What is claimed:

1. A polypeptide comprising an apelin peptide fused to an Fc domain, a fragment of an Fc domain, or variant of an Fc domain.

2. The polypeptide of claim 1, wherein the apelin peptide is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77 (apelin-15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^1]Apelin-13, or a fragment or derivative thereof.

3. The polypeptide of claim 1 or 2, wherein the apelin peptide is apelin-13, or a fragment or derivative thereof.

4. The polypeptide of claim 2, wherein the apelin peptide derivative comprises the amino acid sequence selecting from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43 and SEQ ID NO: 44.

5. The polypeptide of any one of claims 1-3, wherein the apelin peptide is fused to the Fc domain, or fragment thereof, via one or more peptide linkers.

6. The polypeptide of claim 4, wherein the apelin peptide is fused to the Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

7. The polypeptide of claim 5, wherein the apelin peptide is fused to the C-terminus of said Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

8. The polypeptide of claim 5, wherein the apelin peptide is fused to the N-terminus of said Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

9. The polypeptide of any one of claims 1-7 wherein the Fc domain is selected from the group consisting of IgG1 CH2 domain and IgG1 CH3 domain; IgG4 CH2 domain and IgG4 CH3 domain; IgG1 CH2 domain and IgG4 CH3 domain; and IgG4 CH2 domain and an IgG1 CH3 domain.

10. The polypeptide of any one of claims 1-8, wherein the Fc domain comprises an IgG hinge domain, or a fragment or a variant thereof.

11. The polypeptide of any one of claims 1-9, wherein the Fc domain comprises an IgG hinge domain comprising SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:21, or SEQ ID NO: 22.

12. The polypeptide of any one of claims 1-10, wherein the polypeptide forms at least one disulfide bond with a second polypeptide.

13. The polypeptide of any one of claims 1-11, wherein the polypeptide is a monomeric fusion polypeptide capable of forming a dimer.

14. The polypeptide of any one of claims 1-12, wherein the polypeptide has 95% or greater sequence identity to the amino acid sequence comprising SEQ ID NO: 2.

15. The polypeptide of claim 13 comprising the amino acid sequence comprising SEQ ID NO: 2.

16. The polypeptide of any one of claims 1-12, wherein the polypeptide has 95% or greater sequence identity to the amino acid sequence comprising SEQ ID NO: 4.

17. The polypeptide of claim 15 comprising the amino acid sequence comprising SEQ ID NO: 4.

18. A nucleic acid encoding the polypeptide of any one of claims 1-16.

19. A protein comprising the polypeptide of any one of claims 1-16.

20. An apelin receptor (APNLR) binding molecule comprising:

a. an apelin peptide component,
b. a human IgG Fc domain, and
c. at least one linker component.

21. The receptor binding molecule of claim 20, wherein the apelin peptide is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77

(apelin-15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^1]Apelin-13, or a fragment or derivative thereof.

22. The receptor binding molecule of claim 20 or 21, wherein the apelin peptide is apelin-13 (SEQ ID NO: 6), or a fragment or derivative thereof.

23. The receptor binding molecule of claim 21, wherein the apelin peptide derivative comprises the amino acid sequence selecting from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43 and SEQ ID NO: 44.

24. The receptor binding molecule of any one of claims 20-23, wherein the Fc domain is selected from the group consisting of an IgG1 CH2 domain and an IgG1 CH3 domain; an IgG4 CH2 domain and an IgG4 CH3 domain; an IgG1 CH2 domain and an IgG4 CH3 domain; and an IgG4 CH2 domain and an IgG1 CH3 domain; or a fragment or variant thereof.

25. The receptor binding molecule of any one of claims 20-24, wherein the Fc domain comprises an IgG hinge domain, or a fragment or variant thereof.

26. The receptor binding molecule of any one of claims 20-25, wherein the Fc domain comprises an IgG hinge domain selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:21, and SEQ ID NO: 22.

27. The receptor binding molecule of any one of claims 20-27, wherein the receptor binding molecule is an APLNR agonist that exhibits an EC50 of less than about 50 nM, or less than about 25 nM, or less than about 10 nM, or less than about 1 nM.

28. The receptor binding molecule of any one of claims 20-27, wherein the receptor binding molecule has an *in vivo* half-life of at least about 1 hour, or at least about 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours.

29. The receptor binding molecule of any one of claims 20-28, wherein the apelin peptide is fused to the C-terminus of the Fc domain.

30. The receptor binding molecule of claim 29, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 2.

31. The receptor binding molecule of claim 30 comprising the amino acid sequence comprising SEQ ID NO: 2.

32. The receptor binding molecule of claim 29, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 39.

33. The receptor binding molecule of claim 32 comprising the amino acid sequence comprising SEQ ID NO: 39.

34. The receptor binding molecule of claim 29, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 40.

35. The receptor binding molecule of claim 34 comprising the amino acid sequence comprising SEQ ID NO: 40.

36. The receptor binding molecule of claim 29, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 41.

37. The receptor binding molecule of claim 36 comprising the amino acid sequence comprising SEQ ID NO: 41.

38. The receptor binding molecule of any one of claims 20-28, wherein the apelin peptide is fused to the N-terminus of the Fc domain.

39. The receptor binding molecule of claim 38, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 4.

40. The receptor binding molecule of claim 39, comprising the amino acid sequence comprising SEQ ID NO: 4.

41. The receptor binding molecule of any one of claims 20-28, wherein the apelin peptide is fused to the C-terminus of the Fc domain or the N-terminus of the Fc domain via one or more Gly-Ser linkers.

42. A composition comprising a receptor binding molecule of any one of claims 20-41.

43. A nucleic acid molecule encoding the apelin receptor binding molecule of any one of claims 20-41.

44. The nucleic acid molecule of claim 43 linked to a nucleotide sequence encoding a signal peptide.

45. The nucleic acid molecule of claim 44 comprising a nucleotide sequence selected the group consisting of SEQ ID NO: 25 and SEQ ID NO: 26.

46. A vector comprising a nucleic acid molecule of any one of claims 43-45.

47. The vector of claim 46, wherein the nucleic acid molecule is operably linked to an expression control sequence suitable for expression in a host cell.

48. The vector of claim 47, wherein the expression control sequence comprises a promoter selected from the group consisting of SV40, CMV, CMV-IE, CMV-MIE, UbC, RSV, SL3-3, MMTV, Ubi and HIV LTR.

49. The vector of claim 46 or claim 47, wherein the expression control sequence comprises an expression cassette selected from the group consisting of TetR-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter, blasticidin resistance gene driven by the SV40 promoter, and Arc-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter.

50. The vector of claim 48 or claim 49, wherein the promoter is a CMV-MIE/TetO or CMV-MIE/Arc hybrid promoter.

51. The vector of any one of claims 46-50 comprising one or more selectable marker genes selected from the group consisting of bla, bls, BSD, bsr, Sh ble, hpt, tetR, tetM, npt, kanR and pac.

52. A cell comprising a nucleic acid molecule of any one of claims 43-45.

53. The cell of claim 52 comprising a vector of any one of claims 46-51.

54. The cell of claim 52 or claim 53, wherein the nucleic acid is integrated into the genome of the cell.

55. The cell of any one of claims 52-54 comprising a nucleic acid encoding a protein expression enhancer.

56. The cell of any one of claims 52-56 comprising a nucleic acid encoding an XBP polypeptide.

57. The cell of any one of claims 52-56, wherein the cell is a eukaryotic cell.

58. The cell of any one of claims 52-57, wherein the host cell is selected from the group consisting of CHO, COS, retinal cell, Vero, CV1, 293, MDCK, HaK, BHK, HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, tumor cell, a cell line derived from any of the aforementioned cells, and a PER.C6® cell.

59. The cell of any one of claims 52-58, wherein the cell is an animal cell.

60. The cell of any one of claims 52-59, wherein the cell is a mammalian cell.

61. The cell of any one of claims 52-60, wherein the cell is a CHO cell.

62. The cell of any one of claims 52-61, wherein the cell is a CHO-K1 cell.

63. A process for determining activation of an APLN receptor (APLNR), which comprises

a. contacting cells expressing APLNR with a test molecule, under conditions permitting activation of the APLNR,
b. measuring APLNR activity,
c. separately contacting cells expressing APLNR with an apelin Fc-fusion protein under the same conditions as in step (a), and
d. measuring APLNR activity of the cells in step (c) in the same manner as step (b), and

wherein the measurement of APLNR activity in step (b) compared to the measurement of APLNR activity in step (d) determines that the test molecule activates the APLNR.

64. The process of claim 63, wherein a higher measurement of APLNR activity in step (b) compared to step (d) indicates that the test molecule is an APLNR agonist.

65. The process of claim 64, wherein the higher measurement of activity in step (b) is an EC50 less than about 50 nM.

66. The process of claim 65, wherein the higher measurement of activity in step (b) is an EC50 less than about 1 nM.

67. The process of claim 63, wherein step (a) comprises contacting cells with both the test molecule and the apelin Fc-fusion protein, and wherein a lower measurement of APLNR activity in step (b) compared to step (d) indicates that the test molecule is an APLNR antagonist.

68. A recombinant polypeptide, wherein the polypeptide comprises N'-$P1_m$- $X1_n$-X2-X3-P2-A1-C', wherein:

(a) N' is the N-terminus and C' is the C-terminus of the polypeptide,
(b) P1 is a peptide linker,
(c) X1 comprises an IgG hinge domain, or a fragment or variant thereof,
(d) X2 comprises an IgG CH2 domain, or a fragment or variant thereof,
(e) X3 comprises an IgG CH3 domain, or a fragment or variant thereof,
(f) P2 is a peptide linker, and
(g) A1 is an amino acid sequence comprising a human apelin peptide, or a fragment or derivative thereof,

wherein m = 0 or 1, and n = 0 or 1.

69. A recombinant polypeptide, wherein the polypeptide comprises N'-A1-P2-$X1_n$-X2-X3-C', wherein:

(a) N' is the N-terminus and C' is the C-terminus of the polypeptide,
(b) A1 is an amino acid sequence comprising a human apelin peptide, or a fragment or derivative thereof,
(c) P2 is a peptide linker,

(d) X1 comprises an IgG hinge domain, or a fragment or variant thereof,

(e) X2 comprises an IgG CH2 domain, or a fragment or variant thereof, and

(f) X3 comprises an IgG CH3 domain or a fragment or variant thereof,

wherein n = 0 or 1.

70. The recombinant polypeptide of claim 68, wherein m = 0.

71. The recombinant polypeptide of claim 68, wherein m=1 and P1 comprises RSTGSPGSG (SEQ ID NO: 12).

72. The recombinant polypeptide of claim 68 or 69, wherein P2 comprises one or more GlySer linkers.

73. The recombinant polypeptide of claim 72, wherein the GlySer linker comprises SEQ ID NO: 11.

74. The recombinant polypeptide of claims 72 or 73, wherein A1 is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77 (apelin-15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^1]Apelin-13, or a fragment or derivative thereof.

75. The recombinant polypeptide of any one of claims 68-74, wherein X1 comprises an amino acid sequence comprising a fragment of a human IgG heavy chain hinge domain.

76. The recombinant polypeptide of any one of claims 68-75, wherein X1 comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 14, SEQ ID NO 17, SEQ ID NO: 18, SEQ ID NO:21 and SEQ ID NO: 22.

77. The recombinant polypeptide of any one of claims 68-76, wherein X2 comprises the human IgG1 CH2 domain or human IgG4 CH2 domain from positions 238 to 340 (EU numbering).

78. The recombinant polypeptide of any one of claims 68-77, wherein X3 comprises the human IgG1 CH3 domain or human IgG4 CH3 domain from positions 341 to 447 (EU numbering).

79. The recombinant polypeptide of any one of claims 68-78, wherein X2 comprises the amino acid sequence of SEQ ID NO: 15 or SEQ ID NO: 23.

80. The recombinant polypeptide of any one of claims 68-79, wherein X3 comprises the amino acid sequence of SEQ ID NO: 16 or SEQ ID NO: 24.

81. The recombinant polypeptide of claim 68, wherein the polypeptide comprises an amino acid sequence at least 99% identical to the polypeptide selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41.

82. The recombinant polypeptide of claim 69, wherein the polypeptide comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 4.

83. A composition comprising a recombinant polypeptide of any one of claims 68-82.

84. A nucleic acid molecule encoding a recombinant polypeptide of any one of claims 68-82.

85. The nucleic acid molecule of claim 84 encoding a recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4.

86. The nucleic acid molecule of claim 84 or 85 comprising a nucleotide sequence having greater than 99% sequence identity to nucleotide sequence of SEQ ID NO: 27 or SEQ ID NO: 28.

87. The nucleic acid molecule of any one of claims 84-86 encoding a monomeric polypeptide capable of forming a dimer.

88. The nucleic acid molecule of any one of claims 84-87, wherein the nucleic acid molecule encodes an amino acid sequence comprising a signal peptide.

89. The nucleic acid molecule of claim 88, wherein the recombinant polypeptide is expressed in a host cell capable of secreting the polypeptide.

90. The nucleic acid molecule of any one of claims 84-89 comprising a nucleotide sequence of SEQ ID NO: 25 or SEQ ID NO: 26.

91. A vector comprising a nucleic acid molecule of any one of claims 84-90.

92. The vector of claim 91, wherein the nucleic acid molecule is operably linked to an expression control sequence suitable for expression in a host cell.

93. The vector of claim 92, wherein the expression control sequence comprises a promoter selected from the group consisting of SV40, CMV, CMV-IE, CMV-MIE, UbC, RSV, SL3-3, MMTV, Ubi and HIV LTR.

94. The vector of claim 93, wherein the expression control sequence comprises an expression cassette selected from the group consisting of TetR-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter, blasticidin resistance gene driven by the SV40 promoter, and Arc-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter.

95. The vector of claim 92 or claim 93, wherein the promoter is a CMV-MIE/TetO or CMV-MIE/Arc hybrid promoter.

96. The vector of any one of claims 91-95, comprising one or more selectable marker genes selected from the group consisting of bla, bls, BSD, bsr, Sh ble, hpt, tetR, tetM, npt, kanR and pac.

97. A cell comprising a nucleic acid molecule of any one of claims 84-90.

98. The cell of claim 97 comprising a vector of any one of claims 91-96.

99. The cell of claim 97 or claim 98, wherein the nucleic acid is integrated into the genome of the cell.

100. The cell of any one of claims 97-99 comprising a nucleic acid encoding a protein expression enhancer.

101. The cell of any one of claims 97-100 comprising a nucleic acid encoding an XBP polypeptide.

102. The cell of any one of claims 97-102, wherein the cell is a eukaryotic cell.

103. The cell of any one of claims 97-102, wherein the host cell is selected from the group consisting of CHO, COS, retinal cell, Vero, CV1, 293, MDCK, HaK, BHK, HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, tumor cell, a cell line derived from any of the aforementioned cells, and a PER.C6® cell.

104. The cell of any one of claims 97-103, wherein the cell is an animal cell.

105. The cell of any one of claims 97-104, wherein the cell is a mammalian cell.

106. The cell of any one of claims 97-105, wherein the cell is a CHO cell.

107. The cell of any one of claims 97-106, wherein the cell is a CHO-K1 cell.

108. The cell of any one of claims 97-107, wherein the recombinant polypeptide is capable of being secreted.

109. A method of making an isolated fusion protein comprising apelin peptide, said method comprising:

a. transfecting a host cell with a nucleic acid molecule encoding said fusion protein, wherein said nucleic acid molecule comprises a nucleotide sequence encoding a signal peptide, fused to either
    i). a nucleotide sequence encoding an Fc domain of human IgG linked to a nucleotide sequence encoding an apelin peptide, at the N-terminus of said apelin peptide, or
    ii). a nucleotide sequence encoding an apelin peptide linked to a nucleotide sequence encoding an Fc domain of a human IgG, at the N-terminus of said Fc domain,

    and
b. making said fusion protein by expressing the nucleic acid molecule of (a) in said host cell.

110. The method of claim 109, wherein the signal peptide comprises SEQ ID NO: 9.

111. The method of claim 109 or claim 110, wherein the fusion protein optionally comprises a nucleotide sequence encoding a peptide linker fused to the C-terminus of said signal peptide.

112. The method of any one of claims 109-111 further comprising the steps of culturing the host cell of step (b), wherein the host cell is secreting said fusion protein into a cell culture medium; and isolating the fusion protein from the cell culture media.

113. The method of any one of claims 109-112, wherein the isolated fusion protein comprises a polypeptide comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 39, SEQ ID NO.40, and SEQ ID NO;41.

114. The method of any one of claims 109-113, wherein the fusion protein comprises a monomeric fusion polypeptide capable of forming a dimer.

115. The method of any one of claims 109-114, wherein the host cell is selected from the group consisting of CHO, COS, retinal cell, Vero, CV1, 293, MDCK, HaK, BHK, HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, tumor cell, a cell line derived from any of the aforementioned cells, and a PER.C6® cell.

116. A method for treatment of a disease or condition related to apelin in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of the polypeptide of claim 1.

117. The method of claim 116, wherein the disease or condition is selected from the group consisting of cardiovascular disease, acute decompensated heart failure, congestive heart failure, myocardial infarction, cardiomyopathy, ischemia, ischemia/reperfusion injury, pulmonary hypertension, diabetes, obesity, cancer, metastatic disease, fluid homeostasis, hot flash symptoms, pathological angiogenesis, retinopathy, fibrosis and HIV infection.

118. A kit comprising one or more containers filled with at least one apelin fusion protein or polypeptide of any of the preceding claims.

119. A polypeptide comprising an apelin peptide fused to a multimerizing component.

120. The polypeptide of claim 119, wherein the multimerizing component comprises a leucine zipper, a helix-loop motif, a coiled-coil motif, an Fc domain, a fragment of an Fc domain, or a variant of an Fc domain.

121. The polypeptide of claims 119 or 120, wherein the apelin peptide is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77 (apelin-15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5),), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^1]Apelin-13, or a fragment or derivative thereof.

122. The polypeptide of any one of claims 119-121, wherein the apelin peptide is apelin-13.

123. The polypeptide of any one of claims 119-122, wherein the apelin peptide is fused to the multimerizing domain via one or more peptide linkers.

124. The polypeptide of claim 123, wherein the multimerizing domain is an Fc domain,or a fragment thereof, and wherein the apelin peptide is fused to Fc domain or Fc domain fragment via one or more Gly-Ser linkers.

125. The polypeptide of claim 124, wherein the apelin peptide is fused to the C-terminus of said Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

126. The polypeptide of claim 125, wherein the apelin peptide is fused to the N-terminus of said Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

127. The polypeptide of any one of claims 119-126 wherein the multimerizing domain is an Fc domain selected from the group consisting of an IgG1 CH2 domain and an IgG1 CH3 domain; an IgG4 CH2 domain and an IgG4 CH3 domain; an IgG1 CH2 domain and an IgG4 CH3 domain; and an IgG4 CH2 domain and an IgG1 CH3 domain.

128. The polypeptide of any one of claims 119-127, wherein the Fc domain comprises an IgG hinge domain, or a fragment or variant thereof.

129. The polypeptide of any one of claims 128, wherein the Fc domain comprises an IgG hinge domain comprising SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:21, or SEQ ID NO: 22.

130. The polypeptide of any one of claims 119-129, wherein the polypeptide forms at least one disulfide bond with a second polypeptide.

131. A nucleic acid encoding the polypeptide of any one of claims 119-130.

132. A multimeric protein comprising the polypeptide of any one of claims 119-131.

What is claimed:

1. A polypeptide comprising an apelin peptide fused to an Fc domain, a fragment of an Fc domain, or variant of an Fc domain, wherein the N-terminus of the apelin peptide is fused to the C-terminus of the Fc domain or fragment or variant thereof, optionally via a peptide linker.

2. The polypeptide of claim 1, wherein the apelin peptide is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77 (apelin-15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^{1}]Apelin-13, or a fragment or derivative thereof.

3. The polypeptide of claim 2, wherein the apelin peptide is apelin-13, or a fragment or derivative thereof.

4. The polypeptide of claim 2, wherein the apelin peptide derivative comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43 and SEQ ID NO: 44.

5. The polypeptide of claim 1, wherein the apelin peptide is fused to the Fc domain, or fragment thereof, via one or more peptide linkers.

6. The polypeptide of claim 4, wherein the apelin peptide is fused to the Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

7. The polypeptide of claim 5, wherein the apelin peptide is fused to the C-terminus of said Fc domain, or fragment thereof, via one or more Gly-Ser linkers.

8. The polypeptide of claim 1 wherein the Fc domain is selected from the group consisting of IgG1 CH2 domain and IgG1 CH3 domain; IgG4 CH2 domain and IgG4 CH3 domain; IgG1 CH2 domain and IgG4 CH3 domain; and IgG4 CH2 domain and an IgG1 CH3 domain.

9. The polypeptide of claim, wherein the Fc domain comprises an IgG hinge domain, or a fragment or a variant thereof.

10. The polypeptide of claim 9, wherein the Fc domain comprises an IgG hinge domain comprising SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:21, or SEQ ID NO: 22.

11. The polypeptide of claim 1, wherein the polypeptide forms at least one disulfide bond with a second polypeptide.

12. The polypeptide of claim 1, wherein the polypeptide is a monomeric fusion polypeptide capable of forming a dimer.

13. The polypeptide of claim 1, wherein the polypeptide has 95% or greater sequence identity to the amino acid sequence comprising SEQ ID NO: 2.

14. The polypeptide of claim 13 comprising the amino acid sequence comprising SEQ ID NO: 2.

15. The polypeptide of any one of claims 1-14 that has increased serum stability relative to the apelin peptide and exhibits an EC50 of less than 1 nm when measured in an *in vitro* APLNR activation assay.

16. A nucleic acid encoding the polypeptide of any one of claims 1-15.

17. A protein comprising the polypeptide of any one of claims 1-15.

18. An apelin receptor (APNLR) agonist, comprising:

a. an apelin peptide component,

b. a human IgG Fc domain, and

c. optionally at least one linker component,

wherein the N-terminus of the apelin peptide component is fused to the C-terminus of the human IgG Fc domain, optionally via the at least one linker component.

19. The APLNR agonist of claim 18, wherein the apelin peptide is selected from the group consisting of apelin42-77 (apelin-36), apelin61-77 (apelin-17), apelin63-77 (apelin-

15), apelin64-77 (apelin-14), apelin65-77 (apelin-13), apelin66-77 (apelin-12), apelin67-77 (apelin-11), apelin68-77 (apelin-10), apelin73-77 (apelin-5), apelin61-76 (apelin-K16P), apelin61-75 (apelin-K15M), apelin61-74 (apelin-K14P), apelin-F13A, apelin65-76, apelin65-75, apelin66-76, apelin67-76, apelin66-75, apelin 67-75, and [Pyr^{1}]Apelin-13, or a fragment or derivative thereof.

20. The APLNR agonist of claim 18 or 19, wherein the apelin peptide is apelin-13 (SEQ ID NO: 6), or a fragment or derivative thereof.

21. The APLNR agonist of claim 19, wherein the apelin peptide derivative comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43 and SEQ ID NO: 44.

22. The APLNR agonist of any one of claims 18-21, wherein the Fc domain is selected from the group consisting of an IgG1 CH2 domain and an IgG1 CH3 domain; an IgG4 CH2 domain and an IgG4 CH3 domain; an IgG1 CH2 domain and an IgG4 CH3 domain; and an IgG4 CH2 domain and an IgG1 CH3 domain; or a fragment or variant thereof.

23. The APLNR agonist of any one of claims 18-22, wherein the Fc domain comprises an IgG hinge domain, or a fragment or variant thereof.

24. The APLNR agonist of any one of claims 18-23, wherein the Fc domain comprises an IgG hinge domain selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:21, and SEQ ID NO: 22.

25. The APLNR agonist of any one of claims 18-24, wherein the receptor binding molecule is an APLNR agonist that exhibits an EC50 of less than about 50 nM, or less than about 25 nM, or less than about 10 nM, or less than about 1 nM.

26. The APLNR agonist of any one of claims 18-25, wherein the receptor binding molecule has an *in vivo* half-life of at least about 1 hour, or at least about 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours.

27. The APLNR agonist of claim 26, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 2.

28. The APLNR agonist of claim 27 comprising the amino acid sequence comprising SEQ ID NO: 2.

29. The APLNR agonist of claim 26, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 39.

30. The APLNR agonist of claim 29 comprising the amino acid sequence comprising SEQ ID NO: 39.

31. The APLNR agonist of claim 26, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 40.

32. The APLNR agonist of claim 31 comprising the amino acid sequence comprising SEQ ID NO: 40.

33. The APLNR agonist of claim 26, comprising a polypeptide wherein the polypeptide has 95% or greater amino acid sequence identity to the amino acid sequence comprising SEQ ID NO: 41.

34. The APLNR agonist of claim 33 comprising the amino acid sequence comprising SEQ ID NO: 41.

35. The APLNR agonist of any one of claims 18-26, wherein the apelin peptide is fused to the C-terminus of the Fc domain or the N-terminus of the Fc domain via one or more Gly-Ser linkers.

36. A composition comprising the APLNR agonist of any one of claims 18-35.

37. A nucleic acid molecule encoding the APLNR agonist of any one of claims 18-35.

38. The nucleic acid molecule of claim 37 linked to a nucleotide sequence encoding a signal peptide.

39. The nucleic acid molecule of claim 38 comprising the nucleotide sequence of SEQ ID NO: 25.

40. A vector comprising a nucleic acid molecule of any one of claims 37-39.

41. The vector of claim 40, wherein the nucleic acid molecule is operably linked to an expression control sequence suitable for expression in a host cell.

42. The vector of claim 41, wherein the expression control sequence comprises a promoter selected from the group consisting of SV40, CMV, CMV-IE, CMV-MIE, UbC, RSV, SL3-3, MMTV, Ubi and HIV LTR.

43. The vector of claim 40 or claim 41, wherein the expression control sequence comprises an expression cassette selected from the group consisting of TetR-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter, blasticidin resistance gene driven by the SV40 promoter, and Arc-ER_{LBD}T2 fusion gene driven by the CMV-MIE promoter.

44. The vector of claim 42 or claim 43, wherein the promoter is a CMV-MIE/TetO or CMV-MIE/Arc hybrid promoter.

45. The vector of any one of claims 40-44 comprising one or more selectable marker genes selected from the group consisting of bla, bls, BSD, bsr, Sh ble, hpt, tetR, tetM, npt, kanR and pac.

46. A cell comprising a nucleic acid molecule of any one of claims 37-39.

47. The cell of claim 46 comprising a vector of any one of claims 40-45.

48. The cell of claim 46 or claim 47, wherein the nucleic acid is integrated into the genome of the cell.

49. The cell of any one of claims 46-48 comprising a nucleic acid encoding a protein expression enhancer.

50. The cell of any one of claims 46-49 comprising a nucleic acid encoding an XBP polypeptide.

51. The cell of any one of claims 46-50, wherein the cell is a eukaryotic cell.

52. The cell of any one of claims 46-51, wherein the cell is selected from the group consisting of CHO, COS, retinal cell, Vero, CV1, 293, MDCK, HaK, BHK, HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, tumor cell, a cell line derived from any of the aforementioned cells, and a PER.C6® cell.

53. The cell of any one of claims 46-52, wherein the cell is an animal cell.

54. The cell of any one of claims 46-53, wherein the cell is a mammalian cell.

55. The cell of any one of claims 46-54, wherein the cell is a CHO cell.

56. The cell of any one of claims 46-55, wherein the cell is a CHO-K1 cell.

57. A process for determining activation of an APLN receptor (APLNR), which comprises

a. contacting cells expressing APLNR with a test molecule, under conditions permitting activation of the APLNR**,**

b. measuring APLNR activity,

c. separately contacting cells expressing APLNR with an apelin Fc-fusion protein under the same conditions as in step (a), and

d. measuring APLNR activity of the cells in step (c) in the same manner as step (b), and

wherein the measurement of APLNR activity in step (b) compared to the measurement of APLNR activity in step (d) determines that the test molecule activates the APLNR.

58. The process of claim 57, wherein a higher measurement of APLNR activity in step (b) compared to step (d) indicates that the test molecule is an APLNR agonist.

59. The process of claim 58, wherein the higher measurement of activity in step (b) is an EC50 less than about 50 nM.

60. The process of claim 59, wherein the higher measurement of activity in step (b) is an EC50 less than about 1 nM.

61. The process of claim 57, wherein step (a) comprises contacting cells with both the test molecule and the apelin Fc-fusion protein, and wherein a lower measurement of APLNR activity in step (b) compared to step (d) indicates that the test molecule is an APLNR antagonist.

62. A method of making an isolated fusion protein comprising apelin peptide, said method comprising:

a. transfecting a host cell with a nucleic acid molecule encoding said fusion protein, wherein said nucleic acid molecule comprises a nucleotide sequence encoding a signal peptide, fused to either

i). a nucleotide sequence encoding an Fc domain of human IgG linked to a nucleotide sequence encoding an apelin peptide, at the N-terminus of said apelin peptide,

and

b. making said fusion protein by expressing the nucleic acid molecule of (a) in said host cell

63. The method of claim 62, wherein the signal peptide comprises SEQ ID NO: 9.

64. The method of claim 62 or claim 63, wherein the fusion protein optionally comprises a nucleotide sequence encoding a peptide linker fused to the C-terminus of said signal peptide.

65. The method of any one of claims 62-64 further comprising the steps of culturing the host cell of step (b), wherein the host cell is secreting said fusion protein into a cell culture medium; and isolating the fusion protein from the cell culture media.

66. The method of any one of claims 62-65, wherein the isolated fusion protein comprises a polypeptide comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 39, SEQ ID NO.40, and SEQ ID NO;41.

67. The method of any one of claims 62-66, wherein the fusion protein comprises a monomeric fusion polypeptide capable of forming a dimer.

68. The method of any one of claims 62-67, wherein the host cell is selected from the group consisting of CHO, COS, retinal cell, Vero, CV1, 293, MDCK, HaK, BHK, HeLa, HepG2, WI38, MRC 5, Colo25, HB 8065, HL-60, Jurkat, Daudi, A431 (epidermal), CV-1, U937, 3T3, L cell, C127 cell, SP2/0, NS-0, MMT cell, tumor cell, a cell line derived from any of the aforementioned cells, and a PER.C6® cell.

69. The use of a polypeptide according to claims 1-15 in the manufacture of a medicament for the treatment of a disease or condition selected from the group consisting of cardiovascular disease, acute decompensated heart failure, congestive heart failure, myocardial infarction, cardiomyopathy, ischemia, ischemia/reperfusion injury, pulmonary hypertension, diabetes, obesity, cancer, metastatic disease, fluid homeostasis, hot flash symptoms, pathological angiogenesis, retinopathy, fibrosis and HIV infection.