173; and

(b) at least one amino acid substitution that is:

(i) an arginine, glutamic acid, or lysine residue at position 26;

(ii) an arginine, glutamic acid, glutamine, lysine, or threonine residue at position 45;

(iii) a threonine residue at position 52;

(iv) a cysteine, glutamic acid, glycine, or serine residue at position 58;

(v) an alanine, arginine, glutamic acid, or lysine residue at position 60;

(vi) an alanine, arginine, cysteine, or histidine residue at position 78;

(vii) a cysteine or threonine residue at position 86;

(viii) an alanine, arginine, glutamic acid, lysine, or serine residue at position 88;

(ix) an arginine, cysteine, glutamic acid, glutamine, lysine, or threonine residue at position 98;

(x) an arginine, aspartic acid, cysteine, or glutamic acid residue at position 99;

(xi) a lysine or threonine residue at position 111;

(xii) an arginine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, or lysine residue at position 129; or

(xiii) an arginine, glutamic acid, histidine, lysine, or tyrosine residue at position 134;

and combinations thereof.

5. The isolated polypeptide of claim 4, wherein the residue at position 98 is arginine and the residue at position 171 is proline.

6. The isolated polypeptide of claim 4, wherein the polypeptide comprises an amino acid sequence that is at least 85 percent identical to the amino acid sequence of SEQ ID NO: 4, but wherein the at least one amino acid substitution of claim 4(a)(i)-(xi) and 4(b)(i)-(xiii) is not further modified.

7. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 4 having at least one amino acid substitution that is:

(a) a glutamine, lysine or isoleucine residue at position 19;

(b) a histidine, leucine, or phenylalanine residue at position 20;

(c) an isoleucine, phenylalanine, tyrosine, or valine residue at position 21;

(d) an isoleucine, phenylalanine, or valine residue at position 22;

(e) an alanine or arginine residue at position 150;

(f) an alanine or valine residue at position 151;

(g) a histidine, leucine, phenylalanine, or valine residue at position 152;

(h) an alanine, aspartic acid, cysteine, or proline residue at position 170;

(i) an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, serine, threonine, tryptophan, or tyrosine residue at position 171;

(j) a leucine residue at position 172; or

(k) an arginine or glutamic acid residue at position 173;

and combinations thereof.

8. The isolated polypeptide of claim 7, wherein the residue at position 171 is proline.

9. The isolated polypeptide of claim 7, wherein the polypeptide comprises an amino acid sequence that is at least 85 percent identical to the amino acid sequence of SEQ ID NO: 4, but wherein the at least one amino acid substitution of claim 7(a)-(k) is not further modified.

10. An isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 4 having at least one amino acid substitution that is:

(a) an arginine, glutamic acid, or lysine residue at position 26;

(b) an arginine, glutamic acid, glutamine, lysine, or threonine residue at position 45;

(c) a threonine residue at position 52;

(d) a glutamic acid, glycine, or serine residue at position 58;

(e) an alanine, arginine, glutamic acid, or lysine residue at position 60;

(f) an alanine, arginine, or histidine residue at position 78;

(g) an alanine residue at position 88;

(h) an arginine, glutamic acid, glutamine, lysine, or threonine residue at position 98;

(i) an arginine, aspartic acid, cysteine, or glutamic acid residue at position 99;

(j) a lysine or threonine residue at position 111;

(k) an arginine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, or lysine residue at position 129; or

(l) an arginine, glutamic acid, histidine, lysine, or tyrosine residue at position 134;

and combinations thereof.

11. The isolated polypeptide of claim 10, wherein the residue at position 98 is arginine.

12. The isolated polypeptide of claim 10, wherein the polypeptide comprises an amino acid sequence that is at least 85 percent identical to the amino acid sequence of SEQ ID NO: 4, but wherein the at least one amino acid substitution of claim 10(a)-(l) is not further modified.

13. The isolated polypeptide of any of claims 1, 4, 7 or 10, further comprising at least one amino acid substitution that is:

(a) a phenylalanine, proline, alanine, serine or glycine at position 179;

(b) a glutamic acid, glycine, proline, or serine at position 180; or

(c) a lysine, glycine, threonine, alanine, leucine, or proline at position 181.

14. The isolated polypeptide of any of claims 1, 4, 7 or 10, further comprising 1 to 10 amino acid residues fused to the C-terminus of the polypeptide.

15. The isolated polypeptide of claim 10, wherein the 1 to 10 amino acid residues are selected from the group consisting of glycine, proline and combinations thereof.

16. The isolated polypeptide of any of claims 1, 4, 7 or 10, wherein the polypeptide comprises:

(a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal;

(b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or

(c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal.

17. The isolated polypeptide of any of claims 1, 4, 7 or 10, wherein the polypeptide is covalently linked to one or more polymers.

18. The isolated polypeptide of claim 17, wherein the polymer is PEG.

19. A fusion polypeptide comprising the isolated polypeptide of any of claims 1, 4, 7 or 10 fused to a heterologous amino acid sequence.

20. The fusion polypeptide of claim 19, wherein the polypeptide is fused to the heterologous amino acid sequence via a linker.

21. The fusion polypeptide of claim 20, wherein the linker comprises GGGGGSGGGSGGGGS (SEQ ID NO: 23).

22. The fusion polypeptide of claim 20, wherein the heterologous amino acid sequence is an IgG constant domain or fragment thereof.

23. The fusion polypeptide of claim 22, wherein the IgG constant domain comprises the amino acid sequence of SEQ ID NO:13.

24. A multimer comprising two or more copies of the fusion polypeptide of claim 23.

25. A pharmaceutical composition comprising the isolated polypeptide of any of claims 1, 4, 7 or 10 and a pharmaceutically acceptable formulation agent.

26. A method for treating a metabolic disorder comprising administering to a human patient in need thereof the pharmaceutical composition of claim 25.

27. The method of claim 26, wherein the metabolic disorder is diabetes.

28. The method of claim 26, wherein the metabolic disorder is obesity.

29. An isolated nucleic acid encoding the polypeptide of any of claims 1, 4, 7 or 10.

30. A vector comprising the nucleic acid molecule claim 29.

31. A host cell comprising the nucleic acid molecule of claim 29.

32. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the polypeptide comprises:

(a) an amino-terminal truncation of no more than 8 amino acid residues, and wherein the polypeptide is capable of lowering blood glucose in a mammal;

(b) a carboxyl-terminal truncation of no more than 12 amino acid residues, and wherein the polypeptide is capable of lowering blood glucose in a mammal; or

(c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, and wherein the polypeptide is capable of lowering blood glucose in a mammal.

33. An isolated fusion protein comprising:

(a) an IgG constant domain;

(b) a linker sequence fused to the IgG constant domain; and

(c) an FGF21 mutant fused to the linker sequence and comprising the amino acid sequence of SEQ ID NO: 4, wherein an arginine residue has been substituted for the leucine residue at position 98 and a glycine residue has been substituted for the proline residue at position 171.

34. The isolated fusion protein of claim 33, wherein the linker sequence comprises GGGGGSGGGSGGGGS (SEQ ID NO:23).

35. The isolated fusion protein of claim 33, wherein the IgG constant domain comprises SEQ ID NO: 13.

36. The isolated fusion protein of claim 33, wherein the linker sequence comprises GGGGGSGGGSGGGGS (SEQ ID NO:23) and the IgG constant domain comprises the amino acid sequence of SEQ ID NO: 13.

37. The isolated fusion protein of claim 36, wherein the N terminus of the linker is fused to the C terminus of the IgG constant domain and the N terminus of the FGF21 mutant is fused to the C terminus of the linker.

38. A multimer comprising two or more of the fusion proteins of claim 33.

39. The isolated fusion protein of claim 33, wherein the FGF21 mutant further comprises at least one amino acid substitution that is:

(a) a phenylalanine, proline, alanine, serine or glycine at position 179;

(b) a glutamic acid, glycine, proline, or serine at position 180; or

(c) a lysine, glycine, threonine, alanine, leucine, or proline at position 181.

40. The isolated fusion protein of claim 33, wherein the FGF21 mutant further comprises 1 to 10 amino acid residues fused to the C-terminus of the FGF21 mutant.

41. The isolated fusion protein of claim 40, wherein the 1 to 10 amino acid residues are selected from the group consisting of glycine, proline and combinations thereof.

42. The isolated fusion protein of claim 33, wherein the FGF21 mutant comprises:

(a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal;

(b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or

(c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues,

wherein the polypeptide is capable of lowering blood glucose in a mammal.

43. The isolated fusion protein of claim 33, wherein the FGF21 mutant comprises an amino acid sequence that is at least 85 percent identical to the amino acid sequence of SEQ ID NO: 4, but wherein the arginine at position 98 and the glycine at position 171 are not further modified.

44. A pharmaceutical composition comprising the isolated fusion protein of claim 33 or claim 38 and a pharmaceutically acceptable formulation agent.

45. A method for treating a metabolic disorder comprising administering to a human patient in need thereof the pharmaceutical composition of claim 44.

46. The method of claim 45, wherein the metabolic disorder is diabetes.

47. The method of claim 45, wherein the metabolic disorder is obesity.

48. An isolated nucleic acid encoding the fusion protein of claim 33.

49. A vector comprising the nucleic acid molecule claim 48.

50. A host cell comprising the nucleic acid molecule of claim 48.

51. A polypeptide comprising the amino acid sequence of SEQ ID NO:4, further comprising the mutations L98R and P171G.

52. A fusion polypeptide comprising the polypeptide of claim 51 linked to a heterologous sequence.

53. The fusion polypeptide of claim 52, wherein the heterologous sequence is a Fc sequence.

54. The fusion polypeptide of claim 53, wherein the Fc sequence comprises the amino acid sequence of SEQ ID NO:13.

55. The fusion polypeptide of claim 54, wherein the polypeptide is joined to the heterologous sequence by a linker.

56. The fusion polypeptide of claim 55 wherein the linker is GGGGGSGGGSGGGGS (SEQ ID NO:23).

57. The fusion polypeptide of claim 55 wherein the linker is GGGGSGGGGSGGGGS (SEQ ID NO:31).

58. The fusion polypeptide 56, wherein the fusion polypeptide is encoded by the nucleic acid sequence of SEQ ID NO:37.

59. A multimer comprising two or more copies of the fusion polypeptide of claim 58.

60. A pharmaceutical composition comprising the fusion polypeptide of claim 58 and a pharmaceutically acceptable formulation agent.

CLAIMS

What is claimed is:

1. An isolated fusion protein comprising:

(a) an IgG constant domain;

(b) a linker sequence fused to the IgG constant domain; and

(c) an FGF21 mutant fused to the linker sequence and wherein the FGF21 mutant comprises the amino acid sequence of SEQ ID NO: 4, wherein an arginine residue has been substituted for the leucine residue at position 98, and wherein a glutamic acid residue has been substituted for the glycine at position 170.

2. The isolated fusion protein of claim 1, further comprising

(i) an N-terminal truncation of 8 or fewer residues;

(ii) a C terminal truncation of 12 or fewer residues; or

(iii) an N-terminal truncation of 8 or fewer residues and a C terminal truncation of 12 or fewer residues.

3. The isolated fusion protein of claim 2, wherein the polypeptide is capable of lowering blood glucose in a mammal.

4. The isolated fusion protein of claim 1, wherein the polypeptide is covalently linked to one or more polymers.

5. The isolated fusion protein of claim 4, wherein the polymer is PEG.

6. A pharmaceutical composition comprising the isolated fusion protein of claim 1 and a pharmaceutically acceptable formulation agent.

7. The isolated fusion protein of claim 1, further comprising a lysine residue substituted for the alanine at position 45.

8. The isolated fusion protein of claim 7, further comprising

(i) an N-terminal truncation of 8 or fewer residues;

(ii) a C terminal truncation of 12 or fewer residues; or

(iii) an N-terminal truncation of 8 or fewer residues and a C terminal truncation of 12 or fewer residues.

9. The isolated fusion protein of claim 8, wherein the polypeptide is capable of lowering blood glucose in a mammal.

10. The isolated fusion protein of claim 7, wherein the polypeptide is covalently linked to one or more polymers.

11. The isolated fusion protein of claim 10, wherein the polymer is PEG.

12. A pharmaceutical composition comprising the isolated fusion protein of claim 7 and a pharmaceutically acceptable formulation agent.

13. An isolated nucleic acid encoding a fusion protein comprising:

(a) an IgG constant domain;

(b) a linker sequence fused to the IgG constant domain; and

(c) an FGF21 mutant fused to the linker sequence and wherein the FGF21 mutant comprises the amino acid sequence of SEQ ID NO: 4, wherein an arginine residue has been substituted for the leucine residue at position 98, and wherein a glutamic acid residue has been substituted for the glycine at position 170.

14. A vector comprising the nucleic acid molecule of claim 13.

15. A host cell comprising the nucleic acid molecule of claim 13.