Claims

1. A heterodimeric fusion comprising:
   (i) a first heterodimerisation domain connected to at least one Relaxin A chain polypeptide or a variant thereof; and
   (ii) a second heterodimerisation domain connected to at least one Relaxin B chain polypeptide or a variant thereof,
   wherein the first heterodimerisation domain heterodimerises with the second heterodimerisation domain, and wherein the heterodimeric fusion has Relaxin activity.

2. The heterodimeric fusion according to Claim 1, wherein the Relaxin A chain polypeptide and the Relaxin B chain polypeptide are covalently bound by at least one inter-chain disulphide bond.

3. The heterodimeric fusion according to Claim 1 or 2, wherein the Relaxin A chain and the Relaxin B chain are not covalently linked to each other by an amino acid linker.

4. The heterodimeric fusion according to any one of the preceding claims, wherein the Relaxin A chain is a Relaxin-2 A chain and the Relaxin B chain is a Relaxin-2 B chain.

5. The heterodimeric fusion according to any one of the preceding claims, wherein the Relaxin A chain is connected to the first heterodimerisation domain via a connector and the Relaxin B chain is connected to the second heterodimerisation domain via a connector, optionally wherein one or preferably both connectors are polypeptides.

6. The heterodimeric fusion according to Claim 5, wherein one or preferably both of the connectors have a length of between 6 and 40 amino acids, e.g. one or preferably both connectors have a length of 21 amino acids.

7. The heterodimeric fusion according to any one of the preceding claims, wherein the first and second heterodimerisation domains are derived from an immunoglobulin Fc region ("first Fc region" and "second Fc region", respectively), optionally wherein the first and second Fc regions comprise the constant domains CH2 and CH3.

8. The heterodimeric fusion according to Claim 7, wherein the C-terminus of the first Fc region

is connected to the N-terminus of the Relaxin A chain and the C-terminus of the second Fc region is connected to the N-terminus of the Relaxin B chain.

9. The heterodimeric fusion according to Claim 7 or 8, wherein the first and second Fc regions comprise heterodimerisation-promoting amino acid mutations and/or modifications, optionally wherein the heterodimerisation-promoting amino acid mutations are “Fc Knob” and “Fc Hole” mutations, e.g. “Fc Knob” and “Fc Hole” mutations present in the CH3 domains.

10. The heterodimeric fusion according to any one of Claims 7 to 9, wherein the first and second Fc regions are derived from a human IgG1 immunoglobulin.

11. The heterodimeric fusion according to Claim 10, wherein the heterodimerisation-promoting amino acid mutations comprise:
    a. “Fc Hole” mutations Y349C, T366S, L368A and Y407V in one CH3 domain; and
    b. “Fc Knob” mutations S354C and T366W in the other CH3 domain,

    wherein the amino acid numbering is according to the EU index as in Kabat.

12. The heterodimeric fusion according to Claim 11, wherein:
    a. the first Fc region comprises the “Fc Knob” mutations and the second Fc region comprises the “Fc Hole” mutations; or
    b. the second Fc region comprises the “Fc Knob” mutations and the first Fc region comprises the “Fc Hole” mutations.

13. The heterodimeric fusion according to any one of Claims 10 to 12, wherein the first and/or second Fc region comprises the amino acid mutations L234F, L235E, and P331S, wherein the amino acid numbering is according to the EU index as in Kabat.

14. The heterodimeric fusion according to any one of Claims 4 to 13, wherein the Relaxin-2 A chain polypeptide comprises the sequence as set forth in SEQ ID NO: 1 or a variant thereof and the Relaxin-2 B chain polypeptide comprises the sequence as set forth in SEQ ID NO: 2 or a variant thereof.

15. The heterodimeric fusion according to Claim 14, wherein the Relaxin-2 A chain polypeptide comprises the amino acid mutation K9H, K17M or K17I.

16. The heterodimeric fusion according to any one of Claims 5 to 15, wherein both connectors

have the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5].

17. A heterodimeric fusion comprising:

(i) an FcX-con-A fusion polypeptide; and

(ii) an FcY-con-B fusion polypeptide,

wherein:

A is a Relaxin A chain or variant thereof, e.g. a Relaxin-2 A chain or variant thereof;

B is a Relaxin B chain or variant thereof, e.g. Relaxin-2 B chain or variant thereof;

FcY is an Fc region comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and comprises "Fc Hole" amino acid mutations and/or modifications, preferably the amino acid mutations Y349C: T366S:L368A:Y407V;

FcX is an Fc region with "Fc Knob" amino acid mutations and/or modifications, preferably comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and comprises "Fc Knob" amino acid mutations and/or modifications, preferably the amino acid mutations S354C:T366W; and

con is a connector polypeptide, preferably having the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5],

wherein the amino acid numbering is according to the EU index as in Kabat, wherein FcX heterodimerises with FcY, and wherein the heterodimeric fusion has Relaxin activity.

18. The heterodimeric fusion according to any one of the preceding claims, wherein the heterodimeric fusion comprises a fusion polypeptide with the amino acid sequence of SEQ ID NO: 11 and a fusion polypeptide with the amino acid sequence of SEQ ID NO: 20.

19. The heterodimeric fusion according to any one of Claims 8 to 18, wherein the heterodimeric fusion further comprises one or more Fabs, optionally wherein the heterodimeric fusion comprises one Fab linked to the N-terminus of the first Fc region and a second Fab linked to the N-terminus of the second Fc region.

20. The heterodimeric fusion according to any one of the Claims 8 to 19, wherein the heterodimer further comprises a second Relaxin A chain polypeptide or variant thereof connected to the N-terminus of the first Fc region and a second Relaxin B chain polypeptide or variant thereof connected to the N-terminus of the second Fc region, optionally wherein the second Relaxin A chain is connected to the first Fc region via a connector polypeptide and

the second Relaxin B chain is connected to the second Fc region via a connector polypeptide.

21. A heterodimeric fusion comprising:

(i) FcX-B-L-A and FcY, optionally FcY-B-L-A; or

(ii) FcY-B-L-A and FcX, optionally FcX-B-L-A;

wherein:

FcY is an immunoglobulin Fc region with "Fc Hole" amino acid mutations and/or modifications, preferably comprising a CH3 domain having the amino acid mutations Y349C:T366S:L368A:Y407V;

FcX is an immunoglobulin Fc region with "Fc Knob" amino acid mutations and/or modifications, preferably comprising a CH3 domain having the amino acid mutations S354C:T366W;

B is a Relaxin B chain or a variant thereof, e.g. a Relaxin 2 B chain or variant thereof;

A is a Relaxin A chain or a variant thereof, e.g. a Relaxin 2 A chain or variant thereof; and

L is a linker polypeptide, preferably having the amino acid sequence GGGSGGGSGG [SEQ ID NO: 60],

wherein the amino acid numbering is according to the EU index as in Kabat, wherein FcX heterodimerises with FcY, and wherein the heterodimeric fusion has Relaxin activity.

22. The heterodimeric fusion according to Claim 21, wherein the Relaxin B chain is connected to FcX and/or FcY via a connector, optionally a connector polypeptide having a length of between 6 and 40 amino acids, e.g. a length of 21 amino acids.

23. The heterodimeric fusion of any one of the preceding claims, wherein the ratio of Relaxin activity of the heterodimeric fusion over the Relaxin activity of a reference Relaxin protein is between 0.001 and 10.

24. A nucleic acid molecule encoding a heterodimeric fusion of any one of the preceding claims.

25. A vector comprising the nucleic acid molecule of Claim 24.

26. A host cell comprising the vector of Claim 25 or the nucleic acid molecule of Claim 24.

27. A method of producing the heterodimeric fusion of any one of Claims 1 to 23, the method comprising culturing the host cell of Claim 26 and collecting the fusion protein.

28. A pharmaceutical composition comprising the heterodimeric fusion of any one of Claims 1 to 23 and a pharmaceutically acceptable excipient.

29. The heterodimeric fusion of any of one Claims 1 to 23 or the pharmaceutical composition of Claim 28 for use in therapy.

30. The heterodimeric fusion of any of one Claims 1 to 23 or the pharmaceutical composition of Claim 28 for use in the treatment of a subject with heart failure, wherein the heterodimeric fusion or pharmaceutical composition is to be administered to the subject.

31. The heterodimeric fusion for use according to Claim 29 or 30, or the pharmaceutical composition for use according to Claim 29 or 30, wherein the heterodimeric fusion or pharmaceutical composition is to be administered to the subject by subcutaneous injection.

32. The heterodimeric fusion for use according to any one of Claims 29 to 31, or the pharmaceutical composition for use according to any one of Claims 29 to 31, wherein the fusion polypeptide or pharmaceutical composition is to be administered by self-administration.

33. A kit comprising the pharmaceutical composition of Claim 28.