

WHAT IS CLAIMED IS:

1. An orthogonal chimeric receptor polypeptide, comprising:
 - (a) an orthogonal ligand binding domain (oLBD) of an orthogonal receptor which (i) has significantly reduced binding to its native ligand; and which (ii) comprises at least one amino acid substitution relative to the sequence of the native protein;
 - (b) an intracellular domain (ICD) of a second receptor which binds to one or more JAK/STAT proteins and is not the orthogonal receptor; and
 - (c) a transmembrane domain (TMD) that operably joins the oLBD and the ICD.
2. The orthogonal chimeric receptor of claim 1, wherein both the TMD and the ICD are derived from the second receptor.
3. The orthogonal chimeric receptor polypeptide of claim 1 or claim 2, wherein the second receptor is a cytokine receptor.
4. The orthogonal chimeric receptor polypeptide of claim 3, wherein the second receptor is selected from CD121 α ; CDw121 β ; IL-18R α ; IL-18R β ; CD122; CD25; CD124; CD213; CD127; IL-9R; CD21 α 1; CD213 α 2; IL-15R α ; CD131; CD125; CD131; CD126; CD130; IL-11R α ; CD114; CD212; LIFR; OSMR; CD210; IL-20R α , IL-20R β ; IL-14R; CD4; CD217; CD118; CD119; CD40; LT β R; CD120 α ; CD120 β ; CD137 (4-1BB); BCMA, TACI; CD27; CD30; CD95 (Fas); GITR; LT β R; HVEM; OX40; BCMA, TACI; TRAILR1-4; Apo3; RANK, OPG; TGF- β R1; TGF- β R2; TGF- β R3; EpoR; TpoR; Flt-3; CD117; CD115; CDw136;
5. The orthogonal chimeric receptor polypeptide of claim 3 wherein the second receptor is a receptor associated with the common gamma chain (CD132).
6. The orthogonal chimeric receptor polypeptide of claim 5 wherein the second receptor is selected from IL-4 receptor (IL-4R), IL-7 receptor (IL-7R), IL-9 receptor (IL-9R), IL-15R α , IL-21 receptor (IL-21R α).
7. The orthogonal chimeric receptor polypeptide of claim 3 wherein the second receptor is the erythropoietin receptor (EpoR).
8. The orthogonal chimeric receptor polypeptide of any of claims 1-7, wherein the oLBD is an orthogonal variant of the CD122 ligand-binding domain.

9. The orthogonal chimeric receptor polypeptide of claim 8 wherein the CD122 receptor is human CD122 modified at one or more residues selected from R41, R42, Q70, K71, T73, T74, V75, S132, H133, Y134, F135, E136, Q214.

10. The orthogonal chimeric receptor polypeptide of claim 9 wherein the CD122 receptor comprises amino acid substitutions at H133 and Y134.

11. The orthogonal chimeric receptor polypeptide of claim 8 wherein the CD122 receptor is CD122 modified at one or more residues selected from R42, F67, Q71, S72, T74, S75, V76, S133, H134, Y135, I136, E137, R215.

12. The orthogonal chimeric receptor polypeptide of claim 1, comprising an amino acid sequence with at least 75% sequence identity to any of SEQ ID NO:4, 6, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28.

13. The orthogonal chimeric receptor polypeptide of claim 1, comprising an amino acid sequence with at least 95% sequence identity to any of SEQ ID NO:4, 6, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28.

14. A system for selective activation of a receptor in a cell, the system comprising:
(a) an orthogonal chimeric receptor according to any of claims 1-13; and
(b) an engineered orthogonal ligand.

15. The system of claim 14, wherein the orthogonal chimeric receptor is expressed by a mammalian cell.

16. The system of claim 15, wherein the cell is an immune cell or a stem cell.

17. The system of claim 16, wherein the immune cell is a T cell.

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

19. The system of any of claims 14-18, wherein the orthogonal ligand is IL-2.

20. The system of claim 19, wherein the orthologous IL-2 is human IL-2 modified at one or more residues selected from Q13, L14, E15, H16, L19, D20, Q22, M23, G27, and N88.

21. The system of claim 19, wherein the human IL-2 is modified at one or more residues selected from E15, H16, L19, D20, Q22, and M23.

22. The system of claim 19, wherein the orthologous IL-2 is mouse IL-2, modified at one or more residues selected from H27, L28, E29, Q30, M33, D34, Q36, E37, R41, and N103.

23. The system of Claim 19, wherein the mouse IL-2 is modified at one or more residues selected from E29, Q30, M33, D34, Q36, and E37.

24. A nucleic acid encoding the orthologous chimeric receptor of any of claims 1-13.

25. An expression vector comprising the nucleic acid of claim 24.

26. A cell genetically engineered to comprise the vector of claim 25.

27. A method of treating an individual, the method comprising introducing an immune effector cell expressing an orthogonal chimeric receptor according to any of claim 1-13 and selectively activating the cell by contacting with an orthologous ligand.

28. The method of claim 27, wherein the immune effector cell is a T cell.

29. The method of claim 28, wherein the T cell is a CAR T cell.

30. The method of any of claims 27-29, wherein the individual is treated for cancer.

31. The method of any of claims 27-29, wherein the individual is treated for autoimmune disease.

32. The method of any of claims 27-29, wherein the individual is treated for infection.

33. A kit comprising the system of claim 14.