CLAIMS

What is claimed is:

1. A method of treating a neurocutaneous syndrome in a subject, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising:

(a) a polypeptide comprising the structure A-sALP-B; and

(b) a pharmaceutically acceptable excipient,

wherein sALP is the extracellular domain of an alkaline phosphatase,

A is absent or is an amino acid sequence of at least one amino acid, and

B is absent or is an amino acid sequence of at least one amino acid,

thereby treating said syndrome in said subject.

2. The method of claim 1, wherein the amino acid sequence of said polypeptide comprises the amino acid sequence of SEQ ID NOs: 1204 or 1221.

3. The method of claim 1, wherein

the amino acid sequence of said sALP comprises amino acid residues 23-508 of SEQ ID NO: 1215, amino acid residues 18-498 of SEQ ID NO: 1216, amino acid residues 23-508 of SEQ ID NO: 1218, or amino acid residues 18-498 of SEQ ID NO: 1219, or

the amino acid sequence of said sALP consists of amino acid residues 23-512 of SEQ ID NO: 1215, amino acid residues 18-502 of SEQ ID NO: 1216, amino acid residues 23-512 of SEQ ID NO: 1218, or amino acid residues 18-502 of SEQ ID NO: 1219.

4. The method of claim 1 or 3, wherein the amino acid sequence of said sALP comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 1205, or at least 95% sequence identity to SEQ ID NO: 1205, or at least 99% sequence identity to SEQ ID NO: 1205.

5. The method of claim 4, wherein the amino acid sequence of said sALP comprises or consists of the amino acid sequence of SEQ ID NO: 1205.

6. The method of any one of claims 1-5, wherein A and/or B are absent.

7. The method of any one of claims 1-6, wherein A or B comprises a fragment crystallizable region (Fc).

8. The method of any one of claims 1-7, wherein said Fc comprises a C_{H2} domain, a C_{H3} domain, and a hinge region, or wherein said Fc is a constant domain of an immunoglobulin selected from the group consisting of IgG-1, IgG-2, IgG-3, and IgG-4.

9. The method of claim 8, wherein the amino acid sequence of said Fc comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 401, or at least 95% sequence identity to SEQ ID NO: 401, or at least 99% sequence identity to SEQ ID NO: 401.

10. The method of claim 9, wherein the amino acid sequence of said Fc comprises or consists of the amino acid sequence of SEQ ID NO: 401.

11. The method of any one of claims 1-10, wherein A or B comprises I_n, and wherein I represents an aspartic acid or a glutamic acid and n=10 to 16.

12. The method of any one of claims 1-10, wherein said polypeptide does not comprise a polyaspartic acid or polyglutamic acid region longer than three consecutive aspartic acid or glutamic acid residues, or wherein said polypeptide does not comprise a polyaspartic acid or polyglutamic acid region longer than two consecutive aspartic acid or glutamic acid residues.

13. The method of any one of claims 1-10, wherein said polypeptide does not comprise a bone-targeting moiety.

14. The method of any one of claims 1-10, wherein said polypeptide comprises the structure C-sALP-D-Fc-E or the structure C-Fc-D-sALP-E,

C is absent or is an amino acid sequence of at least one amino acid,

D is absent or is an amino acid sequence of at least one amino acid, and

E is absent or is an amino acid sequence of at least one amino acid.

15. The method of claim 14, wherein C and/or E are absent.

16. The method of any one of claims 1-10, wherein said polypeptide comprises the structure C-sALP-D-Fc-G-I_n-H or the structure C-Fc-D-sALP-G-I_n-H,

C is absent or is an amino acid sequence of at least one amino acid,

D is absent or is an amino acid sequence of at least one amino acid,

G is absent or is an amino acid sequence of at least one amino acid,

H is absent or is an amino acid sequence of at least one amino acid,

I represents an aspartic acid or a glutamic acid, and n=10 to 16.

17. The method of claim 16, wherein C and/or H are absent.

18. The method of claim 16 or 17, wherein G is two amino acid residues.

19. The method of claim 18, wherein G is aspartic acid-isoleucine.

20. The method of any one of claims 16-19, wherein I is aspartic acid and n=10.

21. The method of any one of claims 14-20, wherein D is two amino acid residues.

22. The method of claim 21, wherein D is leucine-lysine.

23. The method of any one of claims 1-22, wherein the amino acid sequence of said polypeptide consists of the amino acid sequence of SEQ ID NOs: 1201, 1204, 1220, or 1221.

24. The method of claim 23, wherein the amino acid sequence of said polypeptide consists of the amino acid sequence of SEQ ID NO: 1204.

25. A method of treating a neurocutaneous syndrome in a subject, said method comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition comprising:

(a) a polypeptide comprising the structure V-NP-W; and

(b) a pharmaceutically acceptable excipient,

wherein NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

V is absent or is an amino acid sequence of at least one amino acid, and

W is absent or is an amino acid sequence of at least one amino acid,

thereby treating said syndrome in said subject.

26. The method of claim 25, wherein the amino acid sequence of said polypeptide comprises the amino acid sequence of SEQ ID NOs: 504, 512, 530, or 572.

27. The method of claim 25, wherein said NP comprises the structure:

[N-terminal extension]-[short segment]-[ring domain]-[C-terminal extension],

wherein said ring domain comprises the amino acid sequence of SEQ ID NO: 6, amino acid residues 11-27 of SEQ ID NO: 30, or SEQ ID NO: 95, and each of said N-terminal extension, short segment, and C-terminal extension is, independently, absent or is an amino acid sequence of at least one amino acid.

28. The method of claim 27, wherein said ring domain comprises amino acid residues 6-22 of SEQ ID NO: 126.

29. The method of claim 28, wherein the amino acid at position 17 of SEQ ID NO: 126 is Phe, Leu, Ile, Thr, Val, Ala, Ser, Glu, Arg, Tyr, Cys, Pro, or Asp.

30. The method of claim 27, wherein said ring domain comprises the amino acid sequence of SEQ ID NO: 12.

31. The method of any one of claims 27-30, wherein said short segment and said ring domain together comprise the amino acid sequence of any one of SEQ ID NOs: 4, 13-30, 119-122, 126, or 156-161.

32. The method of any one of claims 27-31, wherein the amino acid sequence of said short segment consists of amino acid residues 1-5, 2-5, 3-5, 4-5, or 5 of SEQ ID NO: 4, amino acid residues 1-10 of SEQ ID NO: 17, amino acid residues 1-5 of SEQ ID NO: 19, amino acid residues 1-3 of SEQ ID NO: 20, amino acid residues 1-5 of SEQ ID NO: 21, or amino acid residues 1-6 of SEQ ID NO: 29.

33. The method of any one of claims 27-32, wherein the amino acid sequence of said N-terminal extension comprises amino acid residues 1-31 or 17-31 of SEQ ID NO: 11.

34. The method of any one of claims 27-32, wherein the amino acid sequence of said N-terminal extension comprises KGANKK (SEQ ID NO: 314) or KGANQK (SEQ ID NO: 315).

35. The method of claim 27, wherein said N-terminal extension, short segment, and ring domain together comprise the amino acid sequence of SEQ ID NO: 11.

36. The method of any one of claims 27-35, wherein said C-terminal extension comprises the amino acid sequence of SEQ ID NOs: 117 or 118 or comprises amino acid residues 23-37 selected from any one of SEQ ID NOs: 101-116.

37. The method of claim 27, wherein the amino acid sequence of said NP consists of SEQ ID NOs: 4 or 11, or the amino acid sequence of any one of SEQ ID NOs: 31-94, or a fragment thereof comprising at least a ring domain, or the amino acid sequence of any one of SEQ ID NOs: 13-29, 100-116, 119-125, 127-233, or 1001-1155.

38. The method of any one of claims 27-37, wherein V and/or W are absent.

39. The method of any one of claims 27-38, wherein V or W comprises a fragment crystallizable region (Fc).

40. The method of claim 39, wherein said Fc comprises a C_{H2} domain, a C_{H3} domain, and a hinge region, or wherein said Fc is a constant domain of an immunoglobulin selected from the group consisting of IgG-1, IgG-2, IgG-3, and IgG-4.

41. The method of claim 40, wherein the amino acid sequence of said Fc comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 401, or at least 95% sequence identity to SEQ ID NO: 401, or at least 99% sequence identity to SEQ ID NO: 401.

42. The method of claim 41, wherein the amino acid sequence of said Fc comprises or consists of the amino acid sequence of SEQ ID NO: 401.

43. The method of any one of claims 27-42, wherein V or W comprises a glycine-rich region.

44. The method of claim 43, wherein the amino acid sequence of V or W consists of one or more glycines and one or more serines.

45. The method of claim 43 or 44, wherein the amino acid sequence of V or W comprises $[(Gly)_m(Ser)]_n(Gly)_p$ or $(Gly)_p[(Ser)(Gly)_m]_n$, and wherein each of m, n, and p is, independently, between 0 and 20.

46. The method of claim 45, wherein m is between 1 and 6; n is between 1 and 10; and p is between 0 and 4.

47. The method of claim 46, wherein m is 4 and n is 1-6.

48. The method of claim 46, wherein combinations of m, n, and p are selected from a single row of Table 2, or wherein the amino acid sequence of V or W comprises the amino acid sequence of any one of SEQ ID NOs: 301-391.

49. The method of any one of claims 27-48, wherein V or W does not comprise a bone-targeting moiety.

50. The method of any one of claims 27-48, wherein V or W comprises a bone-targeting moiety.

51. The method of claim 50, wherein said bone-targeting moiety comprises six consecutive acidic residues.

52. The method of claim 51, wherein said bone-targeting moiety comprises ten consecutive acidic residues.

53. The method of claim 51 or 52, wherein said acidic residues are aspartic acid or glutamic acid.

54. The method of claim 53, wherein said bone-targeting moiety comprises E_6, E_{10}, D_6, or D_{10}.

55. The method of any one of claims 27-54, wherein V or W comprises a cathepsin cleavage sequence.

56. The method of claim 55, wherein said cathepsin cleavage sequence comprises a cathepsin K cleavage sequence.

57. The method of claim 55 or 56, wherein said cathepsin cleavage sequence is HGPQG (SEQ ID NO: 374) or HKLRG (SEQ ID NO: 375).

58. The method of any one of claims 27-57, wherein said polypeptide comprises the structure V-NP-W,

NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

each of V and W is, independently, absent or is an amino acid sequence of at least one amino acid, and

said NP comprises the amino acid sequence of any one of SEQ ID NOs: 17-29, 31-40, 42-94, 101-116, 119-122, 128-161, or 163-233, or V or W comprises the amino acid sequence of any one of SEQ ID NOs: 304-313, 322-333, or 337-391.

59. The method of any one of claims 27-57, wherein said polypeptide comprises the structure V-NP or NP-W,

NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B), and

each of V and W comprises, independently, the amino acid sequence of any one of SEQ ID NOs: 304-313, 322-333, or 337-391.

60. The method of any one of claims 27-57, wherein said polypeptide comprises the structure X-Fc-Y-NP-Z or the structure X-NP-Y-Fc-Z,

NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B), and

each of X, Y, and Z is, independently, absent or is an amino acid sequence of at least one amino acid.

61. The method of claim 60, wherein Y comprises a glycine-rich region.

62. The method of claim 61, wherein the amino acid sequence of Y consists of one or more glycines and one or more serines.

63. The method of claim 62, wherein the amino acid sequence of Y comprises $[(Gly)_m(Ser)]_n(Gly)_p$ or $(Gly)_p[(Ser)(Gly)_m]_n$, and wherein each of m, n, and p is, independently, between 0 and 20.

64. The method of any one of claims 60-63, wherein X is absent, Z is absent, or X and Z are both absent.

65. The method of any one of claims 60-64, wherein X, Y, or Z comprises a bone-targeting moiety.

66. The method of claim 65, wherein said bone-targeting moiety comprises six or ten consecutive acidic residues.

67. The method of claim 66, wherein said acidic residues are aspartic acid or glutamic acid.

68. The method of any one of claims 65-67, wherein said bone-targeting moiety comprises E_6, E_{10}, D_6, or D_{10}.

69. The method of any one of claims 60-68, wherein X, Y, or Z comprises a cathepsin cleavage sequence.

70. The method of claim 69, wherein said cathepsin cleavage sequence comprises a cathepsin K cleavage sequence.

71. The method of any one of claims 25-70, wherein the amino acid sequence of said polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 501-608.

72. The method of claim 71, wherein the amino acid sequence of said polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 502, 504, 506, 512, 514, 516, 530, 560, 562, 564, 572, 574, 576, 584, 586, 588, 596, 598, 600, or 608.

73. The method of claim 72, wherein the amino acid sequence of said polypeptide comprises or consists of the amino acid sequence of SEQ ID NOs: 504, 512, 530, or 572.

74. The method of any one of claims 1-73, wherein said polypeptide is in dimeric form.

75. The method of any one of claims 1-74, wherein said polypeptide is glycosylated or pegylated.

76. The method of any one of claims 1-75, wherein said pharmaceutical composition is administered in a dosage between about 0.2 mg/kg to about 20 mg/kg of said polypeptide.

77. The method of any one of claims 1-75, wherein said pharmaceutical composition is administered in a dosage between about 0.5 mg/kg to about 500 mg/kg of said polypeptide.

78. The method of any one of claims 1-75, wherein said pharmaceutical composition is administered in a dosage between about 10 µg/kg to about 1,000 µg/kg of said polypeptide.

79. The method of any one of claims 1-78, wherein said pharmaceutical composition is administered subcutaneously.

80. The method of any one of claims 1-79, wherein said pharmaceutical composition is administered one time, two times, or three times per week.

81. The method of any one of claims 1-80, wherein said subject is human.

82. The method of any one of claims 1-81, wherein said neurocutaneous syndrome is neurofibromatosis type I.

83. A composition comprising a first polypeptide and a second polypeptide, wherein

a) said first polypeptide comprises the structure A-sALP-B, wherein

i) sALP is the extracellular domain of an alkaline phosphatase,

ii) A is absent or is an amino acid sequence of at least one amino acid, and

iii) B is absent or is an amino acid sequence of at least one amino acid; and

b) said second polypeptide comprises the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid.

84. The composition of claim 83, wherein the amino acid sequence of said first polypeptide comprises the amino acid sequence of SEQ ID NOs: 1204 or 1221 and the amino acid sequence of said second polypeptide comprises the amino acid sequence of SEQ ID NOs: 504, 512, 530, or 572.

85. The composition of claim 83, wherein the amino acid sequence of said sALP of said first polypeptide comprises amino acid residues 23-508 of SEQ ID NO: 1215, amino acid residues 18-498 of SEQ ID NO: 1216, amino acid residues 23-508 of SEQ ID NO: 1218, or amino acid residues 18-498 of SEQ ID NO: 1219, or

the amino acid sequence of said sALP of said first polypeptide consists of amino acid residues 23-512 of SEQ ID NO: 1215, amino acid residues 18-502 of SEQ ID NO: 1216, amino acid residues 23-512 of SEQ ID NO: 1218, or amino acid residues 18-502 of SEQ ID NO: 1219, or

the amino acid sequence of said sALP of said first polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 1205, or at least 95% sequence identity to SEQ ID NO: 1205, or at least 99% sequence identity to SEQ ID NO: 1205.

86. The composition of claim 83 or 85, wherein A and/or B of said first polypeptide are absent.

87. The composition of any one of claims 83-86, wherein A or B of said first polypeptide comprises a fragment crystallizable region (Fc).

88. The composition of any one of claims 83-87, wherein A or B of said first polypeptide comprises I_n, and wherein I represents an aspartic acid or a glutamic acid and n=10 to 16.

89. The composition of any one of claims 83-88, wherein said first polypeptide comprises the structure C-sALP-D-Fc-G-I_n-H,

C is absent or is an amino acid sequence of at least one amino acid,

D is absent or is an amino acid sequence of at least one amino acid,

G is absent or is an amino acid sequence of at least one amino acid,

H is absent or is an amino acid sequence of at least one amino acid,

I represents an aspartic acid or a glutamic acid, and n=10 to 16.

90. The composition of any one of claims 83-89, wherein the amino acid sequence of said first polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 1204.

91. The composition of any one of claims 83-90, wherein said NP of said second polypeptide comprises the structure:

[N-terminal extension]-[short segment]-[ring domain]-[C-terminal extension],

wherein said ring domain comprises the amino acid sequence of SEQ ID NO: 6, amino acid residues 11-27 of SEQ ID NO: 30, or SEQ ID NO: 95, and each of said N-terminal extension, short segment, and C-terminal extension is, independently, absent or is an amino acid sequence of at least one amino acid.

92. The composition of claim 91, wherein said ring domain comprises amino acid residues 6-22 of SEQ ID NO: 126.

93. The composition of claim 92, wherein the amino acid at position 17 of SEQ ID NO: 126 is Phe, Leu, Ile, Thr, Val, Ala, Ser, Glu, Arg, Tyr, Cys, Pro, or Asp.

94. The composition of any one of claims 91-93, wherein the amino acid sequence of said N-terminal extension comprises amino acid residues 1-31 or 17-31 of SEQ ID NO: 11, KGANKK (SEQ ID NO: 314), or KGANQK (SEQ ID NO: 315).

95. The composition of any one of claims 91-94, wherein said C-terminal extension comprises the amino acid sequence of SEQ ID NOs: 117 or 118 or comprises amino acid residues 23-37 selected from any one of SEQ ID NOs: 101-116.

96. The composition of claim 91, wherein the amino acid sequence of said NP consists of SEQ ID NOs: 4 or 11, or the amino acid sequence of any one of SEQ ID NOs: 31-94, or a fragment thereof comprising at least a ring domain, or the amino acid sequence of any one of SEQ ID NOs: 13-29, 100-116, 119-125, 127-233, or 1001-1155.

97. The composition of any one of claims 83-96, wherein V and/or W of said second polypeptide are absent.

98. The composition of any one of claims 83-97, wherein V or W of said second polypeptide comprises a fragment crystallizable region (Fc).

99. The composition of any one of claims 83-98, wherein V or W of said second polypeptide comprises a glycine-rich region.

100. The composition of any one of claims 83-99, wherein V or W of said second polypeptide comprises a bone-targeting moiety.

101. The composition of any one of claims 83-100, wherein V or W of said second polypeptide comprises a cathepsin cleavage sequence.

102. The composition of any one of claims 83-101, wherein said second polypeptide comprises the structure V-NP-W,

NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

each of V and W is, independently, absent or is an amino acid sequence of at least one amino acid, and

said NP comprises the amino acid sequence of any one of SEQ ID NOs: 17-29, 31-40, 42-94, 101-116, 119-122, 128-161, or 163-233, or V or W comprises the amino acid sequence of any one of SEQ ID NOs: 304-313, 322-333, or 337-391.

103. The composition of any one of claims 83-102, wherein said second polypeptide comprises the structure V-NP or NP-W,

NP is said natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B), and

each of V and W comprises, independently, the amino acid sequence of any one of SEQ ID NOs: 304-313, 322-333, or 337-391.

104. The composition of any one of claims 83-103, wherein said second polypeptide comprises the structure X-Fc-Y-NP-Z or the structure X-NP-Y-Fc-Z,

NP is said natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B), and

each of X, Y, and Z is, independently, absent or is an amino acid sequence of at least one amino acid.

105. The composition of claim 104, wherein Y comprises a glycine-rich region.

106. The composition of claim 104 or 105, wherein X is absent, Z is absent, or X and Z are both absent.

107. The composition of any one of claims 104-106, wherein X, Y, or Z comprises a bone-targeting moiety.

108. The composition of any one of claims 104-107, wherein X, Y, or Z comprises a cathepsin cleavage sequence.

109. The composition of any one of claims 83-108, wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 501-608.

110. The composition of claim 109, wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 502, 504, 506, 512, 514, 516, 530, 560, 562, 564, 572, 574, 576, 584, 586, 588, 596, 598, 600, or 608.

111. The composition of claim 110, wherein the amino acid sequence of said second polypeptide comprises or consists of the amino acid sequence of SEQ ID NO: 512.

112. The composition of any one of claims 83-111, wherein said first polypeptide and/or said second polypeptide are in dimeric form.

113. The composition of any one of claims 83-112, wherein said first polypeptide and/or said second polypeptide are glycosylated or pegylated.

114. The composition of any one of claims 83-113, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

115. The composition of any one of claims 83-114, wherein said composition is lyophilized.

116. The composition of any one of claims 83-115, wherein said first polypeptide is present in a dosage between about 0.2 mg/kg to about 20 mg/kg and said second polypeptide is present in a dosage between about 0.5 mg/kg to about 500 mg/kg.

117. The composition of any one of claims 83-116, wherein the amino acid sequence of said first polypeptide comprises the amino acid sequence of SEQ ID NO: 1204 and wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of SEQ ID NOs: 504, 512, 530, or 572.

118. A method of treating a disease or a condition in a subject, said method comprising administering to said subject a therapeutically effective amount of a first polypeptide and a second polypeptide, wherein

a) said first polypeptide comprises the structure A-sALP-B, wherein

i) sALP is the extracellular domain of an alkaline phosphatase,

ii) A is absent or is an amino acid sequence of at least one amino acid, and

iii) B is absent or is an amino acid sequence of at least one amino acid; and

b) said second polypeptide comprises the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid; and

said disease or condition is selected from the group consisting of a neurocutaneous syndrome, a disorder associated with overactivation of FGFR3, a bone or cartilage disorder, a vascular smooth muscle disorder, and a condition for elongation of bone,

thereby treating said disease or said condition in said subject.

119. The method of claim 118, wherein said first polypeptide and said second polypeptide are administered within ten days, five days, or twenty-four hours of each other.

120. The method of claim 118, wherein said first polypeptide and said second polypeptide are administered simultaneously.

121. The method of any one of claims 118-120, wherein said first polypeptide and said second polypeptide are formulated together in a composition or each separately in a composition.

122. The method of claim 121, wherein said composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

123. The method of claim 122, wherein said composition is lyophilized.

124. The method of any one of claims 121-123, wherein said composition is the composition of any one of claims 83-117.

125. The method of any one of claims 118-124, wherein the amino acid sequence of said first polypeptide comprises the amino acid sequence of SEQ ID NO: 1204 and wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of SEQ ID NOs: 504, 512, 530, or 572.

126. The method of any one of claims 118-125, wherein said first polypeptide is present in a dosage between about 0.2 mg/kg to about 20 mg/kg and said second polypeptide is present in a dosage between about 0.5 mg/kg to about 500 mg/kg.

127. The method of any one of claims 118-125, wherein said first polypeptide is present in a dosage between about 0.2 mg/kg to about 20 mg/kg and said second polypeptide is present in a dosage between about 10 μg/kg to about 1,000 μg/kg.

128. The method of any one of claims 118-127, wherein said first polypeptide and said second polypeptide are administered subcutaneously.

129. The method of any one of claims 118-128, wherein said first polypeptide and said second polypeptide are administered one time, two times, or three times per week.

130. The method of any one of claims 118-129, wherein said subject is human.

131. The method of any one of claims 118-130, wherein said disease is said neurocutaneous syndrome.

132. The method of claim 131, wherein said neurocutaneous syndrome is neurofibromatosis type I.

133. A kit comprising:

a) a first polypeptide comprising the structure A-sALP-B, wherein

i) sALP is the extracellular domain of an alkaline phosphatase,

ii) A is absent or is an amino acid sequence of at least one amino acid, and

iii) B is absent or is an amino acid sequence of at least one amino acid; and

b) instructions for administering said first polypeptide to a patient diagnosed with or at risk of developing a neurocutaneous syndrome.

134. The kit of claim 133, further comprising:

(c) a second polypeptide comprising the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid.

135. A kit comprising:

a) a polypeptide comprising the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid; and

b) instructions for administering said polypeptide to a patient diagnosed with or at risk of developing a neurocutaneous syndrome.

136. A kit comprising:

a) a first polypeptide comprising the structure A-sALP-B, wherein

i) sALP is the extracellular domain of an alkaline phosphatase,

ii) A is absent or is an amino acid sequence of at least one amino acid, and

iii) B is absent or is an amino acid sequence of at least one amino acid; and

b) a second polypeptide comprising the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid.

137. The kit of claim 136, wherein said first polypeptide and said second polypeptide are formulated together.

138. The kit of claim 136, wherein said first polypeptide and said second polypeptide are formulated separately and in individual dosage amount.

What is claimed is:

1. Use of a pharmaceutical composition in the manufacture of a medicament for treating a neurocutaneous syndrome in a subject, said pharmaceutical composition comprising:

(a) a polypeptide comprising the structure A-sALP-B; and

(b) a pharmaceutically acceptable excipient,

wherein said sALP is the extracellular domain of an alkaline phosphatase,

A is absent or is an amino acid sequence of at least one amino acid, and

B is absent or is an amino acid sequence of at least one amino acid.

2. The use of claim 1, wherein said alkaline phosphatase is physiologically active toward phosphoethanolamine (PEA), inorganic pyrophosphate (PPi) and/or pyridoxal 5'-phosphate (PLP).

3. The use of claim 1, wherein said alkaline phosphatase is a tissue nonspecific alkaline phosphatase (TNALP), a placental alkaline phosphatase (PLALP), a germ cell alkaline phosphatase (GALP), or an intestinal alkaline phosphatase (IALP).

4. The use of claim 1, wherein said alkaline phosphatase is a tissue nonspecific alkaline phosphatase (TNALP).

5. The use of claim 1, wherein the amino acid sequence of said sALP

(a) comprises amino acid residues 23-508 of SEQ ID NO: 1215, amino acid residues 18-498 of SEQ ID NO: 1216, amino acid residues 23-508 of SEQ ID NO: 1218, or amino acid residues 18-498 of SEQ ID NO: 1219;

(b) consists of amino acid residues 23-512 of SEQ ID NO: 1215, amino acid residues 18-502 of SEQ ID NO: 1216, amino acid residues 23-512 of SEQ ID NO: 1218, or amino acid residues 18-502 of SEQ ID NO: 1219;

(c) comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 1205;

(d) comprises at least 95% sequence identity to SEQ ID NO: 1205;

(e) comprises at least 99% sequence identity to SEQ ID NO: 1205;

(f) comprises the amino acid sequence of SEQ ID NO: 1205; or

(g) consists of the amino acid sequence of SEQ ID NO: 1205.

6. The use of any one of claims 1, wherein A or B comprises a fragment crystallizable region (Fc).

7. The use of claim 6, wherein said Fc:

(a) comprises the amino acid sequence of SEQ ID NO: 401;

(b) comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 401;

(c) comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 401;

(d) comprises an amino acid sequence having at least 99% sequence identity to SEQ ID NO: 401;

(e) is a constant domain of an immunoglobulin selected from the group consisting of IgG-1, IgG-2, IgG-3, and IgG-4; or

(f) comprises a C_{H2} domain, a C_{H3} domain, and a hinge region.

8. The use of any one of claims 1-7, wherein said polypeptide comprises the structure sALP-Fc or the structure Fc-sALP.

9. The use of claim 8, wherein said polypeptide comprises the amino acid sequence of SEQ ID NO: 1220 or 1221.

10. The use of any one of claims 1-7, wherein said polypeptide comprises a bone-targeting moiety.

11. The use of claim 10, wherein said bone-targeting moiety comprises consecutive aspartic acids or glutamic acids.

12. The use of any one of claims 1-7, wherein said polypeptide comprises the structure C-sALP-D-Fc-G-I_n-H or the structure C-Fc-D-sALP-G-I_n-H, wherein:

C is absent or is an amino acid sequence of at least one amino acid,

D is absent or is an amino acid sequence of at least one amino acid,

G is absent or is an amino acid sequence of at least one amino acid,

H is absent or is an amino acid sequence of at least one amino acid, and

I represents an aspartic acid or a glutamic acid, and n=10 to 16.

13. The use of claim 12, wherein:

(a) G is two amino acid residues;

(b) G is aspartic acid-isoleucine;

(c) I is aspartic acid and n=10;

(d) D is two amino acid residues; or

(e) D is leucine-lysine.

14. The use of claim 13, wherein the amino acid sequence of said polypeptide comprises the amino acid sequence of SEQ ID NO: 1201 or 1204.

15. The use of claim 1, wherein said pharmaceutical composition further comprises a second polypeptide comprising the structure V-NP-W, wherein:

(a) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B);

(b) V is absent or is an amino acid sequence of at least one amino acid, and

(c) W is absent or is an amino acid sequence of at least one amino acid.

16. The use of claim 15, wherein said NP of said second polypeptide comprises the structure:

[N-terminal extension]-[short segment]-[ring domain]-[C-terminal extension],

wherein said ring domain comprises the amino acid sequence of SEQ ID NO: 6, amino acid residues 11-27 of SEQ ID NO: 30, or SEQ ID NO: 95, and each of said N-terminal extension, short segment, and C-terminal extension is, independently, absent or is an amino acid sequence of at least one amino acid.

17. The use of claim 16, wherein:

(a) said ring domain comprises amino acid residues 6-22 of SEQ ID NO: 126;

(b) said ring domain comprises amino acid residues 6-22 of SEQ ID NO: 126 and the amino acid at position 17 of SEQ ID NO: 126 is substituted by Phe, Leu, Ile, Thr, Val, Ala, Ser, Glu, Arg, Tyr, Cys, Pro, or Asp;

(c) the amino acid sequence of said N-terminal extension comprises KGANKK (SEQ ID NO: 314), KGANQK (SEQ ID NO: 315), or amino acid residues 1-31 or 17-31 of SEQ ID NO: 11;

(d) said C-terminal extension comprises the amino acid sequence of SEQ ID NOs: 117 or 118, or amino acid residues 23-37 selected from any one of SEQ ID NOs: 101-116; or

(e) the amino acid sequence of said NP consists of SEQ ID NOs: 4 or 11, or the amino acid sequence of any one of SEQ ID NOs: 31-94, or a fragment thereof comprising at least a ring domain, or the amino acid sequence of any one of SEQ ID NOs: 13-29, 100-116, 119-125, 127-233, or 1001-1155.

18. The use of any one of claims 15-17, wherein V or W of said second polypeptide comprises a fragment crystallizable region (Fc).

19. The use of claim 18, wherein said Fc in V or W:

(a) comprises the amino acid sequence of SEQ ID NO: 401;

(b) comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 401;

(c) comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 401;

(d) comprises an amino acid sequence having at least 99% sequence identity to SEQ ID NO: 401;

(e) is a constant domain of an immunoglobulin selected from the group consisting of IgG-1, IgG-2, IgG-3, and IgG-4; or

(f) comprises a C_{H2} domain, a C_{H3} domain, and a hinge region.

20. The use of any one of claims 15-19, wherein V or W of said second polypeptide comprises:

(a) a glycine-rich region;

(b) a bone-targeting moiety; or

(c) a cathepsin cleavage sequence.

21. The use of any one of claims 15-20, wherein said second polypeptide comprises the structure X-Fc-Y-NP-Z or the structure X-NP-Y-Fc-Z, wherein:

(a) X is absent or is an amino acid sequence of at least one amino acid;

(b) Y is absent or is an amino acid sequence of at least one amino acid; and

(c) Z is absent or is an amino acid sequence of at least one amino acid.

22. The use of claim 21, wherein Y comprise:

(a) a glycine-rich region;

(b) $[(Gly)_m(Ser)]_n(Gly)_p$ or $(Gly)_p[(Ser)(Gly)_m]_n$, wherein each of m, n, and p is, independently, between 0 and 20; or

(c) the amino acid sequence of any one of SEQ ID NOs: 301-391.

23. The use of any one of claims 15-22, wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of any one of SEQ ID NOs: 501-608.

24. The use of claim 23, wherein the amino acid sequence of said second polypeptide comprises the amino acid sequence of SEQ ID NO: 572.

25. The use of any one of claims 15-24, wherein at least one of said first polypeptide and said second polypeptide is in dimeric form, glycosylated, or pegylated.

26. The use of any one of claims 1-25, wherein said neurocutaneous syndrome is neurofibromatosis type I.

27. The use of any one of claims 1-26, wherein said subject is a human.

28. A kit comprising:

(a) a first polypeptide comprising the structure A-sALP-B; wherein

(i) said sALP is the extracellular domain of an alkaline phosphatase,

(ii) A is absent or is an amino acid sequence of at least one amino acid, and

(iii) B is absent or is an amino acid sequence of at least one amino acid; and

(b) instructions for administering said first polypeptide to a patient diagnosed with or at risk of developing a neurocutaneous syndrome.

29. The kit of claim 28, further comprising:

(c) a second polypeptide comprising the structure V-NP-W, wherein:

(i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

(ii) V is absent or is an amino acid sequence of at least one amino acid, and

(iii) W is absent or is an amino acid sequence of at least one amino acid.

30. A kit comprising:

a) a first polypeptide comprising the structure A-sALP-B, wherein

i) sALP is the extracellular domain of an alkaline phosphatase,

ii) A is absent or is an amino acid sequence of at least one amino acid, and

iii) B is absent or is an amino acid sequence of at least one amino acid; and

b) a second polypeptide comprising the structure V-NP-W, wherein

i) NP is a natriuretic peptide that is an agonist of natriuretic peptide receptor B (NPR-B),

ii) V is absent or is an amino acid sequence of at least one amino acid, and

iii) W is absent or is an amino acid sequence of at least one amino acid.

31. The kit of claim 30, wherein said first polypeptide and said second polypeptide are formulated together.

32. The kit of claim 30, wherein said first polypeptide and said second polypeptide are formulated separately and in individual dosage amount.