immune cell expressing a modified human CD122 comprising one or more STAT3 binding motifs, and administering a human IL2 polypeptide to the individual, thereby activating immune response in the individual. In some embodiments, the modified human CD122 comprises an orthogonal human CD122, and wherein the human IL2 polypeptide is an orthogonal human IL2 polypeptide, and wherein the orthogonal human IL2 polypeptide binds preferentially to and activates the modified human CD122 than to a native human CD122. In some embodiments, the one or more STAT3 binding motifs comprise a sequence of YX1X2Q, wherein X1 and X2 are any amino acid acids. In some embodiments, X1 is selected from the group consisting of L, R, F, and M, and X2 is selected from the group consisting of R, K, H, and P. In some embodiments, the orthogonal human CD122 comprises a sequence selected from the group consisting of GGYLRQ (SEQ ID NO :2), GGYLKQ (SEQ ID NO: 3), GGYRHQ (SEQ ID NO: 4), GGYLRQ (SEQ ID NO: 5), GGYFKQ (SEQ ID NO: 6), GGYLPQ (SEQ ID NO: 7), GGYMPQ (SEQ ID NO: 8), and GGYDKPH (SEQ ID NO: 9). In some embodiments, the immune cell is a T cell. In some embodiments, the T cell is a CAR-T cell. In some embodiments, the immune cell is CD8+ T cells, and wherein the individual has cancer. In some embodiments, the immune cell is Treg cells, and wherein the individual has an autoimmune disease. In some embodiments, the individual has a viral, bacterial or fungal infection.

[0027a] Also provided is a cell comprising the polynucleotide as described herein.

[0027b] Also provided is a use of a human IL2 polypeptide in the manufacture of a medicament for stimulating an immune cell expressing a modified human CD122 comprising one or more STAT3 binding motifs, wherein the human IL2 polypeptide is to be contacted with the immune cell.

[0027c] Also provided is a human IL2 polypeptide for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0028] In order for the present disclosure to be more readily understood, certain terms and phrases are defined below as well as throughout the specification. The definitions provided herein are non-limiting and should be read in view of the knowledge of one of skill in the art would know.

[0029] Before the present methods and compositions are described, it is to be understood that this invention is not limited to particular method or composition described, as such may, of

course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0030] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and

WHAT IS CLAIMED IS:

1. A polynucleotide encoding a modified human CD122, wherein the modified human CD122 comprises one or more STAT3 binding motifs.

2. The polynucleotide of claim 1, wherein the modified human CD122 comprises an orthogonal human CD122 or native human CD122 fused to one or more STAT3 binding motifs.

3. The polynucleotide of claim 2, wherein the orthogonal human CD122 is modified at one or more residues selected from R41, R42, Q70, K71, T73, T74, V75, S132, H133, Y134, F135, E136, and Q214 relative to native human CD122.

4. The polynucleotide of claim 2, wherein the orthogonal human CD122 is modified at H133 and Y134 relative to native human CD122.

5. The polynucleotide of claim 1, wherein the human CD122 is linked to two or three STAT3 binding motifs.

6. The polynucleotide of claim 1, wherein the modified human CD122 comprises a sequence that is at least 90% identical to SEQ ID NO: 1, wherein the modified human CD122 binds to a native IL2 polypeptide or an orthogonal IL2 polypeptide.

7. The polynucleotide of claim 1, wherein the one or more STAT3 binding motifs comprise a sequence of YX1X2Q, wherein X1 and X2 are any amino acid acids.

8. The polynucleotide of claim 7, wherein X1 is selected from the group consisting of L, R, F, M, and X2 is selected from the group consisting of R, K, H, and P.

9. The polynucleotide of claim 7, wherein the STAT3 recognition motif is selected from the group consisting of

(a) YLRQ (SEQ ID NO :11),

(b) YLKQ (SEQ ID NO: 12),

(c) YRHQ (SEQ ID NO: 13)

(d) YLRQ (SEQ ID NO: 14),

(e) YFKQ (SEQ ID NO: 15),

(f) YLPQ (SEQ ID NO: 16),

(g) YMPQ (SEQ ID NO: 17), and

(h) YDKPH (SEQ ID NO: 18).

10. The polynucleotide of claim 1, wherein the one or more STAT3 binding motifs are fused to a C-terminus of the intracellular domain of the native human CD122 or the orthogonal human CD122, optionally through a linker.

11. The polynucleotide of claim 1, wherein at least one of the STAT3 binding motifs is located between position 355 and position 364 corresponding to native human CD122, and wherein the at least one of the STAT3 recognition motif replaces an amino acid sequence of YFTY, YDPY, or YSEE in native human CD122.

12. The polynucleotide of claim 11, wherein the modified human CD122 is further modified at one or more residues selected from R41, R42, Q70, K71, T73, T74, V75, S132, H133, Y134, F135, E136, and Q214 relative to native human CD122.

13. The polynucleotide of claim 10, wherein the linker comprises a dinucleotide GG.

14. The polynucleotide of claim 13, wherein the modified CD122 comprises an amino acid sequence comprising the linker and at least one of the STAT3 binding motifs, wherein the amino acid sequence is selected from the group consisting of:

(i) GGYLRQ (SEQ ID NO :3),

(j) GGYLKQ (SEQ ID NO: 4),

(k) GGYRHQ (SEQ ID NO: 5),

(l) GGYLRQ (SEQ ID NO: 6),

(m) GGYFKQ (SEQ ID NO: 7),

(n) GGYLPQ (SEQ ID NO: 8),

(o) GGYMPQ (SEQ ID NO: 9), and

(p) GGYDKPH (SEQ ID NO: 10).

15. An expression vector comprising the polynucleotide of any one of claim 1-14.

16. A cell comprising the polynucleotide of any one of claims 1-14.

17. The cell of claim 16, wherein the cell further expresses a chimeric antigen receptor (CAR), and wherein the cell is a human immune cell.

18. The cell of claim 17, wherein the CAR is selected from the group consisting of a CD19 CAR and a BCMA CAR.

19. A kit for selective activation of a receptor in a cell, the kit comprising

(a) a cell expressing a modified human CD122 encoded by the polynucleotide of claim 1, and

(b) a human IL2 polypeptide.

20. The kit of claim 19, wherein the modified human CD122 comprises a native human CD122 encoded by SEQ ID NO: 1, and wherein the human IL2 polypeptide is a native human IL2 polypeptide encoded by SEQ ID NO: 2.

21. The kit of claim 19, wherein the modified human CD122 comprises an orthogonal human CD122, wherein the human IL2 polypeptide is an orthologal human IL2 polypeptide, and wherein the orthogonal human IL2 polypeptide binds preferentially to the modified human CD122 compared to a native human CD122.

22. The kit of claim 21, wherein the orthogonal human IL2 polypeptide comprises at least one amino acid substitution with an amino acid other than that of the native human IL2 polypeptide at a position corresponding to native human CD122 residue T51, R81, or comprises an alanine at a position corresponding to native human CD122 M23, and comprises amino acid substitutions at each of a position corresponding to native human CD122 E15, H16, L19, and D20.

23. The kit of claim 19, wherein the the orthogonal human IL2 polypeptide comprises one or more amino acid substitutions corresponding to native human IL2 positions 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].

24. The kit of claim 19, wherein the modified human CD122 is expressed by a mammalian cell.

25. The kit of claim 24, wherein the mammalian cell is an immune cell.

26. The kit of claim 25, wherein the immune cell is a T cell.

27. The kit of claim 26, wherein the T cell is a chimeric antigen receptor (CAR)-T cell.

28. A method of stimulating an immune cell expressing a modified human CD122 comprising one or more STAT3 binding motifs, the method comprising contacting the immune cell with a human IL2 polypeptide.

29. The method of claim 28, wherein the stimulating occurs ex vivo.

30. Use of a human IL2 polypeptide in the manufacture of a medicament for stimulating an immune cell expressing a modified human CD122 comprising one or more STAT3 binding motifs, wherein the human IL2 polypeptide is to be contacted with the immune cell~~The method of claim 28, wherein the stimulating occurs in vivo~~.

31. The method of claim 28, wherein the modified human CD122 comprises a orthogonal human CD122 or native human CD122 fused to one or more STAT3 binding motifs.

32. The method of claim 28, wherein at least one of the STAT3 binding motifs is located between position 381 and position 390 corresponding to native human CD122, and wherein the at least one of the STAT3 binding motifs replaces an amino acid sequence of YFTY, YDPY, or YSEE in the native human CD122.

33. The ~~method~~ use of claim 30, wherein ~~the method comprises introducing to an individual~~ an immune cell expressing a modified human CD122 comprising one or more STAT3 binding motifs is to be introduced to an individual, and ~~administering~~ a human IL2 polypeptide is to be administered to the individual, thereby activating immune response in the individual.

34. The ~~method~~ use of claim 33, wherein the modified human CD122 comprises an orthogonal human CD122, and wherein the human IL2 polypeptide is an orthogonal human IL2 polypeptide, and wherein the orthogonal human IL2 polypeptide binds preferentially to and activates the modified human CD122 than to a native human CD122.

35. The method of claim 28, wherein the one or more STAT3 binding motifs comprise a sequence of YX1X2Q, wherein X1 and X2 are any amino acid acids.

36. The method of claim 35, wherein X1 is selected from the group consisting of L, R, F, and M, and X2 is selected from the group consisting of R, K, H, and P.

37. The method of claim 34, wherein the orthogonal human CD122 comprises a sequence selected from the group consisting of

GGYLRQ (SEQ ID NO :2),

GGYLKQ (SEQ ID NO: 3)

GGYRHQ (SEQ ID NO: 4)

GGYLRQ (SEQ ID NO: 5)

GGYFKQ (SEQ ID NO: 6)

GGYLPQ (SEQ ID NO: 7)

GGYMPQ (SEQ ID NO: 8), and

GGYDKPH (SEQ ID NO: 9).

38. The ~~method~~ use of claim 33, wherein the immune cell is a T cell.

39. The ~~method~~ use of claim 38, wherein the T cell is a CAR-T cell.

40. The ~~method~~ use of any of claims 33-34 or 38-39, or the method of any of claims 35-37~~9~~, wherein the immune cell is CD8+ T cells, and wherein the individual has cancer.

41. The ~~method~~ use of any of claims 33-34 or 38-39, or the method of any of claims 35-37~~9~~ wherein the immune cell is Treg cells, and wherein the individual has an autoimmune disease.

42. The use~~method~~ of any one of claims 33-34 or 38-39, or the method of any of claims 35-37, wherein the individual has a viral, bacterial or fungal infection.

43. A human IL2 polypeptide for use in therapy.