Claims

1. A fusion protein comprising the polypeptide with structure A-B-C or C-B-A or B-AC or B-C-A or or C-A-B or A-B-C-B-C or or A-B-C-B or A-C-B-C, wherein
A is a GLP-1R (glucagon-like peptide-1 receptor) agonist and
C is an FGF-21 (fibroblast growth factor 21) compound and
B is a linker comprising 1 to 1000 amino acids,
wherein the linker comprises an Fc portion of an immunoglobulin.

2. The fusion protein according to claim 1, wherein the FGF-21 compound is selected from the group of native FGF-21, FGF-21 mimetic and SEQ ID NO: 3.

3. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 80% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

4. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 90% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

5. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 96% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

6. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a FGF-21 mutein, a FGF-21-Fc fusion protein, a FGF-21-HSA fusion protein and/or a PEGylated FGF-21.

7. The fusion protein according to claim 1, wherein the GLP-1R agonist is selected from a bioactive GLP-1, a GLP-1 analogue or a GLP-1 substitute.

8. The fusion protein according to claim 7, wherein the GLP-1R agonist is selected from GLP-1(7-37), GLP-1(7-36)amide, exendin-4, liraglutide, CJC-1131, albugon, albiglutide, exenatide, exenatide-LAR, oxyntomodulin, lixisenatide, geniposide, or a short peptide with GLP-1R agonistic activity.

9. The fusion protein according to claims 1, wherein the linker comprises one or more of the following functional moieties a) to g):

a) a moiety conferring increased stability and/or half-life to the fusion such as an XTENylation or PASylation sequence or Elastin-like polypeptides (ELPs);

b) an entry site for covalent modification of the fusion protein such as a cysteine or lysine residue;

c) a moiety with intra- or extracellular targeting function such as a protein-binding scaffold;

d) a protease cleavage site such as a Factor Xa cleavage site or a cleavage site for another extracellular protease;

e) HSA;

f) an amino acid sequence comprising one or more histidine;

g) an albumin binding domain (ABD).

10. The fusion protein according to claim 1, wherein A is an FGF-21 mutein and C is exenatide, exendin-4 or lixisenatide.

11. The fusion protein according to claim 10, wherein A is an FGF-21 mutein comprising or consisting of SEQ ID NO: 102.

12. The fusion protein according to claim 11, wherein C is exenatide.

13. The fusion protein according to claim 12 for use as a medicament.

14. A pharmaceutical composition comprising the fusion protein of claim 1 together with a pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising the fusion protein of claim 1 together with a pharmaceutically acceptable excipient for use as a medicament.

16. Article of manufacture comprising

a) a pharmaceutical composition according to claim 14 and

b) a container or packaging material.

17. Use of a fusion protein of claim 1 for the manufacture of a medicament for treating a cardiovascular disease and/or diabetes mellitus and/or at least one metabolic syndrome which increases the risk of developing a cardiovascular disease and/or diabetes mellitus.

18. The use of claim 17, wherein the diabetes mellitus is Type 2-diabetes.

19. Use of a fusion protein of claim 1 for the manufacture of a medicament for treating hyperlipidemiaand/or hyperglycemia,.

20. A nucleic acid encoding the fusion protein according to claim 1.

21. A vector comprising the nucleic acid of claim 20 suitable for expression of the encoded protein in a eukaryotic or prokaryotic host.

22. A cell stably or transiently carrying the vector of claim 21 and capable of expressing the fusion protein according to claim 1 under appropriate culture conditions.

23. A method of preparing the fusion protein of claim 1 comprising

a) cultivating a culture of cells under appropriate culture conditions for the fusion protein to be expressed in the cell, or

b) harvesting or purifying the fusion protein from a culture comprising cells that have been cultivated under appropriate conditions for the fusion protein to be expressed, or

c) cultivating the cells according to step a) and purifying the fusion protein according to step b).

Claims

1. A fusion protein comprising the polypeptide with structure A-B-C or C-B-A or B-A-C or B-C-A or C-A-B or A-B-C-B-C or A-B-C-B or A-C-B-C, wherein
A is a GLP-1R (glucagon-like peptide-1 receptor) agonist and
C is an FGF-21 (fibroblast growth factor 21) compound and
B is a linker comprising up to 1000 amino acids,
wherein the linker comprises an Fc portion of an immunoglobulin.

2. The fusion protein according to claim 1, wherein the FGF-21 compound is selected from the group of native FGF-21, FGF-21 mimetic and SEQ ID NO: 3.

3. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 80% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

4. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 90% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

5. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a protein having at least 96% amino acid sequence identity to the amino acid sequence shown in SEQ ID NO: 3 and having FGF-21 activity, a FGF-21 fusion protein and/or a FGF-21 conjugate.

6. The fusion protein according to claim 2, wherein the FGF-21 mimetic is selected from a FGF-21 mutein, a FGF-21-Fc fusion protein, a FGF-21-HSA fusion protein and/or a PEGylated FGF-21.

7. The fusion protein according to claim 1, wherein the GLP-1R agonist is selected from a bioactive GLP-1, a GLP-1 analogue or a GLP-1 substitute.

8. The fusion protein according to claim 7, wherein the GLP-1R agonist is selected from GLP-1(7-37), GLP-1(7-36)amide, exendin-4, liraglutide, CJC-1131, albugon, albiglutide, exenatide, exenatide-LAR, oxyntomodulin, lixisenatide, geniposide, or a short peptide with GLP-1R agonistic activity.

9. The fusion protein according to claim 1, wherein the linker comprises one or more of the following functional moieties a) to g):

a) a moiety conferring increased stability and/or half-life to the fusion such as an XTENylation or PASylation sequence or Elastin-like polypeptides (ELPs);

b) an entry site for covalent modification of the fusion protein such as a cysteine or lysine residue;

c) a moiety with intra- or extracellular targeting function such as a protein-binding scaffold;

d) a protease cleavage site such as a Factor Xa cleavage site or a cleavage site for another extracellular protease;

e) HSA;

f) an amino acid sequence comprising one or more histidine;

g) an albumin binding domain (ABD).

10. The fusion protein according to claim 1, wherein C is an FGF-21 mutein and A is exenatide, exendin-4 or lixisenatide.

11. The fusion protein according to claim 10, wherein C is an FGF-21 mutein comprising or consisting of SEQ ID NO: 102.

12. The fusion protein according to claim 11, wherein A is exenatide.

13. The fusion protein according to claim 12 for use as a medicament.

14. A pharmaceutical composition comprising the fusion protein of claim 1 together with a pharmaceutically acceptable excipient.

15. A pharmaceutical composition comprising the fusion protein of claim 1 together with a pharmaceutically acceptable excipient for use as a medicament.

16. Article of manufacture comprising

a) a pharmaceutical composition according to claim 14 and

b) a container or packaging material.

17. Use of a fusion protein of claim 1 for the manufacture of a medicament for treating a cardiovascular disease and/or diabetes mellitus and/or at least one metabolic syndrome which increases the risk of developing a cardiovascular disease and/or diabetes mellitus, wherein the metabolic syndrome is selected from dyslipidemia, fatty liver disease (FLD), dysglycemia, impaired glucose tolerance (IGT), obesity and/or adipositas.

18. The use of claim 17, wherein the diabetes mellitus is Type 2-diabetes.

19. Use of a fusion protein of claim 1 for the manufacture of a medicament for treating hyperlipidemia and/or hyperglycemia.

20. A nucleic acid encoding the fusion protein according to claim 1.

21. A vector comprising the nucleic acid of claim 20 suitable for expression of the encoded protein in a eukaryotic or prokaryotic host.

22. A cell stably or transiently carrying the vector of claim 21 and capable of expressing the fusion protein according to claim 1 under appropriate culture conditions.

23. A method of preparing the fusion protein of claim 1 comprising

a) cultivating a culture of cells under appropriate culture conditions for the fusion protein to be expressed in the cell, or

b) harvesting or purifying the fusion protein from a culture comprising cells that have been cultivated under appropriate conditions for the fusion protein to be expressed, or

c) cultivating the cells according to step a) and purifying the fusion protein according to step b).