Claims

1. A mutant interleukin-7 (IL-7) polypeptide, comprising at least one amino acid substitution in a position selected from the group of E13, V15, V18, D21, Q22, D25, T72, L77, K81, E84, G85, I88, , Q136, K139, N143 and M147 of human IL-7 according to SEQ ID NO: 52.

2. The mutant interleukin-7 polypeptide of claim 1 wherein said amino acid substitution is selected from the group of E13A, E13K, V15A, V15K, V18A, V18K, D21A, D21K, Q22A, Q22K, D25A, D25K, T72A, L77A, L77K, K81A, K81E, E84A, G85K, G85E, I88K, Q136A, Q136K, K139A, K139E, N143K and M147A.

3. The mutant interleukin-7 polypetide of claim 1 or 2, wherein said amino acid substitution is selected from the group of V15A, V15K, V18A, V18K, L77A, L77K, K81E, G85K, G85E, I88K and N143K.

4. The mutant interleukin-7 polypetide of any of claims 1 to 3, comprising at least the amino acid substitutions K81E and G85K or K81E and G85E.

5. An immunoconjugate comprising (i) a mutant IL-7 polypeptide of any one of claims 1 to 4 and (ii) an antibody that binds to PD-1.

6. An immunoconjugate according to claim 5, wherein the antibody comprises (a) a heavy chain variable region (VH) comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO:1, a HVR-H2 comprising the amino acid sequence of SEQ ID NO:2, a HVR-H3 comprising the amino acid sequence of SEQ ID NO:3, and a FR-H3 comprising the amino acid sequence of SEQ ID NO:7 at positions 71-73 according to Kabat numbering, and (b) a light chain variable region (VL) comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO:4, a HVR-L2 comprising the amino acid sequence of SEQ ID NO:5, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO:6.

7 An immunoconjugate according to claim5, wherein the antibody comprises (a) a heavy chain variable region (VH) comprising a HVR-H1 comprising the amino acid sequence of SEQ ID NO:8, a HVR-H2 comprising the amino acid sequence of SEQ ID NO:9, and a HVR-H3 comprising the

amino acid sequence of SEQ ID NO:10, and (b) a light chain variable region (VL) comprising a HVR-L1 comprising the amino acid sequence of SEQ ID NO:11, a HVR-L2 comprising the amino acid sequence of SEQ ID NO:12, and a HVR-L3 comprising the amino acid sequence of SEQ ID NO:13.

8. An immunoconjugate according to claim5, wherein the antibody comprises (a) a heavy chain variable region (VH) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:14, and (b) a light chain variable region (VL) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO: 17, and SEQ ID NO:18.

9. The immunoconjugate of any one of claims 5 to 8, wherein the immunoconjugate comprises not more than one mutant IL-7 polypeptide.

10. The immunoconjugate of any one of claims 5 to 9, wherein the antibody comprises an Fc domain composed of a first and a second subunit.

11. The immunoconjugate of claim 10, wherein the Fc domain is an IgG class, particularly an IgG_1 subclass, Fc domain.

12. The immunoconjugate of claim 10 or 11, wherein the Fc domain is a human Fc domain.

13. The immunoconjugate of any one of claims 5 to 12, wherein the antibody is an IgG class, particularly an IgG_1 subclass immunoglobulin.

14. The immunoconjugate of any one of claims 10 to 13, wherein the Fc domain comprises a modification promoting the association of the first and the second subunit of the Fc domain.

15. The immunoconjugate of any one of claims 10 to 14, wherein in the CH3 domain of the first subunit of the Fc domain an amino acid residue is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the CH3 domain of the first subunit which is positionable in a cavity within the CH3 domain of the second subunit, and in the CH3 domain of the second subunit of the Fc domain an amino acid residue is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the

CH3 domain of the second subunit within which the protuberance within the CH3 domain of the first subunit is positionable.

16. The immunoconjugate of any one of claims 10 to 15, wherein in the first subunit of the Fc domain the threonine residue at position 366 is replaced with a tryptophan residue (T366W), and in the second subunit of the Fc domain the tyrosine residue at position 407 is replaced with a valine residue (Y407V) and optionally the threonine residue at position 366 is replaced with a serine residue (T366S) and the leucine residue at position 368 is replaced with an alanine residue (L368A) (numberings according to Kabat EU index).

17. The immunoconjugate of claim 16, wherein in the first subunit of the Fc domain additionally the serine residue at position 354 is replaced with a cysteine residue (S354C) or the glutamic acid residue at position 356 is replaced with a cysteine residue (E356C), and in the second subunit of the Fc domain additionally the tyrosine residue at position 349 is replaced by a cysteine residue (Y349C) (numberings according to Kabat EU index).

18. The immunoconjugate of any one of claims 10 to 17, wherein the mutant IL-7 polypeptide is fused at its amino-terminal amino acid to the carboxy-terminal amino acid of one of the subunits of the Fc domain, particularly the first subunit of the Fc domain, optionally through a linker peptide.

19. The immunoconjugate of claim 18, wherein the linker peptide has the amino acid sequence of SEQ ID NO:21.

20. The immunoconjugate of any one of claims 10 to 18, wherein the Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, particularly an Fcγ receptor, and/or effector function, particularly antibody-dependent cell-mediated cytotoxicity (ADCC).

21. The immunoconjugate of claim 20, wherein said one or more amino acid substitution is at one or more position selected from the group of L234, L235, and P329 (Kabat EU index numbering).

22. The immunoconjugate of any one of claims 10 to 21, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329G (Kabat EU index numbering).

23. The immunoconjugate of any one of claims 5 to 22, comprising a polypeptide comprising an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 85, a polypeptide comprising an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 86, and a polypeptide comprising an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence selected from the group of SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 114, SEQ ID NO: 137 and SEQ ID NO:138.

24. The immunoconjugate of any one of claims 5 to 23, essentially consisting of a mutant IL-7 polypeptide and an IgG_1 immunoglobulin molecule, joined by a linker sequence.

25. One or more isolated polynucleotide encoding the mutant IL-7 polpypeptyde according to any one of claims 1 to 4 or the immunoconjugate of any one of claims 5 to 24.

26. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim 23.

27. A host cell comprising the polynucleotide(s) of claim 23 or the vector(s) of claim 24.

28. A method of producing a mutant IL-7 polypeptide or an immunoconjugate comprising a mutant IL-7 polypeptide and an antibody that binds to PD-1, comprising (a) culturing the host cell of claim 26 under conditions suitable for the expression of the mutant IL-7 polypetide or the immunoconjugate, and optionally (b) recovering the mutant IL-7 polypetide or the immunoconjugate.

29. A mutant IL-7 polypetide or an immunoconjugate comprising a mutant IL-7 polypeptide and an antibody that binds to PD-1, produced by the method of claim 28.

30. A pharmaceutical composition comprising the mutant IL-7 polypetide of any one of claims 1 to 4 or 29 or the immunoconjugate of any one of claims 5 to 24 or 29 and a pharmaceutically acceptable carrier.

31. The mutant IL-7 polypetide of any one of claims 1 to 4 or 29 or the immunoconjugate of any one of claims 5 to 24 or 29 for use as a medicament.

32. The mutant IL-7 polypetide of any one of claims 1 to 4 or 29 or the immunoconjugate of any one of claims 5 to 24 or 29 for use in the treatment of a disease.

33. The mutant IL-7 polypeptide or the immunoconjugate for use in the treatment of a disease of claim 32, wherein said disease is cancer.

34. Use of the mutant IL-7 polypeptide of any one of claims 1 to 4 or 29 or the immunoconjugate of any one of claims 5 to 24 or 29 in the manufacture of a medicament for the treatment of a disease.

35. The use of claim 34, wherein said disease is cancer.

36. A method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the mutant IL-7 polypeptide of any one of claims 1 to 5 or 29 or the immunoconjugate of any one of claims 4 to 24 or 29 in a pharmaceutically acceptable form.

37. The method of claim 36, wherein said disease is cancer.

38. A method of stimulating the immune system of an individual, comprising administering to said individual an effective amount of a composition comprising the mutant IL-7 polypetide of any of claims 1 to 4 and 29 or the immunoconjugate of any one of claims 5 to 24 or 29 in a pharmaceutically acceptable form.

~~39. The invention as described hereinbefore.~~