

WHAT IS CLAIMED IS:

1. An engineered human IL-2 polypeptide, which (i) has significantly reduced binding to native human CD122; and which (ii) comprises at least one amino acid substitution with an amino acid other than that of the native protein at residue T51, R81, or comprises amino acid substitution M23A; and (iii) comprises amino acid substitutions at each of E15, H16, L19, D20.
2. The engineered human IL-2 polypeptide of claim 1, wherein the polypeptide comprises one or more amino acid substitutions selected from: [E15D, E15T, E15A, E15S], [H16N, H16Q], [L19V, L19I, L19A], [D20L, D20M], [Q22S, Q22T, Q22E, Q22K, Q22E], [M23A, M23W, M23H, M23Y, M23F, M23Q, M23Y], [G27K, G27S], [R81D, R81Y], [N88E, N88Q], [T51I].
3. The engineered human IL-2 polypeptide of claim 1 or claim 2, wherein the polypeptide comprises amino acid substitutions E15S; H16Q; L19V; and D20L.
4. The engineered human IL-2 polypeptide of any of claims 1-3, further comprising amino acid substitution Q22K.
5. The engineered human IL-2 polypeptide of any of claims 1-4, comprising amino acid substitution T51I.
6. The engineered human IL-2 polypeptide of any of claims 1-5, comprising amino acid substitution R81D or R81Y.
7. The engineered human IL-2 polypeptide of claim 1 comprising a set of amino acid substitutions [E15D, H16N, L19V, D20L, Q22T, M23A].
8. The engineered human IL-2 polypeptide of claim 1 comprising a set of amino acid substitutions[E15D, H16N, L19V, D20L, Q22K, M23A].
9. The engineered human IL-2 polypeptide of claim 1 comprising a set of amino acid substitutions [E15S, H16Q, L19V, D20L, M23Q, R81D, T51I].
10. The engineered human IL-2 polypeptide of claim 1 comprising a set of amino acid substitutions [E15S, H16Q, L19V, D20L,M23Q, R81Y].
11. The engineered human IL-2 polypeptide of any of claims 1-10, wherein the polypeptide binds to and activates an orthogonal human CD122 protein.

12. The engineered human IL-2 polypeptide of claim 11, wherein the orthogonal human CD122 protein is modified at one or more residues selected from R41, R42, Q70, K71, T73, T74, V75, S132, H133, Y134, F135, E136, Q214.

13. The engineered human IL-2 polypeptide of claim 12, wherein the orthogonal human CD122 protein is modified at H133 and Y134.

14. The engineered human IL-2 polypeptide of claim 13, wherein the orthogonal human CD122 protein comprises amino acid substitutions H133D and Y134F.

15. A system for selective activation of a receptor in a cell, the system comprising:

(a) an orthogonal human CD122 receptor comprising amino acid substitutions at H133 and Y134; and

(b) the engineered human IL-2 polypeptide of any of claims 1-10.

16. The system of claim 15, wherein the orthogonal receptor is expressed by a mammalian cell.

17. The system of claim 16, wherein the cell is an immune cell or a stem cell.

18. The system of claim 17, wherein the immune cell is a T cell.

19. The system of claim 18, wherein the T cell is a CAR-T cell.

20. A pharmaceutical composition comprising the engineered human IL-2 polypeptide of any of claims 1-10; and a pharmaceutically acceptable excipient.

21. A nucleic acid encoding the engineered human IL-2 polypeptide of any of claims 1-10.

22. An expression vector comprising the nucleic acid of claim 21.

23. A cell genetically engineered to comprise the vector of claim 22.

24. A method of treating an individual, the method comprising introducing an immune effector cell expressing an orthogonal human CD122 receptor comprising amino acid

substitutions at H133 and Y134, and selectively activating the cell by contacting with an engineered human IL-2 polypeptide according to any of claims 1-10.

25. The method of claim 24, wherein the immune effector cell is a T cell.

26. The method of claim 25, wherein the T cell is a CAR-T cell.

27. The method of any of claims 24-26, wherein the individual is treated for cancer.

28. The method of any of claims 24-26, wherein the individual is treated for autoimmune disease.

29. The method of any of claims 24-26, wherein the individual is treated for infection.

30. A kit comprising the system of claim 15.