CLAIMS

1. An apelin receptor agonist comprising an apelin analogue, wherein the apelin analogue comprises one or more amino acid substitutions as compared to SEQ ID NO: 1 (QRPRLSHKGPMPF),

   wherein the one or more amino acid substitution occurs at position 1, 6, 8, 9, 11, 12, and/or 13.

2. The apelin receptor agonist of claim 1, wherein the one or more amino acid substitutions comprises P12V, K8W, Q1E, M11H, M11A, F13Y, P12A, P12H, F13W, S6Q, and/or G9N.

3. The apelin receptor agonist of claim 1 or 2, wherein the apelin analogue comprises the amino sequence:

   (a) X1-R-P-R-L-S-H-X2-G-P-X3-X4-X5

   wherein

   X1 is Q or E;

   X2 is K or W;

   X3 is M, H, or A;

   X4 is P, V, A, or H; and/or

   X5 is F, Y, or W;

   (b) Q-R-P-R-L-Q-H-K-N-P-M-A-X1

   wherein

   X1 is F or W;

   (c) Q-R-P-R-L-S-H-K-G-P-X1-X2-X3

   wherein

   X1 is M, H, or A;

   X2 is P, V, A, or H; and/or

   X3 is F, Y, or W; or

   (d) X1-R-P-R-L-X2-H-X3-X4-P-X5-X6-X7

wherein
X1 is Q or E;
X2 is S or Q;
X3 is K or W;
X4 is G or N;
X5 is M, H, or A;
X6 is P, V, A or H; and/or
X7 is F, Y or W.

4. The apelin receptor agonist of any one of the preceding claims, wherein the apelin analogue comprises the amino acid sequence of one of SEQ ID NO: 6 (QRPRLSHKGPAPY), SEQ ID NO: 50 (QRPRLSHKGPMHW), SEQ ID NO: 55 (QRPRLSHWGPMAW), SEQ ID NO: 1 (QRPRLSHKGPMPF), SEQ ID NO: 2 (QRPRLSHKGPMVF), SEQ ID NO: 3 (QRPRLSHWGPMPF), SEQ ID NO: 5 (QRPRLSHKGPHPF), SEQ ID NO: 7 (QRPRLSHKGPMAF), SEQ ID NO: 51 (QRPRLSHKGPAAW), SEQ ID NO: 52 (QRPRLSHKGPAAY), SEQ ID NO: 53 (QRPRLQHKNPMAF), and SEQ ID NO: 54 (QRPRLQHKNPMAW).

5. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 6 (QRPRLSHKGPAPY).

6. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 50 (QRPRLSHKGPMHW).

7. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 55 (QRPRLSHWGPMAW).

8. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 53 (QRPRLQHKNPMAF).

9. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 3 (QRPRLSHWGPMPF).

10. The apelin receptor agonist of claim 3 or 4, wherein the apelin analogue comprises the amino acid sequence of SEQ ID NO: 54 (QRPRLQHKNPMAW).

11. An apelin receptor agonist comprising an elabela analogue, wherein the elabela analogue comprises one or more amino acid substitutions as compared to SEQ ID NO: 8 (KLRKHNCLQRRCMPLHSRVPFP),

wherein the one or more amino acid substitution occurs at position 3, 7, 8, 9, 10, 12, 14, 15, 17 and/or 18.

12. The apelin receptor agonist of claim 11, wherein the one or more amino acid substitutions comprise R3N, P14I, S17Q, S17R, Q9K, R18Y, L15Y, C7S, C12Y, R10E, Q9I, L8A, and/or Q9T.

13. The apelin receptor agonist of claim 11 or 12, wherein the elabela analogue comprises the amino sequence:

K-L-Z1-K-H-N-Z2-Z3-Z4-Z5-R-Z6-M-Z7-Z8-H-Z9-Z10-V-P-F-P

wherein

Z1 is R or N;

Z2 is C or S;

Z3 is A or L;

Z4 is Q, I, K, or T;

Z5 is R or E;

Z6 is C or Y;

Z7 is P or I;

Z8 is L or Y;

Z9 is S, Q, or R; and/or

Z10 is R or Y.

14. The apelin receptor agonist of claim 13, wherein the elabela analogue comprises the amino acid sequence of one of SEQ ID NO: 11 (KLRKHNCLQRRCMPLHQRVPFP), SEQ ID NO: 12 (KLRKHNCLQRRCMPLHRRVPFP), SEQ ID NO: 35 (KLRKHNCATRRCMPLHSRVPFP), SEQ ID NO: 8 (KLRKHNCLQRRCMPLHSRVPFP), SEQ ID NO: 9

(KLNKHNCLQRRCMPLHSRVPFP), SEQ ID NO: 10
(KLRKHNCLQRRCMILHSRVPFP), SEQ ID NO: 13
(KLRKHNCLKRRCMPLHSRVPFP), SEQ ID NO: 30
(KLRKHNCLQRRCMPLHSYVPFP), SEQ ID NO: 31
(KLRKHNCLQRRCMPYHSRVPFP), SEQ ID NO: 32
(KLRKHNSLQRRYMPLHSRVPFP), SEQ ID NO: 33
(KLRKHNCLQERCMPLHSRVPFP), and SEQ ID NO: 34
(KLRKHNCLIRRCMPLHSRVPFP).

15. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 35 (KLRKHNCATRRCMPLHSRVPFP).

16. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 11 (KLRKHNCLQRRCMPLHQRVPFP).

17. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 12 (KLRKHNCLQRRCMPLHRRVPFP).

18. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 31 (KLRKHNCLQRRCMPYHSRVPFP).

19. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 34 (KLRKHNCLIRRCMPLHSRVPFP).

20. The apelin receptor agonist of claim 13 or 14, wherein the elabela analogue comprises the amino acid sequence of SEQ ID NO: 8 (KLRKHNCLQRRCMPLHSRVPFP).

21. The apelin receptor agonist of any one of the preceding claims, wherein the apelin analogue or optionally the elabela analogue is fused to a carrier moiety, optionally wherein the N-terminus of the apelin analogue or the elabela analogue is fused to the carrier moiety, optionally wherein the carrier moiety extends a half-life of the apelin receptor agonist.

22. The apelin receptor agonist of claim 21, wherein the carrier moiety comprises an Fc domain, human serum albumin (HSA), an anti-HSA antibody or a fragment thereof, lipids, or PEGs; optionally wherein:

    a. the Fc domain is a monovalent Fc or a bivalent Fc;

    b. wherein the anti-HSA antibody or a fragment there of is an anti-HSA Fab, a nanobody (VHH), an scFv, or a V-NAR, optionally wherein the anti-HSA VHH comprises ALB-23.

23. An apelin receptor agonist comprising an apelin analogue or an elabela analogue, wherein the N-terminus of the apelin analogue or the elabela analogue is fused to a carrier moiety via a linker.

24. The apelin receptor agonist of claim 23, wherein the N-terminus of the apelin analogue or the elabela analogue is fused to the C-terminus of the carrier moiety, optionally wherein the carrier moiety extends a half-life of the apelin receptor agonist and/or comprises an Fc domain, a human serum albumin (HSA), an anti-HSA antibody or a fragment thereof, lipids, or PEGs.

25. The apelin receptor agonist of claim 24, wherein the Fc domain is:

    a. the Fc domain is a monovalent Fc or a bivalent Fc; and/or

    b. the Fc domain is a IgG1, IgG2, IgG3, or IgG4 isotype; and/or

    c. the Fc domain comprises one or more mutations as compared to the wild-type Fc domain; optionally wherein:

        i. the Fc domain is a human IgG1 monovalent Fc, a human IgG1 bivalent Fc, or a human IgG4 monovalent Fc comprising a S228P nutation; or
        ii. the Fc domain comprises SEQ ID NO: 14 or SEQ ID NO:15.

26. The apelin receptor agonist of claim 24, wherein the anti-HSA antibody or a fragment there of is an anti-HSA Fab, a nanobody (VHH), an scFv, or a V-NAR, optionally wherein the anti-HAS VHH comprises ALB-23.

27. The apelin receptor agonist of any one of claims 23-26, wherein the linker comprises GGGGSGGGGSGGGGS (SEQ ID NO: 16).

28. The apelin receptor agonist of any one of the preceding claims comprising an amino acid sequence that is at least 80%, 85%, 90%, 93%, 95%, 98%, 99% identical to SEQ ID NOs: 17-29, 36-41, and 56-61.

29. The apelin receptor agonist of any one of the preceding claims, wherein the apelin receptor agonist has:

a. a $G_{\alpha i}$ signaling assay EC50 value of less than 60 nM, less than 30 nM, less than 20 nM, or less than 10 nM, as measured by the depletion of cAMP;

b. a beta-Arrestin signaling assay EC50 value of less than 1000 nM, 600 nM, less than 500 nM, less than 100 nM, less than 30 nM, or less than 10 nM, and/or

c. an ERK activation assay EC50 value of less than 20 nM, less than 10 nM, less than 5 nM, less than 2 nM, or less than 1 nM.

30. The apelin receptor agonist of any one of the preceding claims for use in treating a disease in a subject in need thereof, optionally wherein the disease is pulmonary arterial hypertension (PAH), systemic sclerosis (SSc), heart failure with preserved ejection fraction (HfpEf), age-associated sarcopenia, or acute kidney injury (AKI).

31. A nucleic acid encoding the apelin receptor agonist of any one of the preceding claims 1-29.

32. A method of producing the apelin receptor agonist of any one of the preceding claims 1-29.