CLAIMS

1. A mutant interleukin-2 (IL-2) polypeptide comprising one or more amino acid substitutions, each compared to a wilde-type IL-2, preferably human IL-2 according to SEQ ID NO: 144, wherein the one or more amino acid substitutions abolishes or reduces binding to the IL-2 receptor, preferably to the intermediate-affinity IL-2 receptor (IL2Rβγ), at neutral pH and facilitate binding to the IL-2 receptor, preferably to the intermediate-affinity IL-2 receptor (IL2Rβγ), at decreased pH.

2. The mutant IL-2 polypeptide of claim 1, wherein said one or more amino acid substitutions is at a position selected from the group of positions corresponding to residue 6, 8, 11, 12, 13, 15, 16, 19, 20, 22, 23, 81, 84, 87, 91, 95, 120, 123, 126, 130, 133 of human IL-2 according to SEQ ID NO: 144.

3. The mutant IL-2 polypeptide of claim 1 or 2, wherein said one or more amino acid substitutions is selected from the group of S6Y, K8E, Q11E, Q11T, L12D, L12E, L12Q, L12S, L12T, Q13H, Q13R, E15Q, H16D, H16E, H16N, H16Q, L19D, L19Q, D20E, D20Q, Q22D, Q22E, Q22H, M23E, M23N, M23Q, R81D, R81E, R81H, R81N, R81Q, D84E, D84Q, S87D, S87E, S87N, S87Q, V91D, V91E, V91N, E95D, E95Q, R120E, R120H, T123E, T123Q, Q126E, Q126H, S130E, T133D, T133E, T133N, T133Q.

4. The mutant IL-2 polypetide of any of claims 1 to 3, wherein the mutant IL-2 polypeptide comprises the amino acid substitutions

(i) L12E, D20E, M23N, R81N, D84E, S87E, R120E, T123E, S130E, T133N;

(ii) Q11E, D20Q, M23E, R81D, D84E, S87E, S130E, T133N;

(iii) L12E, L19D, R81D, R120E, T123E, S130E, T133E;

(iv) R81Q, S87E, V91D, T123E, S130E, T133D;

(v) Q11E, L12E, M23Q, R81D, S87E, V91D, S130E, T133Q;

(vi) Q11E, L19D, R81D, D84E, S130E, T133D;

(vii) R81D, D84Q, S87D, V91N, T123Q, S130E, T133D;

(viii) L19D, R81E, D84E, S87Q, R120H, S130E, T133E;

(iix) L19D, M23N, R81D, T133E;

(ix) Q11E, L12E, M23Q, R81Q, S87D, V91N, E95Q, R120H, T123E, S130E, T133E;

(x) L19D, R81E, S130E, T133D;

(xi) R81Q, S87E, V91D, R120E, S130E, T133D;

(xii) L12Q, L19Q, R81H, V91E, T123E, S130E, T133E;

(xiii) K8E, D20E, M23N, R81H, D84Q, S87E, R120H, S130E, T133D;

(xiv) L12E, L19Q, R81H, R120E, T133D;

(xv) H16E, L19D, Q22E, M23Q, R81D, D84E, S87D, R120H, S130E, T133E;

(xvi) Q11E, L12E, H16Q, L19D, Q22E, M23N, R81E, D84E, S87E, R120H, S130E, T133E;

(xvii) Q11E, H16E, L19D, M23E, R81D, S87E, R120H, Q126E, T133D;

(xviii) Q11E, L12S, E15Q, H16N, L19D, M23E, R81E, D84E, S87D, R120H, S130E, T133E;

(xix) Q11E, H16E, M23E, R81N, D84E, S87E, R120H, Q126E, S130E, T133E;

(xx) Q11E, E15Q, H16E, Q22E, M23E, R81H, D84E, S87E, R120H, S130E, T133D;

(xxi) Q11E, L12D, Q13H, E15Q, H16E, Q22E, M23E, R81N, D84E, S87E, R120H, S130E, T133E;

(xxii) Q11E, E15Q, H16E, L19D, R81E, S87E, R120H, S130E, T133E;

(xxiii) H16E, L19D, M23Q, R81N, D84E, S87D, R120H, S130E, T133D;

(xxiv) Q11E, L12T, E15Q, H16E, L19D, Q22H, R81D, D84E, S87E, R120H, S130E, T133E;

(xxv) Q11E, L12T, E15Q, H16E, L19D, Q22H, M23E, R81E, D84E, S87E, R120H, S130E, T133E;

(xxvi) Q11E, E15Q, H16E, L19D, R81E, D84E, S87E, R120H, S130E, T133E;

(xxvii) H16E, Q22E, M23Q, S87N, R120H, S130E, T133E;

(xxviii) H16E, L19D, Q22D, M23Q, R81D, D84E, S87E, R120H, S130E, T133E;

(xxiix) Q11E, L12E, Q13H, E15Q, H16N, L19D, Q22E, M23Q, R81E, D84E, S87D, E95D, R120H, T133E;

(xxix) Q11E, L12T, H16E, L19D, Q22E, R81D, D84E, S87E, R120H, S130E, T133D;

(xxx) Q11T, L12E, E15Q, H16E, L19D, R81D, D84E, S87E, R120E, S130E, T133D;

(xxxi) Q11E, E15Q, H16E, L19D, R81D, D84E, S87E, R120H, S130E, T133E;

(xxxii) Q11E, E15Q, H16E, L19D, R81Q, D84E, S87E, R120H, S130E, T133E;

(xxxiii) Q11E, L12S, H16E, L19D, M23Q, R81D, D84E, S87E, R120H, S130E, T133E;

(xxxiv) S6Y, L12E, Q13R, H16Q, Q22E, M23Q, R81N, D84E, S87E, R120H, S130E, T133D;

(xxxv) H16D, M23N, R81D, D84E, R120H, S130E, T133E;

(xxxvi) Q11E, L12T , H16Q, L19D, M23E, R81D, D84E, S87E, R120H, S130E, T133E;

(xxxvii) Q11E, L12E, H16N, M23N, R81E, D84E, R120H, S130E, T133E;

(xxxviii) E15Q, H16E, L19D, R81D, D84E, S87E;

(xxxix) Q11E, R120H, S130E, T133D; or

(xl) Q11E, R81D, D84E, S87E, R120H, S130E, T133D.

5. The mutant IL-2 polypeptide of any of claims 1 to 4, wherein the mutant IL-2 polypeptide comprises any amino acid substitution selected from the group T3A, F42A, Y45A, L72G, C125A.

6. The mutant IL-2 polypeptide of any of claims 1 to 5, wherein the mutant IL-2 polypeptide comprises the amino acid substitutions F42A, Y45A and L72G.

7. The mutant IL-2 polypeptide of any of claims 1 to 6, wherein the mutant IL-2 polypeptide comprises the amino acid substitutions T3A, F42A, Y45A, L72G and C125A.

8. The mutant IL-2 polypeptide of any one of claims 1 to 7, wherein said mutant IL-2 polypeptide is linked to a non-IL-2 moiety.

9. The mutant IL-2 polypeptide of any one of claims 1 to 8, wherein said mutant IL-2 polypeptide is linked to a first and a second non-IL-2 moiety.

10. The mutant IL-2 polypeptide of claim 9, wherein said mutant IL-2 polypeptide shares a carboxy-terminal peptide bond with said first non-IL-2 moiety and an amino-terminal peptide bond with said second non-IL-2 moiety.

11. The mutant IL-2 polypeptide of any one of claims 8 to 10, wherein said non-IL-2 moiety is an antigen binding moiety or an effector cell binding moiety.

12. An immunoconjugate comprising a mutant IL-2 polypeptide of any one of claims 1 to 7 and an antigen binding moiety or an effector cell binding moiety.

13. The immunoconjugate of claim 12, wherein said mutant IL-2 polypeptide shares an amino- or carboxy-terminal peptide bond with said antigen binding moiety or the effector cell binding moiety.

14. The immunoconjugate of claims 12 or 13, wherein said immunoconjugate comprises a first and a second antigen binding moiety or a first and a second effector cell antigen binding moiety or an antigen binding moiety and an effector cell binding moiety.

15. The immunoconjugate of claim 14,

(i) wherein said mutant IL-2 polypeptide shares an amino- or carboxy-terminal peptide bond with said first antigen binding moiety and said second antigen binding moiety shares an amino- or carboxy-terminal peptide bond with either a) said mutant IL-2 polypeptide or b) said first antigen binding moiety;

(ii) wherein said mutant IL-2 polypeptide shares an amino- or carboxy-terminal peptide bond with said first effector cell binding moiety and said second effector cell binding moiety shares an amino- or carboxy-terminal peptide bond with either a) said mutant IL-2 polypeptide or b) said first effector cell binding moiety;

(iii) wherein said mutant IL-2 polypeptide shares an amino- or carboxy-terminal peptide bond with the antigen binding moiety and the effector cell binding moiety shares an amino- or carboxy-terminal peptide bond with either a) said mutant IL-2 polypeptide or b) said antigen binding moiety; or

(iv) wherein said mutant IL-2 polypeptide shares an amino- or carboxy-terminal peptide bond with the effector cell binding moiety and the antigen binding moiety shares an amino- or carboxy-terminal peptide bond with either a) said mutant IL-2 polypeptide or b) said effector cell binding moiety.

16. The mutant IL-2 polypeptide of claim 11 or the immunoconjugate of any one of claims 12 to 15, wherein said antigen binding moiety ois an antibody or an antibody fragment.

17. The mutant IL-2 polypeptide of claim 11 or the immunoconjugate of any one of claims 12 to 16, wherein said antigen binding moiety and/or said effector cell binding moiety is selected from a Fab molecule and a scFv molecule.

18. The mutant IL-2 polypeptide of claim 11 or the immunoconjugate of any one of claims 12 to 17, wherein said antigen binding moiety and/or said effector cell binding moiety is an immunoglobulin molecule, particularly an IgG molecule.

19. The mutant IL-2 polypeptide of claim 11 or the immunoconjugate of any one of claims 12 to 18, wherein said antigen binding moiety is directed to an antigen presented on a tumor cell or in a tumor cell environment and/or wherein said effector cell binding moiety is directed to an effector cell present in a tumor cell environment in order to achieve cis-targeting.

20. An isolated polynucleotide encoding the mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19.

21. An expression vector comprising the polynucleotide of claim 20.

22. A host cell comprising the polynucleotide of claim 20 or the expression vector of claim 21.

23. A method of producing a mutant IL-2 polypeptide or an immunoconjugate thereof, comprising culturing the host cell of claim 22 under conditions suitable for the expression of the mutant IL-2 polypeptide or the immunoconjugate.

24. A mutant IL-2 polypeptide or immunoconjugate produced by the method of claim 23.

25. A pharmaceutical composition comprising the mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19 or 24 and a pharmaceutically acceptable carrier.

26. The mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19 or 24 for use in the treatment of a disease in an individual in need thereof.

27. The mutant IL-2 polypeptide or immunoconjugate of claim 26, wherein said disease is cancer.

28. Use of the mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19 or 24 for manufacture of a medicament for treating a disease in an individual in need thereof.

29. A method of treating disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19 or 24 in a pharmaceutically acceptable form.

30. The method of claim 29, wherein said disease is cancer.

31. A method of stimulating the immune system of an individual, comprising administering to said individual a effective amount of a composition comprising the mutant IL-2 polypeptide or immunoconjugate of any one of claims 1 to 19 or 24 in a pharmaceutically acceptable form.

~~32. The invention as described hereinbefore.~~