

CLAIMS

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 or 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.
4. The recombinant polypeptide of any one of claims 1 to 3, 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.
5. The recombinant polypeptide of claim 4, further comprising a combination of amino acid substitutions at positions corresponding to amino acid residues X116, X124, X128 of SEQ ID NO: 1.
6. The recombinant polypeptide of any one of claims 1 to 5, 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.
7. The recombinant polypeptide of any one of claims 1 to 6, 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.

8. The recombinant polypeptide of any one of claims 1 to 7, 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.

9. 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.

10. The recombinant polypeptide of claim 9, 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.

11. The recombinant polypeptide of any one of claims 9 to 10, wherein the one or more amino acid substitution reduces or 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.

12. The recombinant polypeptide of any one of claims 9 to 11, 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.

13. The recombinant polypeptide of claim 12, further comprising a combination of amino acid substitutions at positions corresponding to amino acid residues X116, X124, X128 of SEQ ID NO: 6.

14. The recombinant polypeptide of any one of claims 9 to 13, 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.

15. The recombinant polypeptide of any one of claims 9 to 14, 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.

16. The recombinant polypeptide of any one of claims 9 to 15, 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.

17. The recombinant polypeptide of any one of claims 1 to 16, wherein:

- (a) 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; and/or
- (b) 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; and/or
- (c) 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; and/or
- (d) 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.

18. The recombinant polypeptide of claim 17, wherein the biased IL-22 signaling comprises a reduction in a STAT1-mediated pro-inflammatory function while substantially retains its STAT3-mediated function.

19. The recombinant polypeptide of any one of claims 17 to 18, 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.

20. The recombinant polypeptide of claim 19, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

21. The recombinant polypeptide of any one of claims 19 to 20, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.

22. 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 21.

23. A recombinant cell comprising:

- a) a recombinant polypeptide according to any one of claims 1 to 21; and/or
- b) a recombinant nucleic acid according to claim 22.

24. The recombinant cell of claim 23, wherein the recombinant cell is a eukaryotic cell.

25. The recombinant cell of claim 24, wherein the eukaryotic cell is a mammalian cell

26. A cell culture comprising at least one recombinant cell of any one of claims 23 to 25, and a culture medium.

27. A method for producing a polypeptide comprising:

- a) providing one or more recombinant cells of any one of claims 23 to 26; 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.

28. The method of claim 27, further comprising structurally modifying the produced polypeptide to increase half-life.

29. The method of claim 28, 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.

30. A recombinant polypeptide produced by the method of any one of claims 27 to 29.

31. A pharmaceutical composition comprising:

- a) a recombinant polypeptide according to any one of claims 1-21 and 30;

- b) a recombinant nucleic acid according to claim 22;
 - c) a recombinant cell according to any one of claims to 23 to 25; and/or
 - d) a pharmaceutically acceptable carrier.
- 32. Use of a composition comprising:
 - a) a recombinant polypeptide according to any one of claims 1-21 and 30;
 - b) a recombinant nucleic acid according to claim 22;
 - c) a recombinant cell according to any one of claims to 23 to 25; and/or
 - d) a pharmaceutically composition according to claim 31,
 in the preparation of a medicament for modulating IL-22-mediated signaling in a subject.
- 33. Use of a composition comprising:
 - a) a recombinant polypeptide according to any one of claims 1-21 and 30;
 - b) a recombinant nucleic acid according to claim 22;
 - c) a recombinant cell according to any one of claims to 23 to 25; and/or
 - d) a pharmaceutically composition according to claim 31,
 in the preparation of a medicament for the treatment of a condition in a subject.
- 34. The use of any one of claims 32 to 33, wherein
 - (a) the composition to be administered 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; and/or
 - (b) 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; and/or
 - (c) 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;
 - (d) 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.
- 35. The use of claim 34, wherein the biased IL-22 signaling comprises a reduction in a STAT1-mediated pro-inflammatory function while substantially retains its STAT3-mediated function.

36. The use of any one of claims 34 to 35, 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.

37. The use of claim 36, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

38. The use of any one of claims 36 to 37, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.

39. The use of any one of claims 33 to 38, wherein

(a) the composition to be administered 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; and/or

(b) the composition to be administered 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.

40. The use of any one of claims 33 to 39, wherein:

(a) the pharmaceutical composition to be administered does not inhibit T-cell activity in the subject; and/or

(b) the composition to be administered enhances epithelial protection and regeneration.

41. The use of any one of claims 33 to 40, wherein the condition is an immune disease, or a chronic infection.

42. The use of claim 41, wherein the immune disease is an autoimmune disease.

43. The use of any one of claims 33 to 42, wherein the subject is a mammal.

44. The use of any one of claims 33 to 43, wherein the subject has or is suspected of having a condition associated with IL-22 mediated signaling.

45. The use of any one of claims 33 to 44, wherein the composition is to be administered to the subject individually as a first therapy or in combination with a second therapy.

46. 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 1-21 and 30;
- b) a recombinant nucleic acid according to claim 22;
- c) a recombinant cell according to any one of claims 23 to 25; and/or
- d) a pharmaceutical composition according to claim 31.