CLAIMS

What is claimed:

1. An isolated polypeptide comprising the amino acid sequence of the formula:

$X_{aa}^{1}X_{aa}^{2}$ $Cys^{3}X_{aa}^{4}X_{aa}^{5}X_{aa}^{6}X_{aa}^{7}X_{aa}^{8}X_{aa}^{9}Cys^{10}X_{aa}^{11}X_{aa}^{12}X_{aa}^{13}X_{aa}^{14}Asp^{15}X_{aa}^{16}$ Cys^{17}

$Cys^{18}X_{aa}^{19}X_{aa}^{20}X_{aa}^{21}X_{aa}^{22}X_{aa}^{23}$ $Cys^{24}X_{aa}^{25}X_{aa}^{26}X_{aa}^{27}X_{aa}^{28}X_{aa}^{29}Trp^{30}$

$Cys^{31}Lys^{32}Tyr^{33}X_{aa}^{34}Phe^{35}X_{aa}^{36}X_{aa}^{37}X_{aa}^{38}$

or a pharmaceutically acceptable salt thereof,

wherein:

X_{aa}^{1} is absent and X_{aa}^{2} is any amino acid residue;

X_{aa}^{4} is an acidic, hydrophobic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{5} is a Gly, Ala, hydrophobic, or basic amino acid residue;

X_{aa}^{6} is a Gly, Ala, 2-Abu, 2-Aib, Ile, Leu, Val, Nle, or Nva;

X_{aa}^{7} is a Gly, Ala, aromatic, or hydrophobic amino acid residue;

X_{aa}^{8} is a basic, acidic, or neutral hydrophilic amino acid residue, or an Ala residue;

X_{aa}^{9} is a basic or neutral hydrophilic amino acid residue;

X_{aa}^{11} is any amino acid residue;

X_{aa}^{12} is a Pro, acidic, neutral, or hydrophobic amino acid residue;

X_{aa}^{13} is any amino acid residue;

X_{aa}^{14} is any amino acid residue;

X_{aa}^{16} is a basic, neutral hydrophilic, or acidic amino acid residue, or an Ala residue;

X_{aa}^{19} is any amino acid residue;

X_{aa}^{20} is a Pro, Gly, basic, or neutral hydrophilic residue;

X_{aa}^{21} is a basic, hydrophobic, or neutral hydrophilic amino acid residue;

X_{aa}^{22} is a hydrophobic or basic amino acid residue;

X_{aa}^{23} is a hydrophobic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{25} is a Ser, Ala, or a neutral hydrophilic amino acid residue;

X_{aa}^{26} is an Ala, acidic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{27} is an acidic, basic, neutral hydrophilic or hydrophobic residue;

X_{aa}^{28} is an aromatic or basic amino acid residue;

X_{aa}^{29} is an acidic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{34} is any amino acid residue;

each of X_{aa}^{36}, X_{aa}^{37}, and X_{aa}^{38} is independently absent or is independently a neutral, basic, or hydrophobic amino acid residue;

and wherein the isolated polypeptide selectively inhibits Nav1.7 sodium channels relative to Nav1.4 and Nav1.5 sodium channels.

Support: original claims 1, 4, 23, and 25; paragraphs [0026], [00222] and [00461]

2. The isolated polypeptide of Claim 1 wherein X_{aa}^4 is selected from Ala, Glu, Asp, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Cit residues.

3. The isolated polypeptide of Claim 1, wherein X_{aa}^5 is selected from Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

4. The isolated polypeptide of Claim 1, wherein X_{aa}^7 is selected from Gly, Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, norleucine, norvaline, Pro, 2-pyridinylalanine, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

5. The isolated polypeptide of Claim 1, wherein X_{aa}^8 is selected from Ala, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Ser, Thr, Asn, Gln, Cit, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Glu residues.

6. The isolated polypeptide of Claim 1, wherein X_{aa}^9 is selected from Ala, Pro, Met, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, and Cit residues.

7. The isolated polypeptide of Claim 1, wherein X_{aa}^{11} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

8. The isolated polypeptide of Claim 1, wherein X_{aa}^{12} is selected from alanine, valine, leucine, isoleucine, proline, serine, threonine, aspartic acid, glutamatic acid, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, Cha, and 4-phenyl-phenylalanine (Bip), cyclohexylglycine (Chg), cyclohexylalanine (Cha), asparagine, glutamine, methionine, hydroxyproline, phenylalanine, tryptophan, and tyrosine.

9. The isolated polypeptide of Claim 1, wherein X_{aa}^{13} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

10. The isolated polypeptide of Claim 1, wherein X_{aa}^{14} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

11. The isolated polypeptide of Claim 1, wherein X_{aa}^{16} is selected from Ala, Pro, Met, Arg, Lys, His, Pra, Atz, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, Cit, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Glu residues.

12. The isolated polypeptide of Claim 1, wherein X_{aa}^{19} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine,

N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

13. The isolated polypeptide of Claim 1, wherein X_{aa}^{20} is selected from Ala, Gly, Pro, Met, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, and Cit residues.

14. The isolated polypeptide of Claim 1, wherein X_{aa}^{21} is selected from Ala, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, and Cit residues.

15. The isolated polypeptide of Claim 1, wherein X_{aa}^{22} is selected from Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

16. The isolated polypeptide of Claim 1, wherein X_{aa}^{23} is selected from Ala, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, and Cit residues.

17. The isolated polypeptide of Claim 1, wherein X_{aa}^{25} is selected from Ala, Gly Pro, Met, Gln, Asn, Ser, Thr, and Cit residues.

18. The isolated polypeptide of Claim 1, wherein X_{aa}^{26} is selected from Ala, Pro, Met, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, Glu, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, Gln, Asn, Ser, Thr, and Cit residues.

19. The isolated polypeptide of Claim 1, wherein X_{aa}^{27} is selected from Thr, Leu, Ile, Val, Ser, Met, Gln, Asn, Phe, Tyr, Trp, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 4-phenyl-phenylalanine (Bip), Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Gly residues.

20. The isolated polypeptide of Claim 1, wherein X_{aa}^{28} is selected from Phe, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, 1-Nal, 2-Nal, 2-pyridyl-alanine, 3-pyridyl-alanine, 4-pyridyl-alanine, 4-piperidinyl-alanine, and 4-phenyl-phenylalanine (Bip) residues.

21. The isolated polypeptide of Claim 1, wherein X_{aa}^{29} is selected from Ala, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, Phe, Gly, His, Lys, Asn, Pro, Gln, Arg, Ser, Thr, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, and Dab residues.

22. The isolated polypeptide of Claim 1, wherein X_{aa}^{34} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, 2-pyridyl-alanine, 3-pyridyl-alanine, 4-carboxy-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

23. The isolated polypeptide of Claim 1, wherein each of X_{aa}^{36} , X_{aa}^{37}, and X_{aa}^{38} is independently absent or is independently selected from Ala, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

24. The isolated polypeptide of Claim 1, wherein the carboxy-terminal residue is amidated.

25. The isolated polypeptide of Claim 1, wherein the isolated polypeptide comprises the amino acid sequence of the formula:

Asp-Cys-Leu-Gly-Xaa^{5}-Xaa^{6}-Arg-Lys-Cys-Xaa^{10}-Pro-Asp-Xaa^{13}-Asp-Lys-Cys-Cys-Arg-Pro-Asn-Leu-Val-Cys-Ser-Arg-Xaa^{26}-His-Xaa^{28}-Trp-Cys-Lys-Tyr-Val-Phe, wherein:

Xaa^{5} is a Gly, Ala, 2-Abu, 2-Aib, Ile, Leu, Val, Nle, or Nva residue;

Xaa^{6} is a Gly, Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, norleucine, norvaline, Pro, 2-pyridinylalanine, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, or 4-phenyl-phenylalanine (Bip) residue;

Xaa^{10} is a Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), or 4-phenyl-phenylalanine (Bip) residue;

Xaa^{13} is a Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 2-Abu, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), or 4-phenyl-phenylalanine (Bip) residue;

Xaa^{26} is a Thr, Leu, Ile, Val, Ser, Met, Gln, Asn, Phe, Tyr, Trp, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 4-phenyl-phenylalanine (Bip), Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, or Gly residue; and

Xaa^{28} is a Ala, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, Phe, Gly, His, Lys, Asn, Pro, Gln, Arg, Ser, Thr, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, or Dab residue.

26. The isolated polypeptide of Claim 25, wherein Xaa^{5} is Ala.

27. The isolated polypeptide of Claim 25 or Claim 26, wherein Xaa^{6} is Phe or Leu.

28. The isolated polypeptide of Claim 27, wherein Xaa^{10} is Glu.

29. The isolated polypeptide of any one of Claims 25 to 28, wherein Xaa^{13} is Atz.

30. The isolated polypeptide of any one of Claims 25 to 29, wherein Xaa^{26} is Leu.

31. The isolated polypeptide of any one of Claims 25 to 30, wherein Xaa^{28} is Arg.

32. The isolated polypeptide of Claim 1, wherein $X_{aa}{}^{6}$ is Ala.

33. The isolated polypeptide of Claim 32, wherein $X_{aa}{}^{27}$ is Glu.

34. The isolated polypeptide of Claim 32, wherein $X_{aa}{}^{29}$ is Asp, Glu, or Gln.

35. The isolated polypeptide of Claim 32, comprising an amino acid sequence selected from SEQ ID NOS: 22, 252, 255-263, 419-429, 435, 436, 438, 439, 518-521, 524, 525, 562-576, 579, 580, 602, 691, 696-703, 715, 721-735, 737-749, 756, 757, 761, 762, 764-771, 787, 788, 790-796, 798, 800, 802, 803, 809-812, 1028, 1030-1040, 1043-1047, 1062-1065, and 1068-1070.

36. The isolated polypeptide of Claim 32, comprising an amino acid sequence selected from SEQ ID NOS: 1082, 1096, 1110, 1124, 1135, 1146, 1157, 1165, 1173, 1181, 1192, 1203, 1214, 1222, 1230, 1238, 1249, 1260, 1271, 1279, 1287, 1295, 1306, 1317, 1328, 1336, 1344, 1352, 1360, 1368, 1376, 1384, 1392, 1400, 1408, 1416, 1424, 1432, 1440, 1448, 1456, 1464, 1472, 1480, 1488, 1496, 1504, 1512, 1520, 1528, 1536, 1544, 1552, 1560, 1568, 1576, 1584, 1592, 1600, 1608, 1616, 1624, 1632, 1640, 1658, 1672, 1686, 1700, 1711, 1722, 1733, 1741, 1749, 1757, 1768, 1779, 1790, 1798, 1806, 1814, 1825, 1836, 1847, 1855, 1863, 1871, 1882, 1893, 1904, 1912, 1920, 1928, 1936, 1944, 1952, 1960, 1968, 1976, 1984, 1992, 2000, 2008, 2016, 2024, 2032, 2040, 2048, 2056, 2064, 2072, 2080, 2088, 2096, 2104, 2112, 2120, 2128, 2136, 2144, 2152, 2160, 2168, 2176, 2184, 2192, 2200, 2208, 2216, 2234, 2248, 2262, 2276, 2287, 2298, 2309, 2317, 2325, 2333, 2344, 2355, 2366,

2374, 2382, 2390, 2401, 2412, 2423, 2431, 2439, 2447, 2458, 2469, 2480, 2488, 2496, 2504, 2512, 2520, 2528, 2536, 2544, 2552, 2560, 2568, 2576, 2584, 2592, 2600, 2608, 2616, 2624, 2632, 2640, 2648, 2656, 2664, 2672, 2680, 2688, 2696, 2704, 2712, 2720, 2728, 2736, 2744, 2752, 2760, 2768, 2776, 2784, 2792, 2808, 2822, 2833, 2844, 2855, 2863, 2871, 2879, 2890, 2901, 2912, 2920, 2928, 2936, 2944, 2952, 2960, 2968, 2976, 2984, 2992, 3000, 3008, 3016, 3024, 3032, 3040, 3048, 3056, 3064, 3072, and 3080.

37. The isolated polypeptide of Claim 32, comprising an amino acid sequence selected from SEQ ID NOS: 597-601 and 813-1027.

38. The isolated polypeptide of Claim 1, wherein X_{aa}^{6} is Gly.

39. The isolated polypeptide of Claim 38, wherein X_{aa}^{27} is Glu.

40. The isolated polypeptide of Claim 38, wherein X_{aa}^{29} is Asp, Glu, or Gln.

41. The isolated polypeptide of Claim 38, comprising an amino acid sequence selected from SEQ ID NOS: 265, 751, 752, 754, 755, 1081, 1095, 1109, 1123, 1134, 1145, 1156, 1164, 1172, 1180, 1191, 1202, 1213, 1221, 1229, 1237, 1248, 1259, 1270, 1278, 1286, 1294, 1305, 1316, 1327, 1335, 1343, 1351, 1359, 1367, 1375, 1383, 1391, 1399, 1407, 1415, 1423, 1431, 1439, 1447, 1455, 1463, 1471, 1479, 1487, 1495, 1503, 1511, 1519, 1527, 1535, 1543, 1551, 1559, 1567, 1575, 1583, 1591, 1599, 1607, 1615, 1623, 1631, 1639, 1657, 1671, 1685, 1699, 1710, 1721, 1732, 1740, 1748, 1756, 1767, 1778, 1789, 1797, 1805, 1813, 1824, 1835, 1846, 1854, 1862, 1870, 1881, 1892, 1903, 1911, 1919, 1927, 1935, 1943, 1951, 1959, 1967, 1975, 1983, 1991, 1999, 2007, 2015, 2023, 2031, 2039, 2047, 2055, 2063, 2071, 2079, 2087, 2095, 2103, 2111, 2119, 2127, 2135, 2143, 2151, 2159, 2167, 2175, 2183, 2191, 2199, 2207, 2215, 2233, 2247, 2261, 2275, 2286, 2297, 2308, 2316, 2324, 2332, 2343, 2354, 2365, 2373, 2381, 2389, 2400, 2411, 2422, 2430, 2438, 2446, 2457, 2468, 2479, 2487, 2495, 2503, 2511, 2519, 2527, 2535, 2543, 2551, 2559, 2567, 2575, 2583, 2591, 2599, 2607, 2615, 2623, 2631, 2639, 2647, 2655, 2663, 2671, 2679, 2687, 2695, 2703, 2711, 2719, 2727, 2735, 2743, 2751, 2759, 2767, 2775, 2783, 2791, 2807, 2821, 2832, 2843, 2854, 2862, 2870, 2878, 2889, 2900, 2911, 2919, 2927, 2935, 2943, 2951, 2959, 2967, 2975, 2983, 2991, 2999, 3007, 3015, 3023, 3031, 3039, 3047, 3055, 3063, 3071, and 3079.

42. The isolated polypeptide of Claim 1, wherein X_{aa}^{6} is 2-Abu.

43. The isolated polypeptide of Claim 42, wherein X_{aa}^{27} is Glu.

44. The isolated polypeptide of Claim 42, wherein X_{aa}^{29} is Asp, Glu, or Gln.

45. The isolated polypeptide of Claim 42, comprising an amino acid sequence selected from SEQ ID NOS: 605, 636, 649, 706, 707, 753, 758, 797, 799, 801, 804, 807, 808, 1029, 1041, 1042, 1048, 1066, 1067, 1083, 1097, 1111, 1125, 1136, 1147, 1158, 1166, 1174, 1182, 1193, 1204, 1215, 1223, 1231, 1239, 1250, 1261, 1272, 1280, 1288, 1296, 1307, 1318, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433, 1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1537, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1641, 1659, 1673, 1687, 1701, 1712, 1723, 1734, 1742, 1750, 1758, 1769, 1780, 1791, 1799, 1807, 1815, 1826, 1837, 1848, 1856, 1864, 1872, 1883, 1894, 1905, 1913, 1921, 1929, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2235, 2249, 2263, 2277, 2288, 2299, 2310, 2318, 2326, 2334, 2345, 2356, 2367, 2375, 2383, 2391, 2402, 2413, 2424, 2432, 2440, 2448, 2459, 2470, 2481, 2489, 2497, 2505, 2513, 2521, 2529, 2537, 2545, 2553, 2561, 2569, 2577, 2585, 2593, 2601, 2609, 2617, 2625, 2633, 2641, 2649, 2657, 2665, 2673, 2681, 2689, 2697, 2705, 2713, 2721, 2729, 2737, 2745, 2753, 2761, 2769, 2777, 2785, 2793, 2809, 2823, 2834, 2845, 2856, 2864, 2872, 2880, 2891, 2902, 2913, 2921, 2929, 2937, 2945, 2953, 2961, 2969, 2977, 2985, 2993, 3001, 3009, 3017, 3025, 3033, 3041, 3049, 3057, 3065, 3073, and 3081.

46. The isolated polypeptide of Claim 1, wherein X_{aa}^{6} is Nle.

47. The isolated polypeptide of Claim 46, wherein X_{aa}^{27} is Glu.

48. The isolated polypeptide of Claim 46, wherein X_{aa}^{29} is Asp, Glu, or Gln.

49. The isolated polypeptide of Claim 46, comprising an amino acid sequence selected from SEQ ID NOS: 607, 638, 651, 1085, 1099, 1113, 1127, 1138, 1149, 1160, 1168, 1176, 1184, 1195, 1206, 1217, 1225, 1233, 1241, 1252, 1263, 1274, 1282, 1290, 1298, 1309, 1320, 1331, 1339, 1347, 1355, 1363, 1371, 1379, 1387, 1395, 1403, 1411, 1419, 1427, 1435, 1443, 1451, 1459, 1467, 1475, 1483, 1491, 1499, 1507, 1515, 1523, 1531, 1539, 1547, 1555, 1563, 1571, 1579, 1587, 1595, 1603, 1611, 1619, 1627, 1635, 1643, 1661, 1675, 1689, 1703, 1714, 1725, 1736, 1744, 1752, 1760, 1771,

1782, 1793, 1801, 1809, 1817, 1828, 1839, 1850, 1858, 1866, 1874, 1885, 1896, 1907, 1915, 1923, 1931, 1939, 1947, 1955, 1963, 1971, 1979, 1987, 1995, 2003, 2011, 2019, 2027, 2035, 2043, 2051, 2059, 2067, 2075, 2083, 2091, 2099, 2107, 2115, 2123, 2131, 2139, 2147, 2155, 2163, 2171, 2179, 2187, 2195, 2203, 2211, 2219, 2237, 2251, 2265, 2279, 2290, 2301, 2312, 2320, 2328, 2336, 2347, 2358, 2369, 2377, 2385, 2393, 2404, 2415, 2426, 2434, 2442, 2450, 2461, 2472, 2483, 2491, 2499, 2507, 2515, 2523, 2531, 2539, 2547, 2555, 2563, 2571, 2579, 2587, 2595, 2603, 2611, 2619, 2627, 2635, 2643, 2651, 2659, 2667, 2675, 2683, 2691, 2699, 2707, 2715, 2723, 2731, 2739, 2747, 2755, 2763, 2771, 2779, 2787, 2795, 2811, 2825, 2836, 2847, 2858, 2866, 2874, 2882, 2893, 2904, 2915, 2923, 2931, 2939, 2947, 2955, 2963, 2971, 2979, 2987, 2995, 3003, 3011, 3019, 3027, 3035, 3043, 3051, 3059, 3067, 3075, and 3083.

50. The isolated polypeptide of Claim 1, wherein X_{aa}^{6} is Nva.

51. The isolated polypeptide of Claim 50, wherein X_{aa}^{27} is Glu.

52. The isolated polypeptide of Claim 50, wherein X_{aa}^{29} is Asp, Glu, or Gln.

53. The isolated polypeptide of Claim 50, comprising an amino acid sequence selected from SEQ ID NOS: 606, 637, 650, 705, 708, 759, 760, 805, 806, 1084, 1098, 1112, 1126, 1137, 1148, 1159, 1167, 1175, 1183, 1194, 1205, 1216, 1224, 1232, 1240, 1251, 1262, 1273, 1281, 1289, 1297, 1308, 1319, 1330, 1338, 1346, 1354, 1362, 1370, 1378, 1386, 1394, 1402, 1410, 1418, 1426, 1434, 1442, 1450, 1458, 1466, 1474, 1482, 1490, 1498, 1506, 1514, 1522, 1530, 1538, 1546, 1554, 1562, 1570, 1578, 1586, 1594, 1602, 1610, 1618, 1626, 1634, 1642, 1660, 1674, 1688, 1702, 1713, 1724, 1735, 1743, 1751, 1759, 1770, 1781, 1792, 1800, 1808, 1816, 1827, 1838, 1849, 1857, 1865, 1873, 1884, 1895, 1906, 1914, 1922, 1930, 1938, 1946, 1954, 1962, 1970, 1978, 1986, 1994, 2002, 2010, 2018, 2026, 2034, 2042, 2050, 2058, 2066, 2074, 2082, 2090, 2098, 2106, 2114, 2122, 2130, 2138, 2146, 2154, 2162, 2170, 2178, 2186, 2194, 2202, 2210, 2218, 2236, 2250, 2264, 2278, 2289, 2300, 2311, 2319, 2327, 2335, 2346, 2357, 2368, 2376, 2384, 2392, 2403, 2414, 2425, 2433, 2441, 2449, 2460, 2471, 2482, 2490, 2498, 2506, 2514, 2522, 2530, 2538, 2546, 2554, 2562, 2570, 2578, 2586, 2594, 2602, 2610, 2618, 2626, 2634, 2642, 2650, 2658, 2666, 2674, 2682, 2690, 2698, 2706, 2714, 2722, 2730, 2738, 2746, 2754, 2762, 2770, 2778, 2786, 2794, 2810, 2824, 2835, 2846, 2857, 2865, 2873, 2881, 2892, 2903, 2914, 2922, 2930, 2938, 2946, 2954, 2962, 2970, 2978, 2986, 2994, 3002, 3010, 3018, 3026, 3034, 3042, 3050, 3058, 3066, 3074, and 3082.

54. The isolated polypeptide of Claim 1, comprising an amino acid sequence selected from SEQ ID NOS: 22, 262, 640, 1028, 1031, 1035, and 1046-1048.

55. The isolated polypeptide of Claim 1 or Claim 25, wherein the polypeptide is covalently linked to a half-life extending moiety.

56. The isolated polypeptide of Claim 55, wherein the half-life extending moiety is polyethylene glycol of molecular weight of about 1000 Da to about 100000 Da, an IgG Fc domain, a transthyretin, or a human serum albumin.

57. The isolated polypeptide of Claim 55, wherein the half-life extending moiety comprises a human immunoglobulin or a human immunoglobulin Fc domain, or both.

58. The isolated polypeptide of Claim 57, wherein the isolated polypeptide is covalently linked to an immunoglobulin or immunoglobulin Fc domain to form a monovalent immunoglobulin-peptide or Fc-peptide conjugate.

59. The isolated polypeptide of Claim 57, wherein two copies of the isolated polypeptide are covalently linked to an immunoglobulin or immunoglobulin Fc domain to form a bivalent immunoglobulin-peptide or Fc-peptide conjugate.

60. A pharmaceutical composition, comprising the isolated polypeptide of any of Claims 1 to 59, and a pharmaceutically acceptable carrier.

61. Use of a prophylactically effective amount of the isolated polypeptide of any one of Claims 1 to 59 in the manufacture of a medicament for preventing pain.

62. Use of a therapeutically effective amount of the isolated polypeptide of any one of Claims 1 to 59 in the manufacture of a medicament for treating pain.

63. The use of Claim 62, wherein the pain is chronic pain, acute pain, or persistent pain.

64. The use of Claim 63, wherein the chronic pain is associated with cancer, chemotherapy, osteoarthritis, fibromyalgia, primary erythromelalgia, post-herpetic neuralgia, painful diabetic neuropathy, idiopathic painful neuropathy, neuromas, paroxysmal extreme pain disorder, migraine, trigeminal neuralgia, orofacial pain, cluster headaches, complex regional pain syndrome (CRPS), failed back surgery syndrome, sciatica, interstitial cystitis, pelvic pain, lower back pain, inflammation-induced pain, or joint pain.

65. The use of Claim 63, wherein the acute or persistent pain is associated with trauma, burn, or surgery.

66. The isolated polypeptide of Claim 1, wherein X_{aa}^{29} is an acidic or neutral hydrophilic residue.

67. The isolated polypeptide of Claim 66, wherein X_{aa}^{29} is selected from Ala, Asp, Glu, Gly, Asn, Gln, Ser, Thr, phosphoserine, phosphotyrosine, and gamma-carboxyglutamic acid residues.

CLAIMS

What is claimed:

1. A composition of matter comprising an isolated polypeptide comprising the amino acid sequence of the formula:

$X_{aa}^{1}X_{aa}^{2}X_{aa}^{3}X_{aa}^{4}X_{aa}^{5}X_{aa}^{6}X_{aa}^{7}X_{aa}^{8}X_{aa}^{9}X_{aa}^{10}X_{aa}^{11}X_{aa}^{12}X_{aa}^{13}X_{aa}^{14}Asp^{15}X_{aa}^{16}X_{aa}^{17}$
$X_{aa}^{18}X_{aa}^{19}X_{aa}^{20}X_{aa}^{21}X_{aa}^{22}X_{aa}^{23}X_{aa}^{24}X_{aa}^{25}X_{aa}^{26}X_{aa}^{27}X_{aa}^{28}X_{aa}^{29}X_{aa}^{30}$
$X_{aa}^{31}Lys^{32}X_{aa}^{33}X_{aa}^{34}X_{aa}^{35}X_{aa}^{36}X_{aa}^{37}X_{aa}^{38}$//SEQ ID NO:475

or a pharmaceutically acceptable salt thereof,

wherein:

$X_{aa}^{1}X_{aa}^{2}$ is absent; or X_{aa}^{1} is any amino acid residue and X_{aa}^{2} is any amino acid residue; or X_{aa}^{1} is absent and X_{aa}^{2} is any amino acid residue;

X_{aa}^{3} is Cys, if X_{aa}^{18} is Cys; or X_{aa}^{3} is SeCys, if X_{aa}^{18} is SeCys; or X_{aa}^{3} is an alkyl amino acid residue, if X_{aa}^{18} is an alkyl amino acid residue;

X_{aa}^{4} is an acidic, hydrophobic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{5} is a Gly, Ala, hydrophobic, or basic amino acid residue;

X_{aa}^{6} is a Gly, Ala, 2-Abu, Nle, Nva, or hydrophobic amino acid residue;

X_{aa}^{7} is a Gly, Ala, aromatic, or hydrophobic amino acid residue;

X_{aa}^{8} is a basic, acidic, or neutral hydrophilic amino acid residue, or an Ala residue;

X_{aa}^{9} is a basic or neutral hydrophilic amino acid residue;

X_{aa}^{10} is Cys if X_{aa}^{24} is Cys; or X_{aa}^{10} is SeCys if X_{aa}^{24} is SeCys;

X_{aa}^{11} is any amino acid residue;

X_{aa}^{12} is a Pro, acidic, neutral, or hydrophobic amino acid residue;

X_{aa}^{13} is any amino acid residue;

X_{aa}^{14} is any amino acid residue;

X_{aa}^{16} is a basic, neutral hydrophilic, or acidic amino acid residue, or an Ala residue;

X_{aa}^{17} is a Cys if X_{aa}^{31} is Cys; or X_{aa}^{17} is a SeCys if X_{aa}^{31} is SeCys;

X_{aa}^{18} is a Cys, SeCys, or an alkyl amino acid residue;

X_{aa}^{19} is any amino acid residue;

X_{aa}^{20} is a Pro, Gly, basic, or neutral hydrophilic residue;

X_{aa}^{21} is a basic, hydrophobic, or neutral hydrophilic amino acid residue;

X_{aa}^{22} is a hydrophobic or basic amino acid residue;

X_{aa}^{23} is a hydrophobic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{24} is a Cys or SeCys residue;

X_{aa}^{25} is a Ser, Ala, or a neutral hydrophilic amino acid residue;

X_{aa}^{26} is an Ala, acidic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{27} is an acidic, basic, neutral hydrophilic or hydrophobic residue;

X_{aa}^{28} is an aromatic or basic amino acid residue;

X_{aa}^{29} is an acidic, basic, or neutral hydrophilic amino acid residue;

X_{aa}^{30} is a Trp, 5-bromoTrp, 6-bromoTrp, 5-chloroTrp, 6-chloroTrp, 1-Nal, 2-Nal, or thioTrp residue;

X_{aa}^{31} is a Cys or SeCys;

X_{aa}^{33} is a hydrophobic or aromatic amino acid residue;

X_{aa}^{34} is any amino acid residue;

X_{aa}^{35} is a hydrophobic amino acid residue;

each of X_{aa}^{36} , X_{aa}^{37} , and X_{aa}^{38} is independently absent or is independently a neutral, basic, or hydrophobic amino acid residue;

and wherein:

if X_{aa}^{3} and X_{aa}^{18} are both Cys residues, there is a disulfide bond between residue X_{aa}^{3} and residue X_{aa}^{18}; or if X_{aa}^{3} and X_{aa}^{18} are both SeCys residues, there is a diselenide bond between residue X_{aa}^{3} and residue X_{aa}^{18};

if X_{aa}^{10} and X_{aa}^{24} are both Cys residues, there is a disulfide bond between residue X_{aa}^{10} and residue X_{aa}^{24}; or if X_{aa}^{10} and X_{aa}^{24} are both SeCys residues, there is a diselenide bond between residue X_{aa}^{10} and residue X_{aa}^{24};

if X_{aa}^{17} and X_{aa}^{31} are both Cys residues, there is a disulfide bond between residue X_{aa}^{17} and residue X_{aa}^{31}; or if X_{aa}^{17} and X_{aa}^{31} are both SeCys residues, there is a diselenide bond between residue X_{aa}^{17} and residue X_{aa}^{31};

the amino-terminal residue is optionally acetylated, biotinylated, or 4-pentynoylated, or PEGylated; and

the carboxy-terminal residue is optionally amidated.

2. The composition of matter of Claim 1 wherein X_{aa}^{4} is selected from Ala, Glu, Asp, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Cit residues.

3. The composition of matter of Claim 1, wherein X_{aa}^5 is selected from Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

4. The composition of matter of Claim 1, wherein X_{aa}^6 is selected from Ala, Gly, 2-Abu, Phe, Ile, Leu, Met, Val, Trp, Tyr, proline, thiaproline, methionine, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclopentylglycine (Cpg), phenylglycine, N-methylleucine, N-methylphenylalanine, N-methylvaline, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

5. The composition of matter of Claim 1, wherein X_{aa}^7 is selected from Gly, Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, norleucine, norvaline, Pro, 2-pyridinylalanine, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

6. The composition of matter of Claim 1, wherein X_{aa}^8 is selected from Ala, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Ser, Thr, Asn, Gln, Cit, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Glu residues.

7. The composition of matter of Claim 1, wherein X_{aa}^9 is selected from Ala, Pro, Met, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, and Cit residues.

8. The composition of matter of Claim 1, wherein X_{aa}^{11} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz,

homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

9. The composition of matter of Claim 1, wherein X_{aa}^{12} is selected from alanine, valine, leucine, isoleucine, proline, serine, threonine, aspartic acid, glutamatic acid, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, Cha, and 4-phenyl-phenylalanine (Bip), cyclohexylglycine (Chg), cyclohexylalanine (Cha), asparagine, glutamine, methionine, hydroxyproline, phenylalanine, tryptophan, and tyrosine.

10. The composition of matter of Claim 1, wherein X_{aa}^{13} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

11. The composition of matter of Claim 1, wherein X_{aa}^{14} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

12. The composition of matter of Claim 1, wherein X_{aa}^{16} is selected from Ala, Pro, Met, Arg, Lys, His, Pra, Atz, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, Cit, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Glu residues.

13. The composition of matter of Claim 1, wherein X_{aa}^{19} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, homolysine,

ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

14. The composition of matter of Claim 1, wherein X_{aa}^{20} is selected from Ala, Gly, Pro, Met, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Gln, Asn, Ser, Thr, and Cit residues.

15. The composition of matter of Claim 1, wherein X_{aa}^{21} is selected from Ala, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, and Cit residues.

16. The composition of matter of Claim 1, wherein X_{aa}^{22} is selected from Ala, Phe, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

17. The composition of matter of Claim 1, wherein X_{aa}^{23} is selected from Ala, Phe, Pro, Ile, Leu, Met, Val, Trp, Tyr, Arg, Lys, His, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, cyclohexylglycine (Chg), cyclohexylalanine (Cha), glycine, norleucine, norvaline, 1-Nal, 2-Nal, 4-phenyl-phenylalanine (Bip), Gln, Asn, Ser, Thr, and Cit residues.

18. The composition of matter of Claim 1, wherein X_{aa}^{25} is selected from Ala, Gly Pro, Met, Gln, Asn, Ser, Thr, and Cit residues.

19. The composition of matter of Claim 1, wherein X_{aa}^{26} is selected from Ala, Pro, Met, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, glycine, Glu, Asp, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, Gln, Asn, Ser, Thr, and Cit residues.

20. The composition of matter of Claim 1, wherein X_{aa}^{27} is selected from Thr, Leu, Ile, Val, Ser, Met, Gln, Asn, Phe, Tyr, Trp, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 4-phenyl-phenylalanine (Bip), Arg, Lys, His, homolysine, ornithine, arginine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, and Gly residues.

21. The composition of matter of Claim 1, wherein X_{aa}^{28} is selected from Phe, Trp, Tyr, Arg, Lys, His, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, 1-Nal, 2-Nal, 2-pyridyl-alanine, 3-pyridyl-alanine, 4-pyridyl-alanine, 4-piperidinyl-alanine, and 4-phenyl-phenylalanine (Bip) residues.

22. The composition of matter of Claim 1, wherein X_{aa}^{29} is selected from Ala, Asp, Glu, phosphoserine, phosphotyrosine, gamma-carboxyglutamic acid, Phe, Gly, His, Lys, Asn, Pro, Gln, Arg, Ser, Thr, Tyr, Pra, Atz, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, and Dab residues.

23. The composition of matter of Claim 1, wherein X_{aa}^{33} is selected from Phe, Ile, Leu, Met, Val, Trp, Tyr, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, 2-pyridyl-alanine, 3-pyridyl-alanine, 4-pyridyl-alanine, 4-piperidinyl-alanine, and 4-phenyl-phenylalanine (Bip) residues.

24. The composition of matter of Claim 1, wherein X_{aa}^{34} is selected from Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, Pra, Atz,

homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, 2-pyridyl-alanine, 3-pyridyl-alanine, 4-carboxy-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

25. The composition of matter of Claim 1, wherein X_{aa}^{35} is selected from Phe, Ile, Leu, Met, Val, Trp, Tyr, norleucine, norvaline, 1-Nal, 2-Nal, 1'NMe-Trp, cyclohexylglycine (Chg), cyclohexylalanine (Cha), 2-chloro-phenylalanine, 4-chloro-phenylalanine, 3,4-dichlorophenylalanine, 4-trifluoromethyl-phenylalanine, and 4-phenyl-phenylalanine (Bip) residues.

26. The composition of matter of Claim 1, wherein each of X_{aa}^{36}, X_{aa}^{37}, and X_{aa}^{38} is independently absent or is independently selected from Ala, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr, homolysine, ornithine, N-methyl-arginine, ω-aminoarginine, ω-methyl-arginine, 1-methyl-histidine, 3-methyl-histidine, homoarginine, N-methyl-lysine, N-ε-methyl lysine, Dab, norleucine, norvaline, 1-Nal, 2-Nal, cyclohexylglycine (Chg), cyclohexylalanine (Cha), and 4-phenyl-phenylalanine (Bip) residues.

27. The composition of matter of Claim 1, wherein X_{aa}^{3} and X_{aa}^{18} are alkyl residues.

28. The composition of matter of Claim 27, wherein X_{aa}^{3} and X_{aa}^{18} are, independently, Ala or 2-Abu residues.

29. The composition of matter of Claim 1, wherein the carboxy-terminal residue is amidated.

30. The composition of matter of Claim 1, wherein the isolated polypeptide comprises the amino acid sequence of the formula:

$X_{aa}^{1}X_{aa}^{2}$ $Cys^{3}X_{aa}^{4}$ $X_{aa}^{5}Ala^{6}$ $X_{aa}^{7}X_{aa}^{8}X_{aa}^{9}Cys^{10}X_{aa}^{11}X_{aa}^{12}X_{aa}^{13}X_{aa}^{14}Asp^{15}$ X_{aa}^{16}
$Cys^{17}Cys^{18}X_{aa}^{19}$ X_{aa}^{20} $X_{aa}^{21}X_{aa}^{22}X_{aa}^{23}$ $Cys^{24}X_{aa}^{25}$ $X_{aa}^{26}X_{aa}^{27}X_{aa}^{28}X_{aa}^{29}X_{aa}^{30}$
$Cys^{31}Lys^{32}X_{aa}^{33}X_{aa}^{34}X_{aa}^{35}$ $X_{aa}^{36}X_{aa}^{37}X_{aa}^{38}$// SEQ ID NO:476.

31. The composition of matter of Claim 1, wherein X_{aa}^{6} is Ala.

32. The composition of matter of Claim 31, wherein X_{aa}^{27} is Glu.

33. The composition of matter of Claim 31, wherein X_{aa}^{29} is Asp, Glu, or Gln.

34. The composition of matter of Claim 31, comprising an amino acid sequence selected from SEQ ID NOS: 22, 252-263, 419-439, 518-521, 524, 525, 562-580, 602, 691, 692, 696-703, 715, 721-735, 737-749, 756, 757, 761, 762, 764-771, 787-796, 798, 800, 802, 803, 809-812, 1028, 1030-1040, 1043-1047, 1062-1065, and 1068-1070.

35. The composition of matter of Claim 31, comprising an amino acid sequence selected from SEQ ID NOS: 1082, 1096, 1110, 1124, 1135, 1146, 1157, 1165, 1173, 1181, 1192, 1203, 1214, 1222, 1230, 1238, 1249, 1260, 1271, 1279, 1287, 1295, 1306, 1317, 1328, 1336, 1344, 1352, 1360, 1368, 1376, 1384, 1392, 1400, 1408, 1416, 1424, 1432, 1440, 1448, 1456, 1464, 1472, 1480, 1488, 1496, 1504, 1512, 1520, 1528, 1536, 1544, 1552, 1560, 1568, 1576, 1584, 1592, 1600, 1608, 1616, 1624, 1632, 1640, 1658, 1672, 1686, 1700, 1711, 1722, 1733, 1741, 1749, 1757, 1768, 1779, 1790, 1798, 1806, 1814, 1825, 1836, 1847, 1855, 1863, 1871, 1882, 1893, 1904, 1912, 1920, 1928, 1936, 1944, 1952, 1960, 1968, 1976, 1984, 1992, 2000, 2008, 2016, 2024, 2032, 2040, 2048, 2056, 2064, 2072, 2080, 2088, 2096, 2104, 2112, 2120, 2128, 2136, 2144, 2152, 2160, 2168, 2176, 2184, 2192, 2200, 2208, 2216, 2234, 2248, 2262, 2276, 2287, 2298, 2309, 2317, 2325, 2333, 2344, 2355, 2366, 2374, 2382, 2390, 2401, 2412, 2423, 2431, 2439, 2447, 2458, 2469, 2480, 2488, 2496, 2504, 2512, 2520, 2528, 2536, 2544, 2552, 2560, 2568, 2576, 2584, 2592, 2600, 2608, 2616, 2624, 2632, 2640, 2648, 2656, 2664, 2672, 2680, 2688, 2696, 2704, 2712, 2720, 2728, 2736, 2744, 2752, 2760, 2768, 2776, 2784, 2792, 2808, 2822, 2833, 2844, 2855, 2863, 2871, 2879, 2890, 2901, 2912, 2920, 2928, 2936, 2944, 2952, 2960, 2968, 2976, 2984, 2992, 3000, 3008, 3016, 3024, 3032, 3040, 3048, 3056, 3064, 3072, and 3080.

36. The composition of matter of Claim 31, comprising an amino acid sequence selected from SEQ ID NOS: 597-601 and 813-1027.

37. The composition of matter of Claim 1, wherein X_{aa}^{6} is Gly.

38. The composition of matter of Claim 37, wherein X_{aa}^{27} is Glu.

39. The composition of matter of Claim 37, wherein X_{aa}^{29} is Asp, Glu, or Gln.

40. The composition of matter of Claim 37, comprising an amino acid sequence selected from SEQ ID NOS: 265, 751, 752, 754, 755, 1081, 1095, 1109, 1123, 1134, 1145, 1156, 1164, 1172, 1180, 1191, 1202, 1213, 1221, 1229, 1237, 1248, 1259, 1270, 1278, 1286, 1294, 1305, 1316, 1327, 1335, 1343, 1351, 1359, 1367, 1375, 1383, 1391, 1399, 1407, 1415, 1423, 1431, 1439, 1447, 1455, 1463, 1471, 1479, 1487, 1495, 1503, 1511, 1519, 1527, 1535, 1543, 1551, 1559, 1567, 1575, 1583, 1591, 1599, 1607, 1615, 1623, 1631, 1639, 1657, 1671, 1685, 1699, 1710, 1721, 1732, 1740, 1748, 1756, 1767, 1778, 1789, 1797, 1805, 1813, 1824, 1835, 1846, 1854, 1862, 1870, 1881, 1892, 1903, 1911, 1919, 1927, 1935, 1943, 1951, 1959, 1967, 1975, 1983, 1991, 1999, 2007, 2015, 2023, 2031, 2039, 2047, 2055, 2063, 2071, 2079, 2087, 2095, 2103, 2111, 2119, 2127, 2135, 2143, 2151, 2159, 2167, 2175, 2183, 2191, 2199, 2207, 2215, 2233, 2247, 2261, 2275, 2286, 2297, 2308, 2316, 2324, 2332, 2343, 2354, 2365, 2373, 2381, 2389, 2400, 2411, 2422, 2430, 2438, 2446, 2457, 2468, 2479, 2487, 2495, 2503, 2511, 2519, 2527, 2535, 2543, 2551, 2559, 2567, 2575, 2583, 2591, 2599, 2607, 2615, 2623, 2631, 2639, 2647, 2655, 2663, 2671, 2679, 2687, 2695, 2703, 2711, 2719, 2727, 2735, 2743, 2751, 2759, 2767, 2775, 2783, 2791, 2807, 2821, 2832, 2843, 2854, 2862, 2870, 2878, 2889, 2900, 2911, 2919, 2927, 2935, 2943, 2951, 2959, 2967, 2975, 2983, 2991, 2999, 3007, 3015, 3023, 3031, 3039, 3047, 3055, 3063, 3071, and 3079.

41. The composition of matter of Claim 1, wherein X_{aa}^{6} is 2-Abu.

42. The composition of matter of Claim 41, wherein X_{aa}^{27} is Glu.

43. The composition of matter of Claim 41, wherein X_{aa}^{29} is Asp, Glu, or Gln.

44. The composition of matter of Claim 41, comprising an amino acid sequence selected from SEQ ID NOS: 605, 636, 649, 706, 707, 718, 753, 758, 797, 799, 801, 804, 807, 808, 1029, 1041, 1042, 1048, 1066, 1067, 1083, 1097, 1111, 1125, 1136, 1147, 1158, 1166, 1174, 1182, 1193, 1204, 1215, 1223, 1231, 1239, 1250, 1261, 1272, 1280, 1288, 1296, 1307, 1318, 1329, 1337, 1345, 1353, 1361, 1369, 1377, 1385, 1393, 1401, 1409, 1417, 1425, 1433,

1441, 1449, 1457, 1465, 1473, 1481, 1489, 1497, 1505, 1513, 1521, 1529, 1537, 1545, 1553, 1561, 1569, 1577, 1585, 1593, 1601, 1609, 1617, 1625, 1633, 1641, 1659, 1673, 1687, 1701, 1712, 1723, 1734, 1742, 1750, 1758, 1769, 1780, 1791, 1799, 1807, 1815, 1826, 1837, 1848, 1856, 1864, 1872, 1883, 1894, 1905, 1913, 1921, 1929, 1937, 1945, 1953, 1961, 1969, 1977, 1985, 1993, 2001, 2009, 2017, 2025, 2033, 2041, 2049, 2057, 2065, 2073, 2081, 2089, 2097, 2105, 2113, 2121, 2129, 2137, 2145, 2153, 2161, 2169, 2177, 2185, 2193, 2201, 2209, 2217, 2235, 2249, 2263, 2277, 2288, 2299, 2310, 2318, 2326, 2334, 2345, 2356, 2367, 2375, 2383, 2391, 2402, 2413, 2424, 2432, 2440, 2448, 2459, 2470, 2481, 2489, 2497, 2505, 2513, 2521, 2529, 2537, 2545, 2553, 2561, 2569, 2577, 2585, 2593, 2601, 2609, 2617, 2625, 2633, 2641, 2649, 2657, 2665, 2673, 2681, 2689, 2697, 2705, 2713, 2721, 2729, 2737, 2745, 2753, 2761, 2769, 2777, 2785, 2793, 2809, 2823, 2834, 2845, 2856, 2864, 2872, 2880, 2891, 2902, 2913, 2921, 2929, 2937, 2945, 2953, 2961, 2969, 2977, 2985, 2993, 3001, 3009, 3017, 3025, 3033, 3041, 3049, 3057, 3065, 3073, and 3081.

45. The composition of matter of Claim 1, wherein X_{aa}^{6} is Nle.

46. The composition of matter of Claim 45, wherein X_{aa}^{27} is Glu.

47. The composition of matter of Claim 45, wherein X_{aa}^{29} is Asp, Glu, or Gln.

48. The composition of matter of Claim 45, comprising an amino acid sequence selected from SEQ ID NOS: 607, 638, 651, 1085, 1099, 1113, 1127, 1138, 1149, 1160, 1168, 1176, 1184, 1195, 1206, 1217, 1225, 1233, 1241, 1252, 1263, 1274, 1282, 1290, 1298, 1309, 1320, 1331, 1339, 1347, 1355, 1363, 1371, 1379, 1387, 1395, 1403, 1411, 1419, 1427, 1435, 1443, 1451, 1459, 1467, 1475, 1483, 1491, 1499, 1507, 1515, 1523, 1531, 1539, 1547, 1555, 1563, 1571, 1579, 1587, 1595, 1603, 1611, 1619, 1627, 1635, 1643, 1661, 1675, 1689, 1703, 1714, 1725, 1736, 1744, 1752, 1760, 1771, 1782, 1793, 1801, 1809, 1817, 1828, 1839, 1850, 1858, 1866, 1874, 1885, 1896, 1907, 1915, 1923, 1931, 1939, 1947, 1955, 1963, 1971, 1979, 1987, 1995, 2003, 2011, 2019, 2027, 2035, 2043, 2051, 2059, 2067, 2075, 2083, 2091, 2099, 2107, 2115, 2123, 2131, 2139, 2147, 2155, 2163, 2171, 2179, 2187, 2195, 2203, 2211, 2219, 2237, 2251, 2265, 2279, 2290, 2301, 2312, 2320, 2328, 2336, 2347, 2358, 2369, 2377, 2385, 2393, 2404, 2415, 2426, 2434, 2442, 2450, 2461, 2472, 2483, 2491, 2499, 2507, 2515, 2523, 2531, 2539, 2547, 2555, 2563, 2571, 2579, 2587, 2595, 2603, 2611, 2619, 2627, 2635, 2643, 2651, 2659, 2667, 2675, 2683, 2691, 2699, 2707, 2715, 2723, 2731, 2739, 2747, 2755, 2763,

2771, 2779, 2787, 2795, 2811, 2825, 2836, 2847, 2858, 2866, 2874, 2882, 2893, 2904, 2915, 2923, 2931, 2939, 2947, 2955, 2963, 2971, 2979, 2987, 2995, 3003, 3011, 3019, 3027, 3035, 3043, 3051, 3059, 3067, 3075, and 3083.

49. The composition of matter of Claim 1, wherein X_{aa}^{6} is Nva.

50. The composition of matter of Claim 49, wherein X_{aa}^{27} is Glu.

51. The composition of matter of Claim 49, wherein X_{aa}^{29} is Asp, Glu, or Gln.

52. The composition of matter of Claim 49, comprising an amino acid sequence selected from SEQ ID NOS: 606, 637, 650, 705, 708, 717, 759, 760, 805, 806, 1084, 1098, 1112, 1126, 1137, 1148, 1159, 1167, 1175, 1183, 1194, 1205, 1216, 1224, 1232, 1240, 1251, 1262, 1273, 1281, 1289, 1297, 1308, 1319, 1330, 1338, 1346, 1354, 1362, 1370, 1378, 1386, 1394, 1402, 1410, 1418, 1426, 1434, 1442, 1450, 1458, 1466, 1474, 1482, 1490, 1498, 1506, 1514, 1522, 1530, 1538, 1546, 1554, 1562, 1570, 1578, 1586, 1594, 1602, 1610, 1618, 1626, 1634, 1642, 1660, 1674, 1688, 1702, 1713, 1724, 1735, 1743, 1751, 1759, 1770, 1781, 1792, 1800, 1808, 1816, 1827, 1838, 1849, 1857, 1865, 1873, 1884, 1895, 1906, 1914, 1922, 1930, 1938, 1946, 1954, 1962, 1970, 1978, 1986, 1994, 2002, 2010, 2018, 2026, 2034, 2042, 2050, 2058, 2066, 2074, 2082, 2090, 2098, 2106, 2114, 2122, 2130, 2138, 2146, 2154, 2162, 2170, 2178, 2186, 2194, 2202, 2210, 2218, 2236, 2250, 2264, 2278, 2289, 2300, 2311, 2319, 2327, 2335, 2346, 2357, 2368, 2376, 2384, 2392, 2403, 2414, 2425, 2433, 2441, 2449, 2460, 2471, 2482, 2490, 2498, 2506, 2514, 2522, 2530, 2538, 2546, 2554, 2562, 2570, 2578, 2586, 2594, 2602, 2610, 2618, 2626, 2634, 2642, 2650, 2658, 2666, 2674, 2682, 2690, 2698, 2706, 2714, 2722, 2730, 2738, 2746, 2754, 2762, 2770, 2778, 2786, 2794, 2810, 2824, 2835, 2846, 2857, 2865, 2873, 2881, 2892, 2903, 2914, 2922, 2930, 2938, 2946, 2954, 2962, 2970, 2978, 2986, 2994, 3002, 3010, 3018, 3026, 3034, 3042, 3050, 3058, 3066, 3074, and 3082.

53. The composition of matter of Claim 1, comprising an amino acid sequence selected from SEQ ID NOS: 3-30, 32-72, 74-134, 136-178, 180-211, 218-239, 241-305, 307-363, 366-386, 388-432, 434-474, 515-527, 532-588, 590, 591, 593-775, 777, 778, 780-788, 790-1049, and 1062-3086.

54. A composition of matter, comprising an amino acid sequence selected from SEQ ID NOS: 3-134, 136-305, 307-386, 388-474, 515-527, 532-588, 590, 591, 593-1049, and 1062-3086.

55. An isolated nucleic acid encoding any of SEQ ID NOS: 3-134, 136-305, 307-386, 388-474, 515-527, 532-588, 590, 591, 593-1049, or 1062-3086 that does not include a non-canonical amino acid.

56. An expression vector comprising the nucleic acid of Claim 55.

57. A recombinant host cell comprising the expression vector of Claim 56.

58. The composition of matter of any of Claims 1, 30, 31, 37, 41, 45, 49, 53, or 54, further comprising an optional linker moiety and a pharmaceutically acceptable, covalently linked half-life extending moiety.

59. The composition of matter of Claim 58, wherein the half-life extending moiety is polyethylene glycol of molecular weight of about 1000 Da to about 100000 Da, an IgG Fc domain, a transthyretin, or a human serum albumin.

60. The composition of matter of Claim 58, wherein the half-life extending moiety comprises a human immunoglobulin or a human immunoglobulin Fc domain, or both.

61. The composition of matter of Claim 60 having a configuration as set forth in any of Figures 12A-N, or Figures 88-91.

62. The composition of matter of Claim 60, wherein the composition comprises a monovalent immunoglobulin-peptide or Fc-peptide conjugate.

63. The composition of matter of Claim 60, wherein the composition comprises a bivalent immunoglobulin-peptide or Fc-peptide conjugate.

64. A pharmaceutical composition, comprising the composition of matter of any of Claims 1, 30, 31, 37, 41, 45, 49, 53, 54, or 59-63, and a pharmaceutically acceptable carrier.

65. Use of a prophylactically effective amount of the composition of matter of any of Claims 1, 30, 31, 37, 41, 45, 49, 53, 54, or 59-63 in the manufacture of a medicament for preventing pain.

66. Use of a therapeutically effective amount of the composition of matter of any of Claims 1, 30, 31, 37, 41, 45, 49, 53, 54, or 59-63 in the manufacture of a medicament for treating pain.

67. The use of Claim 66, wherein the pain is chronic pain, acute pain, or persistent pain.

68. The use of Claim 67, wherein the chronic pain is associated with cancer, chemotherapy, osteoarthritis, fibromyalgia, primary erythromelalgia, post-herpetic neuralgia, painful diabetic neuropathy, idiopathic painful neuropathy, neuromas, paroxysmal extreme pain disorder, migraine, trigeminal neuralgia, orofacial pain, cluster headaches, complex regional pain syndrome (CRPS), failed back surgery syndrome, sciatica, interstitial cystitis, pelvic pain, lower back pain, inflammation-induced pain, or joint pain.

69. The use of Claim 67, wherein the acute or persistent pain is associated with trauma, burn, or surgery.

70. The composition of matter of Claim 1 or 30, wherein X_{aa}^{29} is an acidic or neutral hydrophilic residue.

71. The composition of matter of Claim 70, wherein X_{aa}^{29} is selected from Ala, Asp, Glu, Gly, Asn, Gln, Ser, Thr, phosphoserine, phosphotyrosine, and gamma-carboxyglutamic acid residues.

72. The composition of matter of Claim 70, comprising an amino acid sequence selected from SEQ ID NOS: 1071-2798.