Claims

1. An immunoconjugate comprising (i) an antibody that binds to PD-1 and (ii) a polypeptide that signals through IL-2Rβγ, particularly an IL-2 polypetide or an IL-15 polypeptide.

2. An immunoconjugate according to claim 1, wherein the IL-2 polypeptide is a mutant IL-2 polypeptide,
wherein the mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G (numbering relative to the human IL-2 sequence SEQ ID NO: 19).

3. An immunoconjugate according to claim 1, wherein the IL-2 polypeptide is a mutant IL-2 polypeptide,
wherein the mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G (numbering relative to the human IL-2 sequence SEQ ID NO: 19); and
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.

4. An immunoconjugate according to claim 1, wherein the IL-2 polypeptide is a mutant IL-2 polypeptide,
wherein the mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G (numbering relative to the human IL-2 sequence SEQ ID NO: 19); and
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.

5. An immunoconjugate according to claim 1, wherein the IL-2 polypeptide is a mutant IL-2 polypeptide,
wherein the mutant IL-2 polypeptide is a human IL-2 molecule comprising the amino acid substitutions F42A, Y45A and L72G (numbering relative to the human IL-2 sequence SEQ ID NO: 19); and
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.

6. The immunoconjugate of any one of claims 2 to 5, wherein the mutant IL-2 polypeptide further comprises the amino acid substitution T3A and/or the amino acid substitution C125A.

7. The immunoconjugate of any one of claims 2 to 6, wherein the mutant IL-2 polypeptide comprises the sequence of SEQ ID NO: 20.

8. The immunoconjugate of any one of claims 2 to 7, wherein the immunoconjugate comprises not more than one mutant IL-2 polypeptide.

9. The immunoconjugate of any one of claims 2 to 8, wherein the antibody comprises an Fc domain composed of a first and a second subunit.

10. The immunoconjugate of claim 9, wherein the Fc domain is an IgG class, particularly an IgG_1 subclass, Fc domain.

11. The immunoconjugate of claim 9 or 10, wherein the Fc domain is a human Fc domain.

12. The immunoconjugate of any one of claims 2 to 11, wherein the antibody is an IgG class, particularly an IgG_1 subclass immunoglobulin.

13. The immunoconjugate of any one of claims 9 to 12, wherein the Fc domain comprises a modification promoting the association of the first and the second subunit of the Fc domain.

14. The immunoconjugate of any one of claims 9 to 13, 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.

15. The immunoconjugate of any one of claims 9 to 14, 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).

16. The immunoconjugate of claim 15, 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).

17. The immunoconjugate of any one of claims 9 to 16, wherein the mutant IL-2 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.

18. The immunoconjugate of claim 17, wherein the linker peptide has the amino acid sequence of SEQ ID NO:21.

19. The immunoconjugate of any one of claims 9 to 17, 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).

20. The immunoconjugate of claim 19, 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).

21. The immunoconjugate of any one of claims 9 to 20, wherein each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329G (Kabat EU index numbering).

22. The immunoconjugate of any one of claims 2 to 21, 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:22, 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:23 or SEQ ID NO:24, 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 the sequence of SEQ ID NO:25.

23. The immunoconjugate of any one of claims 2 to 22, essentially consisting of a mutant IL-2 polypeptide and an IgG_1 immunoglobulin molecule, joined by a linker sequence.

24. One or more isolated polynucleotide encoding the immunoconjugate of any one of claims 2 to 23.

25. One or more vector, particularly expression vector, comprising the polynucleotide(s) of claim 24.

26. A host cell comprising the polynucleotide(s) of claim 24 or the vector(s) of claim 25.

27. A method of producing an immunoconjugate comprising a mutant IL-2 polypeptide and an antibody that binds to PD-1, comprising (a) culturing the host cell of claim 25 under conditions suitable for the expression of the immunoconjugate, and optionally (b) recovering the immunoconjugate.

28. An immunoconjugate comprising a mutant IL-2 polypeptide and an antibody that binds to PD-1, produced by the method of claim 27.

29. A pharmaceutical composition comprising the immunoconjugate of any one of claims 2 to 23 or 28 and a pharmaceutically acceptable carrier.

30. The immunoconjugate of any one of claims 2 to 23 or 28 for use as a medicament.

31. The immunoconjugate of any one of claims 2 to 23 or 28 for use in the treatment of a disease.

32. The immunoconjugate for use in the treatment of a disease of claim 31, wherein said disease is cancer.

33. Use of the immunoconjugate of any one of claims 2 to 23 or 28 in the manufacture of a medicament for the treatment of a disease.

34. The use of claim 33, wherein said disease is cancer.

35. A method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the immunoconjugate of any one of claims 2 to 23 or 28 in a pharmaceutically acceptable form.

36. The method of claim 35, wherein said disease is cancer.

37. A method of stimulating the immune system of an individual, comprising administering to said individual an effective amount of a composition comprising the immunoconjugate of any one of claims 2 to 23 or 28 in a pharmaceutically acceptable form.

38. The invention as described hereinbefore.