

CLAIMS

1. A recombinant human interleukin 22 (hIL-22) variant comprising:
 - the amino acid sequence of a mature wild-type human IL-22 polypeptide as set forth in amino acid residues 34–179 of SEQ ID NO: 1; and
 - one or more amino acid substitution at a position corresponding to an amino acid residue selected from the group consisting of S45, N46, Q48, Q49, R55, Q116, E117, R124, and R128, wherein the amino acid positions are numbered in accordance with SEQ ID NO: 1,
 - and optionally further comprising a deletion of the N-terminal alanine residue, and wherein the recombinant hIL-22 variant is a partial agonist.
2. The recombinant hIL-22 variant of claim 1, wherein the one or more amino acid substitution is at a position corresponding to an amino acid residue selected from the group consisting of S45, N46, Q49, Q116, R124, and R128 of SEQ ID NO: 1.
3. The recombinant hIL-22 variant of claim 1 or 2, wherein the recombinant hIL-22 variant comprises the following amino acid substitutions:
 - a) R55E;
 - b) R55L;
 - c) R55A;
 - d) E117A;
 - e) N46A/E117A;
 - f) Q116A/R124A/R128A;
 - g) Q116A/R124D/R128A;
 - h) D43A/Q116A/R124A/R128A;
 - i) S45E/Q116A/R124A/R128A; or
 - j) Q48A/Q116A/R124A/R128A.
4. The recombinant hIL-22 variant of claim 1 or 2, wherein the one or more amino acid substitutions is selected from the group consisting of S45R, S45G, Q49S, Q49G, Q116W, Q116K, R124Y, and R128K.

5. The recombinant hIL-22 variant of any one of claims 1 to 4, 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.
6. The recombinant hIL-22 variant of any one of claims 1 to 5, 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.
7. The recombinant hIL-22 variant of claim 6, wherein the biased IL-22 signaling comprises a reduction in a STAT1-mediated pro-inflammatory function while substantially retains its STAT3-mediated function.
8. The recombinant hIL-22 variant of claim 6 or 7, 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.
9. The recombinant hIL-22 variant of claim 8, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

10. The recombinant hIL-22 variant of claim 8 or 9, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.
11. A recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide according to any one of claims 1 to 10.
12. A recombinant cell comprising:
 - a) a recombinant hIL-22 variant according to any one of claims 1 to 10; and/or
 - b) a recombinant nucleic acid according to claim 11.
13. The recombinant cell of claim 12, wherein the recombinant cell is a eukaryotic cell.
14. The recombinant cell of claim 13, wherein the eukaryotic cell is a mammalian cell
15. A cell culture comprising at least one recombinant cell of any one of claims 12 to 14, and a culture medium.
16. A method for producing a polypeptide comprising:
 - a) providing one or more recombinant cells of any one of claims 12 to 14; 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.
17. The method of claim 16, further comprising structurally modifying the produced polypeptide to increase half-life.
18. The method of claim 17, 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.

19. A pharmaceutical composition comprising:
- a) a recombinant hIL-22 variant according to any one of claims 1-10;
 - b) a recombinant nucleic acid according to claim 11;
 - c) a recombinant cell according to any one of claims to 12 to 14; and/or
 - d) a pharmaceutically acceptable carrier.
20. Use of a composition comprising:
- a) a recombinant hIL-22 variant according to any one of claims 1-10;
 - b) a recombinant nucleic acid according to claim 11;
 - c) a recombinant cell according to any one of claims to 12 to 14; and/or
 - d) a pharmaceutically composition according to claim 19,
- in the preparation of a medicament for modulating IL-22-mediated signaling in a subject in need thereof, wherein the subject has or is suspected of having a health condition associated with IL-22 mediated signaling, and wherein the health condition is an immune disease, or a chronic infection.
21. Use of a composition comprising:
- a) a recombinant hIL-22 variant according to any one of claims 1-10;
 - b) a recombinant nucleic acid according to claim 11;
 - c) a recombinant cell according to any one of claims to 12 to 14; and/or
 - d) a pharmaceutically composition according to claim 19,
- in the preparation of a medicament for the treatment of a health condition associated with IL-22 mediated signaling in a subject in need thereof, wherein the health condition is an immune disease or a chronic infection.
22. The use of any one of claims 20 to 21, 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.

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

24. The use of any one of claims 22 to 23, 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.

25. The use of claim 24, wherein the STAT3-mediated function is selected from the group consisting of tissue protection, tissue regeneration, cell proliferation, and cell survival.

26. The use of any one of claims 24 to 25, wherein the STAT1-mediated pro-inflammatory function is selected from the group consisting of cytokine production, chemokine production, and immune cell recruitment.

27. The use of any one of claims 21 to 26, 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.

28. The use of any one of claims 21 to 27, 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.
29. The use of any one of claims 21 to 28, wherein the immune disease is an autoimmune disease associated with IL-22 mediated signaling.
30. The use of any one of claims 21 to 29, wherein the subject is a mammal.
31. 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.
32. 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 hIL-22 variant according to any one of claims 1-10;
 - b) a recombinant nucleic acid according to claim 11;
 - c) a recombinant cell according to any one of claims 12 to 14; and/or
 - d) a pharmaceutical composition according to claim 19.