Publication No. WO 2018/138170 describes analogs that are fusions of the A chain and B chain having a linker of at least fifteen amino acids and a half-life extending moiety to improve t½. Intl. Patent Application Publication No. WO 2017/201340 describes analogs that are fusions of the A chain and B chain having a variable light chain fragment to improve t½. Intl. Patent Application Publication No. WO 2015/067791 describes analogs that are carrier-linked prodrugs, especially PEG-based carriers, to improve t½ (*see also*, WO 2012/024452 for additional PEG-linked analogs). Intl. Patent Application Publication No. WO 2014/102179 describes analogs that are fusions of the A chain and B chain having a Fc moiety of IgG2 or IgG4 to improve t½. Intl. Patent Application Publication No. WO 2013/004607 describes analogs that are fusions of the A chain and B chain having a linker of at least five amino acids but less than fifteen amino acids to improve t½ or that are fusions of the A chain and B chain having a Fc domain of antibodies to improve t½.

[0005] In view of the increases in understanding the various physiological roles of RLNs, there remains a need for long-acting RLN analogs having an improved t½.

Summary

[0005a] In an aspect of the present disclosure, there is provided 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 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 similarity 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 similarity 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 similarity 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.

[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 sequence having at least 90% sequence similarity thereto 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 sequence having at least 90% sequence similarity thereto 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 sequence having at least 90% sequence similarity thereto 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 of claim 17, for use in a therapy.

[0005g] In a further aspect of the present disclosure, there is provided a disclosed herein, or a pharmaceutical composition disclosed herein, for use in treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders.

[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.

[0005i] In a further aspect of the present disclosure, there is provided a compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 to 13 and 45 to 66 or a sequence having at least 90% sequence similarity thereto.

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 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 similarity 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 similarity 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 similarity 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 Claims 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 Claims 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 Claims 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 sequence having at least 90% sequence similarity thereto 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 sequence having at least 90% sequence similarity thereto 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 sequence having at least 90% sequence similarity thereto 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 method of treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders in an individual, the method comprising the step of:~~

~~administering to the individual an effective amount of a compound of any one of Claims 1 to 16 or a pharmaceutical composition of Claim 17.~~

~~19~~18. A compound of any one of Claims 1 to 16, or a pharmaceutical composition of claim 17, for use in a therapy.

~~20~~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.

~~21~~20. Use of a compound of any one of Claims 1 to 16, or the pharmaceutical composition of claim 17, in the manufacture of ~~for manufacturing~~ a medicament for treating cardiac, pulmonary and/or renal conditions, diseases and/or disorders.

~~22~~21. A compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 10 to 13 and 45 to 66 ~~of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:10)~~ or a sequence having at least 90% sequence similarity thereto.

~~23. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV~~

~~ADLYPYWGQGTLVTVSSPP (SEQ ID NO:11) or a sequence having at least 90% sequence similarity thereto.~~

~~24. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKGREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:12) or a sequence having at least 90% sequence similarity thereto.~~

~~25. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKGREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSSPP (SEQ ID NO:13) or a sequence having at least 90% sequence similarity thereto.~~

~~26. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRTVSSTAVAWFRQAPGKEREFVAGIGGS VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAVRPGRPLITSRD ANLYDYWGQGTLVTVSS (SEQ ID NO:45) or a sequence having at least 90% sequence similarity thereto.~~

~~27. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDSTAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSRV ANLYPYWGQGTLVTVSS (SEQ ID NO:46) or a sequence having at least 90% sequence similarity thereto.~~

~~28. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASYRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:47) or a sequence having at least 90% sequence similarity thereto.~~

~~29. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGAYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:48) or a sequence having at least 90% sequence similarity thereto.~~

~~30. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDETYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:49) or a sequence having at least 90% sequence similarity thereto.~~

~~31. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDQTYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSK VADLYPYWGQGTLVTVSS (SEQ ID NO:50) or a sequence having at least 90% sequence similarity thereto.~~

~~32. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITAYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:51) or a sequence having at least 90% sequence similarity thereto.~~

~~33. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITEYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:52) or a sequence having at least 90% sequence similarity thereto.~~

~~34. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITQYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:53) or a sequence having at least 90% sequence similarity thereto.~~

~~35. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITSYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:54) or a sequence having at least 90% sequence similarity thereto.~~

~~36. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITTYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:55) or a sequence having at least 90% sequence similarity thereto.~~

~~37. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGKPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:56) or a sequence having at least 90% sequence similarity thereto.~~

~~38. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGQPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:57) or a sequence having at least 90% sequence similarity thereto.~~

~~39. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG~~

~~VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGSPLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:58) or a sequence having at least 90% sequence similarity thereto.~~

~~40. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRELITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:59) or a sequence having at least 90% sequence similarity thereto.~~

~~41. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRQLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:60) or a sequence having at least 90% sequence similarity thereto.~~

~~42. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRSLITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:61) or a sequence having at least 90% sequence similarity thereto.~~

~~43. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPEITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:62) or a sequence having at least 90% sequence similarity thereto.~~

~~44. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPGITSKV~~

~~ADLYPYWGQGTLVTVSS (SEQ ID NO:63) or a sequence having at least 90% sequence similarity thereto.~~

~~45. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPQITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:64) or a sequence having at least 90% sequence similarity thereto.~~

~~46. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPTITSKV ADLYPYWGQGTLVTVSS (SEQ ID NO:65) or a sequence having at least 90% sequence similarity thereto.~~

~~47. A compound comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGG VDITYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAARPGRPLITEKV ADLYPYWGQGTLVTVSS (SEQ ID NO:66) or a sequence having at least 90% sequence similarity thereto.~~