

CLAIMS

WHAT IS CLAIMED IS:

1. A recombinant polypeptide comprising:
an amino acid sequence having at least 70% sequence identity to an interleukin 22 (IL-22) polypeptide having the amino acid sequence of SEQ ID NO: 1;
and further comprising one or more amino acid substitution at a position corresponding to an amino acid residue selected from the group consisting of X43, X49, X45, X46, X116, X124, and X128 of SEQ ID NO: 1.
2. The recombinant polypeptide of claim 1, wherein the amino acid sequence further comprising an additional amino acid substitution at a position corresponding to an amino acid residue selected from the group consisting of X48, X55, and X117 of SEQ ID NO: 1.
3. The recombinant polypeptide of any one of claims 1 to 2, wherein the one or more amino acid substitution reduces IL10R β -binding affinity of the recombinant IL-22 polypeptide compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.
4. The recombinant polypeptide of any one of claims 1 to 2, wherein the one or more amino acid substitution increases IL10R β -binding affinity of the recombinant IL-22 polypeptide compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.
5. The recombinant polypeptide of any one of claims 1 to 4, wherein the one or more amino acid substitution is at a position corresponding to an amino acid residue selected from the group consisting of X43, X45, X46, X48, X49, X55, and X117 of SEQ ID NO: 1.
6. The recombinant polypeptide of claim 5, further comprising a combination of amino acid substitutions at positions corresponding to amino acid residues X116, X124, X128 of SEQ ID NO: 1.
7. The recombinant polypeptide of any one of claims 1 to 6, wherein the amino acid sequence comprises an amino acid substitution corresponding to amino acid residue X55 or X117 of SEQ ID NO: 1.
8. The recombinant polypeptide of any one of claims 1 to 7, wherein the one or more amino acid substitution is independently selected from the group consisting of an alanine substitution, an arginine substitution, an aspartic acid substitution, a histidine substitution, a

glutamic acid substitution, a lysine substitution, a serine substitution, a tryptophan substitution, and combinations of any thereof.

9. The recombinant polypeptide of any one of claims 1 to 8, wherein the one or more amino acid substitution is at a position corresponding to an amino acid residue selected from the group consisting of D43, S45, N46, Q49, Q116, R124, and R128 of SEQ ID NO: 1.

10. The recombinant polypeptide of any one of claims 1 to 9, comprising an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 1, and further comprising the amino acid substitutions corresponding to the following amino acid substitutions:

- a) R55A;
- b) E117A;
- c) N46A/E117A;
- d) Q116A/R124A/R128A;
- e) Q116A/R124D/R128A;
- f) D43A/Q116A/R124A/R128A;
- g) S45E/Q116A/R124A/R128A; and
- h) Q48A/Q116A/R124A/R128A.

11. The recombinant polypeptide of any one of claims 1 to 9, comprising an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 1, and further comprising an amino acid substitution corresponding an amino acid residue selected from the group consisting of D43H, D43R, S45R, S45G, Q49S, Q49G, Q116W, Q116K, R124Y, and R128K.

12. A recombinant polypeptide comprising:

an amino acid sequence having at least 70% sequence identity to an interleukin 22 (IL-22) polypeptide having the amino acid sequence of SEQ ID NO: 6;

and further comprising one or more amino acid substitution at a position corresponding to an amino acid residue selected from the group consisting of X43, X45, X46, X49, X116, X124, and X128 of SEQ ID NO: 6.

13. The recombinant polypeptide of claim 12, wherein the amino acid sequence further comprising an additional amino acid substitution at a position corresponding to an amino acid residue selected from the group consisting of X48, X55, and X117 of SEQ ID NO: 6.

14. The recombinant polypeptide of any one of claims 12 to 13, wherein the one or more amino acid substitution reduces IL10R β -binding affinity of the recombinant IL-22

polypeptide compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

15. The recombinant polypeptide of any one of claims 12 to 13, wherein the one or more amino acid substitution increases IL10R β -binding affinity of the recombinant IL-22 polypeptide compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

16. The recombinant polypeptide of any one of claims 12 to 15, wherein the one or more amino acid substitution is at a position corresponding to an amino acid residue selected from the group consisting of X43, X45, X46, X48, X55, and X117 of SEQ ID NO: 6.

17. The recombinant polypeptide of claim 16, further comprising a combination of amino acid substitutions at positions corresponding to amino acid residues X116, X124, X128 of SEQ ID NO: 6.

18. The recombinant polypeptide of any one of claims 12 to 17, wherein the amino acid sequence comprises an amino acid substitution corresponding to amino acid residue X55 or X117 of SEQ ID NO: 6.

19. The recombinant polypeptide of any one of claims 12 to 18, wherein the one or more amino acid substitution is independently selected from the group consisting of an alanine substitution, an arginine substitution, an aspartic acid substitution, a histidine substitution, a glutamic acid substitution, a lysine substitution, a serine substitution, a tryptophan substitution, and combinations of any thereof.

20. The recombinant polypeptide of any one of claims 12 to 19, wherein the one or more amino acid substitution is at a position corresponding to an amino acid residue selected from the group consisting of E43, S45, N46, Q48, R55, Q116, E117, K124, Q128 of SEQ ID NO: 6.

21. The recombinant polypeptide of any one of claims 12 to 20, comprising an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 6, and further comprising the amino acid substitutions corresponding to the following amino acid substitutions:

- a) R55A;
- b) E117A;
- c) N46A/E117A;
- d) Q116A/K124A/Q128A;

- e) Q116A/K124D/Q128A;
- f) E43A/Q116A/K124A/Q128A;
- g) S45E/Q116A/K124A/Q128A; and
- h) Q48A/Q116A/K124A/Q128A.

22. The recombinant polypeptide of any one of claims 12 to 20, comprising an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 6, and further comprising an amino acid substitution corresponding an amino acid residue selected from the group consisting of E43H, E43R, S45R, S45G, Q49S, Q49G, Q116W, Q116K, Q124Y, and Q128K.

23. The recombinant polypeptide of any one of claims 1 to 22, wherein one or more amino acid substitution results in a tissue-selective IL-22 signaling compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

24. The recombinant polypeptide of claim 23, wherein the tissue-selective IL-22 signaling comprises a reduction of IL-22 signaling in the skin while substantially retains IL-22 signaling in the pancreas and/or the gastrointestinal tract.

25. The recombinant polypeptide of any one of claims 23 to 24, wherein the tissue-selective IL-22 signaling comprises a reduction of IL-22 signaling in the liver while substantially retains IL-22 signaling in the pancreas and/or the gastrointestinal tract.

26. The recombinant polypeptide of any one of claims 1 to 25, wherein the one or more amino acid substitution results in a biased IL-22 signaling compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

27. The recombinant polypeptide of claim 26, wherein the biased IL-22 signaling comprises a reduction in a STAT1-mediated pro-inflammatory function while substantially retains its STAT3-mediated function.

28. The recombinant polypeptide of any one of claims 26 to 27, wherein the biased IL-22 signaling comprises a ratio of STAT1-mediated signaling to STAT3-mediated signaling ranging from 1:1.5 to 1:10.

29. The recombinant polypeptide of claim 28, the STAT1-mediated signaling and/or STAT3-mediated signaling is determined by an assay selected from the group consisting of by a gene expression assay, a phospho-flow signaling assay, and an enzyme-linked immunosorbent assay (ELISA).

30. The recombinant polypeptide of any one of claims 27 to 29, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

31. The recombinant polypeptide of any one of claims 27 to 30, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.

32. The recombinant polypeptide of any one of claims 27 to 31, wherein the STAT1-mediated pro-inflammatory function is reduced about 20% to about 100%, as determined by a gene expression assay, a phospho-flow signaling assay, and/or an enzyme-linked immunosorbent assay (ELISA).

33. A recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide that comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of the polypeptide of any one of claims 1 to 32.

34. The nucleic acid molecule of claim 33, wherein the nucleic acid sequence is operably linked to a heterologous nucleic acid sequence.

35. The nucleic acid molecule of any one of claims 33 to 34, wherein the nucleic acid molecule is further defined as an expression cassette or an expression vector.

36. A recombinant cell comprising:

- a) a recombinant polypeptide according to any one of claims 1 to 32; and/or
- b) a recombinant nucleic acid according to any one of claims 33 to 35.

37. The recombinant cell of claim 36, wherein the recombinant cell is a eukaryotic cell.

38. The recombinant cell of claim 37, wherein the eukaryotic cell is a mammalian cell

39. A cell culture comprising at least one recombinant cell of any one of claims 36 to 38, and a culture medium.

40. A method for producing a polypeptide comprising:

- a) providing one or more recombinant cells of any one of claims 1 to 32; and
- b) culturing the one or more recombinant cells in a culture medium such that the cells produce the polypeptide encoded by the recombinant nucleic acid molecule.

41. The method of claim 40, further comprising isolating and/or purifying the produced polypeptide.

42. The method of any one of claims 40 to 41, further comprising structurally modifying the produced polypeptide to increase half-life.
43. The method of claim 42, wherein said modification comprises one or more alterations selected from the group consisting of fusion to a human Fc antibody fragment, fusion to albumin, and PEGylation.
44. A recombinant polypeptide produced by the method of any one of claims 40 to 43.
45. A pharmaceutical composition comprising:
- a) a recombinant polypeptide according to any one of claims 1-32 and 44;
 - b) a recombinant nucleic acid according to any one of claims 33 to 35;
 - c) a recombinant cell according to any one of claims 36 to 38; and/or
 - d) a pharmaceutically acceptable carrier.
46. The pharmaceutical composition of claim 45, wherein the composition comprises a recombinant polypeptide according to any one of claims 1-32 and 44, and a pharmaceutically acceptable carrier.
47. The pharmaceutical composition of claim 45, wherein the composition comprises a recombinant nucleic acid according to any one of claims 33 to 35, and a pharmaceutically acceptable carrier.
48. A method for modulating IL-22-mediated signaling in a subject, the method comprising administering to the subject a composition comprising:
- a) a recombinant polypeptide according to any one of claims 1-32 and 44;
 - b) a recombinant nucleic acid according to any one of claims 33 to 35;
 - c) a recombinant cell according to any one of claims 36 to 38; and/or
 - d) a pharmaceutically composition according to claims 45 to 47.
49. A method for the treatment of a condition in a subject in need thereof, the method comprising administering to the subject a composition comprising:
- a) a recombinant polypeptide according to any one of claims 1-32 and 44;
 - b) a recombinant nucleic acid according to any one of claims 33 to 35;
 - c) a recombinant cell according to any one of claims 36 to 38; and/or
 - d) a pharmaceutically composition according to claims 45 to 47.

50. The method of any one of claims 48 to 49, wherein the administered composition results in a tissue-selective IL-22 signaling in the subject compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

51. The recombinant polypeptide of claim 50, wherein the tissue-selective IL-22 signaling comprises a reduction of IL-22 signaling in the skin while substantially retains IL-22 signaling in the pancreas and/or the gastrointestinal tract.

52. The recombinant polypeptide of any one of claims 50 to 51, wherein the tissue-selective IL-22 signaling comprises a reduction of IL-22 signaling in the liver while substantially retains IL-22 signaling in the pancreas and/or the gastrointestinal tract.

53. The method of any one of claims 48 to 52, wherein the administered composition results in a biased IL-22 signaling in the subject compared to a reference IL-22 polypeptide lacking the one or more amino acid substitution.

54. The method of claim 53, wherein the biased IL-22 signaling comprises a reduction in a STAT1-mediated pro-inflammatory function while substantially retains its STAT3-mediated function.

55. The method of any one of claims 53 to 54, wherein the biased IL-22 signaling comprises a ratio of STAT1-mediated signaling to STAT3-mediated signaling ranging from 1:1.5 to 1:10.

56. The method of claim 55, wherein the STAT1-mediated signaling and/or STAT3-mediated signaling is determined by an assay selected from the group consisting of by a gene expression assay, a phospho-flow signaling assay, and an enzyme-linked immunosorbent assay (ELISA).

57. The method of any one of claims 54 to 56, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

58. The method of any one of claims 54 to 57, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.

59. The method of claim 58, wherein the STAT1-mediated pro-inflammatory function is reduced about 20% to about 100%.

60. The method of claim 59, wherein the STAT1-mediated pro-inflammatory function is determined by a gene expression assay, a phospho-flow signaling assay, and/or an enzyme-linked immunosorbent assay (ELISA).

61. The methods of any one of claims 48 to 60, wherein the administered composition results in a reduced capacity to induce expression of a pro-inflammatory gene selected from CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, IL-1 β , and IL-6 in the subject.

62. The method of any one of claims 48 to 61, wherein the administered composition substantially retains its capacity to induce expression of a gene selected from Reg3 β , Reg3 γ , Muc1, Muc2, Muc10, BCL-2, Cyclin-D, Claudin-2, LCN2, and β -Defensin in the subject.

63. The method of any one of claims 48 to 62, wherein the administration of the pharmaceutical composition does not inhibit T-cell activity in the subject.

64. The method of any one of claims 48 to 63, wherein the administered composition enhances epithelial protection and regeneration.

65. The method of any one of claims 48 to 64, wherein the condition is an immune disease, or a chronic infection.

66. The method of claim 65, wherein the immune disease is an autoimmune disease.

67. The method of claim 66, wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, insulin-dependent diabetes mellitus, hemolytic anemias, rheumatic fever, thyroiditis, Crohn's disease, myasthenia gravis, glomerulonephritis, autoimmune hepatitis, multiple sclerosis, alopecia areata, psoriasis, vitiligo, dystrophic epidermolysis bullosa, systemic lupus erythematosus, graft vs. host disease, ulcerative colitis, pancreatitis, psoriatic arthritis, and diabetic foot ulcer.

68. The method of claim 66, wherein the autoimmune disease is acute pancreatitis.

69. The method of any one of claims 48 to 68, wherein the subject is a mammal.

70. The method of claim 69, wherein the mammal is a human.

71. The method of any one of claims 48 to 70, wherein the subject has or is suspected of having a condition associated with IL-22 mediated signaling.

72. The method of any one of claims 48 to 71, wherein the composition is administered to the subject individually as a first therapy or in combination with a second therapy.

73. The method of claim 72, wherein the second therapy is selected from the group consisting of chemotherapy, radiotherapy, immunotherapy, hormonal therapy, or toxin therapy.
74. The method of any one of claims 72 to 73, wherein the first therapy and the second therapy are administered concomitantly.
75. The method of any one of claims 72 to 74, wherein the first therapy is administered at the same time as the second therapy.
76. The method of any one of claims 72 to 74, wherein the first therapy and the second therapy are administered sequentially.
77. The method of claim 76, wherein the first therapy is administered before the second therapy.
78. The method of claim 76, wherein the first therapy is administered after the second therapy.
79. The method of claim 76, wherein the first therapy is administered before and/or after the second therapy.
80. The method of any one of claims 72 to 79, wherein the first therapy and the second therapy are administered in rotation.
81. The method of any one of claims 72 to 73, wherein the first therapy and the second therapy are administered together in a single formulation.
82. A kit for modulating IL-22-mediated signaling in a subject, or treating a condition in a subject in need thereof, the kit comprising:
- a) a recombinant polypeptide according to any one of claims 1-32 and 44;
 - b) a recombinant nucleic acid according to any one of claims 33 to 35;
 - c) a recombinant cell according to any one of claims 36 to 39; and/or
 - d) a pharmaceutical composition according to any one of claims 45 to 47.