

CLAIMS

1. An inducible chimeric cytokine receptor comprising at least two identical polypeptide monomers each comprising an N-terminal to C-terminal orientation of:

an FK506 Binding Protein (FKBP) extracellular dimerization domain comprising the amino acid sequence of SEQ ID NO: 218;

an intracellular tyrosine kinase activating domain comprising the wild-type thrombopoietin receptor (TPOR/MPLR) tyrosine kinase activating domain amino acid sequence of SEQ ID NO: 96; and

an intracellular tyrosine effector domain comprising at least two STAT-activation domains obtained from two cytokine receptors,

wherein the at least two STAT-activation domains comprise the interleukin-7 receptor (IL7R) amino acid sequence of SEQ ID NO: 134 and the interleukin-12 receptor b2 (IL12Rb2) amino acid sequence of SEQ ID NO: 155 in tandem.
2. The inducible chimeric cytokine receptor of claim 1, wherein the extracellular dimerization domain binds to a ligand AP1903, AP20187, dimeric FK506, or a dimeric FK506-like analog.
3. The inducible chimeric cytokine receptor of claim 1, wherein the inducible chimeric cytokine receptor comprises a membrane-targeting motif.
4. The inducible chimeric cytokine receptor of claim 3, wherein the membrane-targeting motif comprises a myristoylation motif.
5. The inducible chimeric cytokine receptor of one of claim 1, wherein the receptor is myristoylated.
6. The inducible chimeric cytokine receptor of claim 1, wherein each polypeptide monomer comprises the sequence of SEQ ID NO: 46.
7. The inducible chimeric cytokine receptor of claim 1, wherein each polypeptide monomer comprises the sequence of SEQ ID NO: 19.

8. The inducible chimeric cytokine receptor of claim 1, wherein each polypeptide monomer comprises the sequence of SEQ ID NO: 243.
9. A polynucleotide comprising a nucleic acid sequence encoding the inducible chimeric cytokine receptor of any one of claims 1-8.
10. An expression vector comprising the polynucleotide of claim 9.
11. An engineered immune cell comprising at least one inducible chimeric cytokine receptor of any one of claims 1-8 or at least one polynucleotide of claim 9.
12. The engineered immune cell of claim 11, wherein the cell comprises at least two inducible chimeric cytokine receptors of any one of claims 1-8 or at least two polynucleotides of claim 9.
13. The engineered immune cell of claim 11 or 12, wherein the cell comprises at least three or four inducible chimeric cytokine receptors of any one of claims 1-8 or at least three or four polynucleotides of claim 9.
14. The engineered immune cell of any one of claims 11-13, wherein, when more than one inducible chimeric cytokine receptor is present, the dimerization domain, the tyrosine kinase activating domain, and the tyrosine effector domain of each receptor can be the same or different.
15. The engineered immune cell of any one of claims 11-14, wherein the cell further comprises a chimeric antigen receptor (CAR) or a polynucleotide encoding a CAR.
16. The engineered immune cell of any one of claims 11-15, wherein the immune cell is selected from the group consisting of: T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell.
17. The engineered immune cell of any one of claims 11-16, wherein the immune cell is a T cell.
18. A method of preparing an engineered immune cell, the method comprising introducing a polynucleotide of claim 9 or an expression vector of claim 10 into an immune cell.

19. The method of claim 18, wherein the immune cell is selected from the group consisting of: T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell.
20. The method of claim 18 or 19, wherein the immune cell is a T cell.
21. An isolated immune cell comprising:
 - (i) at least one inducible chimeric cytokine receptor of any one of claims 1-8; and
 - (ii) a chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain, a transmembrane domain, and an intracellular signaling domain.
22. The isolated immune cell of claim 21, wherein cell comprises at least two, three, or four inducible chimeric cytokine receptors.
23. The isolated immune cell of claim 21, wherein the extracellular ligand binding domain of the CAR specifically binds BCMA, EGFRvIII, Flt-3, WT-1, CD20, CD23, CD30, CD38, CD70, CD33, CD133, LeY, NKG2D, CS1, CD44v6, ROR1, CD19, Claudin-18.2 (Claudin-18A2, or Claudin18 isoform 2), DLL3 (Delta-like protein 3, Drosophila Delta homolog 3, Delta3), Muc17 (Mucin17, Muc3, Muc3), FAP alpha (Fibroblast Activation Protein alpha), Ly6G6D (Lymphocyte antigen 6 complex locus protein G6d, c6orf23, G6D, MEGT1, NG25), RNF43 (E3 ubiquitin-protein ligase RNF43, or RING finger protein 43).
24. The isolated immune cell of any one of claims 21-23, wherein the immune cell is selected from the group consisting of: T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell.
25. The isolated immune cell of any one of claims 21-24, wherein the immune cell is a T cell.
26. The isolated immune cell of any one of claims 21-25, wherein the isolated immune cell exhibits improved persistence upon contact with a ligand that binds to the dimerization domain relative to persistence of an isolated immune cell that does not express the inducible chimeric cytokine receptor.

27. The isolated immune cell of any one of claims 21-26, wherein the isolated immune cell exhibits increased activation of STAT upon contact with a ligand that binds to the dimerization domain relative to activation of STAT exhibited by an isolated immune cell that does not express the inducible chimeric cytokine receptor.
28. The isolated immune cell of claim 27, wherein the activation of STAT by the isolated immune cell, upon contact with a ligand that binds to the dimerization domain, increases with the dose of the ligand compared to activation of STAT shown by the isolated immune cell that does not express the inducible chimeric cytokine receptor.
29. The isolated immune cell of any one of claims 21-28, wherein the isolated immune cell exhibits increased cytotoxicity upon contact with a ligand that binds to the dimerization domain compared to cytotoxicity exhibited by an isolated immune cell that does not express the inducible chimeric cytokine receptor.
30. The isolated immune cell of any one of claims 21-29, wherein the isolated immune cell expands upon contact with a ligand that binds to the dimerization domain compared to an isolated immune cell that does not express the inducible chimeric cytokine receptor.
31. The isolated immune cell of any one of claims 21-30, wherein the level of cell markers for stem cell memory (Tscm) and/or central memory (Tcm) on the isolated immune cell are increased or maintained upon contact with a ligand that binds to the dimerization domain compared to the level of these markers on an isolated immune cell that does not express the inducible chimeric cytokine receptor.
32. The isolated immune cell of any one of claims 21-31, wherein the isolated immune cell is a T cell.
33. A method of generating an isolated immune cell comprising an inducible chimeric cytokine receptor of any one of claims 1-8, wherein the method comprises the steps of:
 - (a) providing an immune cell;
 - (b) introducing into the immune cell a polynucleotide that encodes a chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain, a transmembrane domain, and an intracellular signaling domain; and

- (c) introducing into the immune cell a polynucleotide that encodes the inducible chimeric cytokine receptor.
34. The method of claim 33, wherein step c) comprises stably expressing the inducible chimeric cytokine receptor into the cell.
 35. The method of claim 33 or 34, wherein in step c), the polynucleotide that encodes the inducible chimeric cytokine receptor is introduced into the cell by a transposon/transposase system, a viral-based gene transfer system, or electroporation.
 36. The method of any one of claims 33-35, wherein in step b), the polynucleotide that encodes the chimeric antigen receptor is introduced into the cell by a transposon/transposase system or a viral-based gene transfer system.
 37. The method of claim 35 or 36, wherein the viral-based gene transfer system comprises recombinant retrovirus or lentivirus.
 38. The method of any one of claims 33-37, wherein step (b) occurs prior to step (c).
 39. The method of any one of claims 33-37, wherein step (c) occurs prior to step (b).
 40. The method of any one of claims 33-39, wherein the immune cell is selected from the group consisting of: T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell.
 41. The method of any one of claims 33-40, wherein the immune cell is a T cell.
 42. A pharmaceutical composition comprising the isolated immune cell of any one of claims 21-32.
 43. Use of the isolated immune cell of any one of claims 21-32 or the pharmaceutical composition of claim 42 in the manufacture of a medicament for treating a disorder in a subject, wherein the disorder is a viral disease, a bacterial disease, a cancer, an inflammatory disease, an immune disease, or an aging- associated disease.
 44. The use of claim 43, wherein the medicament are to be provided to the subject more than once.

45. The use of claim 43 or 44, wherein the medicament are to be provided to the subject at least about 1, 2, 3, 4, 5, 6, 7, or more days apart.
46. The use of any one of claims 43-45, wherein the subject is one that has been previously treated with a therapeutic agent prior to administration of the medicament.
47. The use of claim 46, wherein the therapeutic agent is an antibody or chemotherapeutic agent.
48. The use according to claim 43, wherein the cancer is a hematological malignancy or a solid cancer.
49. The use according to claim 48, wherein the hematological malignancy is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia (CEL), myelodysplasia syndrome (MDS), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM).
50. The use according to claim 48, wherein the solid cancer is selected from biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, breast cancer, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, lung cancer, malignant melanoma, osteosarcoma, ovarian cancer, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, or uterine cancer.
51. The engineered immune cell of any one of claims 11-17, wherein the cell is an autologous T cell.
52. The engineered immune cell of any one of claims 11-17, wherein the cell is an allogeneic T cell.
53. The isolated immune cell of any one of claims 21-32, wherein the cell is an autologous T cell.

54. The isolated immune cell of any one of claims 21-32, wherein the cell is an allogeneic T cell.