CLAIMS

1. A fusion protein comprising an FGF21 variant and an Fc region, wherein the FGF21 variant comprises at least the following mutations relative to the full length hFGF21 sequence SEQ ID NO:1: Q55C, R105K, G148C, K150R, P158S, S195A, P199G, and G202A.

2. A fusion protein comprising an FGF21 variant and an Fc region, wherein the FGF21 variant comprises at least the following mutations relative to the full length hFGF21 sequence SEQ ID NO:1: Q55C, A109T, G148C, K150R, P158S, S195A, P199G, and G202A.

3. The fusion protein of claim 1 or claim 2, wherein the Fc region is linked to the FGF21 variant via a linker.

4. The fusion protein of claim 3, wherein the linker is 1 to 20 amino acids in length, optionally wherein the linker comprises glycine and serine residues.

5. The fusion protein of any one of claims 1-4, wherein the FGF21 variant is fused to said Fc region by a GS linker.

6. The fusion protein of any one of claims 1-5, wherein the Fc region of the fusion protein is a modified Fc fragment.

7. The fusion protein of any one of claims 1-6, wherein the Fc region is a modified Fc fragment with a LALA mutation.

8. The fusion protein of any one of claims 1-7, comprising at least one disulfide bond engineered between Gln55Cys and a cysteine residue at one of Cys103, Cys121, Gly148Cys, Asn149Cys, Ser151Cys, Pro152Cys, His153Cys, Arg154Cys, Asp155Cys, Pro156Cys, Ala157Cys, Arg159Cys, Gly160Cys, Pro161Cys, Ala162Cys, and Arg163Cys.

9. The fusion protein of any one of claims 1-7, comprising at least one disulfide bond engineered between Gly148Cys and a cysteine residue at one of Cys103, Cys121, Arg47Cys,

Tyr48Cys, Leu49Cys, Tyr50Cys, Thr51Cys, Asp52Cys, Asp53Cys, Ala54Cys, Gln55Cys, Gln56Cys, Thr57Cys, Glu58Cys, Gly160Cys, Pro161Cys, Ala162Cys, Arg163Cys, and Phe164Cys.

10. The fusion protein of any one of claims 1-9, comprising an engineered disulfide bond between Gln55Cys and Gly148Cys.

11. The fusion protein of any one of claims 1-7, wherein the FGF21 variant comprises a disulfide bond between C103 and C121, positions referring to the amino acid position of the full length hFGF21 sequence SEQ ID NO: 1.

12. A fusion protein of any one of claims 1 or 3-10, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO: 11.

13. A fusion protein of any one of claims 1 or 3-10, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO: 12.

14. A fusion protein of any one of claims 2-10, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO: 10.

15. The fusion protein of any one of claims 2-10, wherein the fusion protein comprises the amino acid sequence of SEQ ID NO: 13.

16. A pharmaceutical composition comprising the fusion protein according to any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, for use in achieving one or more biological activities selected from the group consisting of: lowering blood glucose, lowering insulin levels, lowering triglyceride levels, lowering cholesterol levels, reducing liver lipid levels, reducing liver triglyceride levels, reducing body weight, improving glucose tolerance, and improving insulin sensitivity in a patient.

18. The pharmaceutical composition of claim 16, wherein said patient suffers from one or

more disorders selected from the group consisting of: obesity, type 1 and type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, metabolic syndrome, diabetic complications, gastroparesis, disorders associated with severe inactivating mutations in the insulin receptor, and other metabolic disorders.

19. The pharmaceutical composition of claim 18, wherein said disorder is obesity, type 2 diabetes mellitus, NASH, dyslipidemia, or hyperglycemia.

20. The pharmaceutical composition of claim 16, for use in the treatment of a metabolic disorder in a patient.

21. The pharmaceutical composition of claim 20, wherein the metabolic disorder is obesity, diabetes mellitus, NASH, dyslipidemia, or hyperglycemia, optionally wherein the metabolic disorder is type 2 diabetes mellitus.

22. Use of the fusion protein of any one of claims 1-15, in the manufacture of a medicament for use in achieving one or more biological activities selected from the group consisting of: lowering blood glucose, lowering insulin levels, lowering triglyceride levels, lowering cholesterol levels, reducing liver lipid levels, reducing liver triglyceride levels, reducing body weight, improving glucose tolerance, and improving insulin sensitivity in a patient.

23. The use of claim 22, wherein said patient suffers from one or more disorders selected from the group consisting of: obesity, type 1 and type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, metabolic syndrome, diabetic complications, gastroparesis, disorders associated with severe inactivating mutations in the insulin receptor, and other metabolic disorders.

24. The use of claim 23, wherein said disorder is obesity, type 2 diabetes mellitus, NASH, dyslipidemia, or hyperglycemia.

25. Use of the fusion protein of any one of claims 1-15, in the manufacture of a medicament

for use in a method of treating a metabolic disorder in a patient.

26. The use of claim 25, wherein the metabolic disorder is obesity, diabetes mellitus, NASH, dyslipidemia, or hyperglycemia, optionally wherein the metabolic disorder is type 2 diabetes mellitus.

27. A polynucleotide encoding the fusion protein of any one of claims 1 to 15.

28. A vector comprising the polynucleotide of claim 27.

29. A host cell comprising the vector of claim 28 or the polynucleotide of claim 27.

30. A method of producing a fusion protein, comprising expressing the fusion protein with the host cell of claim 29, optionally wherein the method further comprises purifying the fusion protein.