wherein L_1 is a first linker comprising an amino acid sequence selected from the group consisting of $(GGGGQ)_n$ (SEQ ID NO:14), $(PGPQ)_n$ (SEQ ID NO:17) and $(PGPA)_n$ (SEQ ID NO:18), and wherein n can be from 1 to 10, and

wherein L_2 is a second linker comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:22, 23 and 67; or

a pharmaceutically acceptable salt thereof.

[0005b] In another aspect of the present disclosure, there is provided a compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

[0005c] In a further aspect of the present disclosure, there is provided a compound consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

[0005d] In another aspect of the present disclosure, there is provided a compound consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

[0005e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising: a compound disclosed herein or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable buffer.

[0005f] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in a therapy.

[0005g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders, wherein the cardiac, pulmonary, and/or renal conditions, disease, and/or disorders are selected from the group consisting of acute heart failure, chronic heart failure, atherosclerosis, coronary artery disease, diabetes, stroke, hypercholesterolemia, hypertension, ischemia, vasoconstriction, ventricular hypertrophy, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease and diabetes nephropathy.

[0005h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture

of a medicament for treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders, wherein the cardiac, pulmonary, and/or renal conditions, disease, and/or disorders are selected from the group consisting of acute heart failure, chronic heart failure, atherosclerosis, coronary artery disease, diabetes, stroke, hypercholesterolemia, hypertension, ischemia, vasoconstriction, ventricular hypertrophy, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease and diabetes nephropathy.

[0005i] In a further aspect of the present disclosure, there is provided a compound that binds serum albumin comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 to 13.

Description

[0006] To address this need, the disclosure first describes single-chain RLN analogs having principal activity at the RXFP1 receptor (*i.e.*, act as RXFP1 receptor agonists). Such RXFP1 receptor agonists include a basic structure from an amino-terminus (N-terminus) to a carboxy-terminus (C-terminus) of:

VHH-L_1-A-L_2-B,

VHH-L_1-B-L_2-A,

A-L_2-B-L_1-VHH, or

B-L_2-A-L_1-VHH,

where VHH is a moiety that can act as a pharmacokinetic enhancer, A is a RLN A chain, B is a RLN B chain, L_1 is a first linker, and L_2 is a second linker.

[0007] In some instances, the VHH moiety can have an amino acid sequence of SEQ ID NO:10, 11, 12 or 13, especially SEQ ID NO:10 or 12. In other instances, the VHH moiety can have one or more additions, deletions, insertions or substitutions such that the VHH moiety has an amino acid sequence having at least about 90% to about 99% sequence similarity to any one of SEQ ID NOS:10, 11, 12 or 13 (*see*, *e.g.*, SEQ ID NOS:45-66).

[0008] In some instances, the A chain can have an amino acid sequence of SEQ ID NO:2, 5 or 8, especially SEQ ID NO:5. In other instances, the A chain can have one or more additions, deletions, insertions or substitutions such that the A chain has an amino acid

CLAIMS

The invention claimed is:

1. A compound comprising a structure of:

VHH-L_1-A-L_2-B,

VHH-L_1-B-L_2-A,

A-L_2-B-L_1-VHH, or

B-L_2-A-L_1-VHH,

wherein VHH binds serum albumin and comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:10, 11, 12 and 13 or a sequence having at least 90% sequence identity thereto,

wherein A is a relaxin A chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 5 and 8 or a sequence having at least 90% sequence identity thereto,

wherein B is a relaxin B chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:3, 6 and 9 or a sequence having at least 90% sequence identity thereto,

wherein L_1 is a first linker comprising an amino acid sequence selected from the group consisting of $(GGGGQ)_n$ (SEQ ID NO:14), $(PGPQ)_n$ (SEQ ID NO:17) and $(PGPA)_n$ (SEQ ID NO:18), and wherein n can be from 1 to 10, and

wherein L_2 is a second linker comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:22, 23 and 67; or

a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein A is SEQ ID NO:2.

3. The compound of Claim 1 or 2, wherein B is SEQ ID NO:3.

4. The compound of Claim 1, wherein A is SEQ ID NO:5.

5. The compound of Claim 1 or 2, wherein B is SEQ ID NO:6.

6. The compound of Claim 1, wherein A is SEQ ID NO:5 and lacks the first four amino acids (desA1-4).

7. The compound of Claim 1, wherein B is SEQ ID NO:6 and lacks the first amino acid (desB1).

8. The compound of Claim 1, wherein A is SEQ ID NO:5 and lacks the first four amino acids (desA1-4), and wherein B is SEQ ID NO:6 and lacks the first amino acid (desB1).

9. The compound of Claim 1, wherein A is SEQ ID NO:8.

10. The compound of Claim 1 or 2, wherein B is SEQ ID NO:9.

11. The compound of any one of Claims 1 to 10, wherein L_1 is SEQ ID NO:19.

12. The compound of any one of Claims 1 to 10, wherein L_1 is SEQ ID NO:20.

13. The compound of any one of Claims 1 to 10, wherein L_1 is SEQ ID NO:21.

14. A compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

15. A compound consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

16. A compound consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS:24 to 39 or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising:

a compound of any one of Claims 1 to 16 or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable buffer.

18. A compound of any one of Claims 1 to 16, or a pharmaceutical composition of claim 17, for use in a therapy.

19. A compound of any one of Claims 1 to 16, or a pharmaceutical composition of claim 17, for use in treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders, wherein the cardiac, pulmonary, and/or renal conditions, disease, and/or disorders are selected from the group consisting of acute heart failure, chronic heart failure, atherosclerosis, coronary artery disease, diabetes, stroke, hypercholesterolemia, hypertension, ischemia, vasoconstriction, ventricular hypertrophy, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease and diabetes nephropathy.

20. Use of a compound of any one of Claims 1 to 16, or the pharmaceutical composition of claim 17, in the manufacture of a medicament for treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders, wherein the cardiac, pulmonary, and/or renal conditions, disease, and/or disorders are selected from the group consisting of acute heart failure, chronic heart failure, atherosclerosis, coronary artery disease, diabetes, stroke, hypercholesterolemia, hypertension, ischemia, vasoconstriction, ventricular hypertrophy, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease and diabetes nephropathy.

21. A compound that binds serum albumin comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 to 13.