[0013] In one example, there is a polynucleotide that encodes an engineered cytokine receptor polypeptide, and the polypeptide comprises the following operably linked components: a) one or more cytokine receptor endodomains; b) a transmembrane domain that comprises one or more mutations that promote homodimerization of the engineered receptor; and c) optionally, or not, one or more extracellular domains that are not an endogenous extracellular domain for the corresponding one or more cytokine receptor endodomains in component a), wherein the extracellular domain is not derived from a cytokine receptor. In certain examples there are one or more cells that comprise such a polynucleotide.

[0013a] In one aspect, the present disclosure refers to a polynucleotide that encodes an engineered cytokine receptor polypeptide, said polypeptide comprising the following components: a) one or more cytokine receptor endodomains; b) a transmembrane domain derived from the transmembrane domain of interleukin-7 (IL-7) cytokine receptor alpha that comprises one or more mutations that promote homodimerization of the receptor polypeptide, wherein the mutations comprise at least the introduction of one cysteine into the transmembrane domain, or the introduction of one proline into the transmembrane domain, or both; and c) one or more extracellular domains that are not an endogenous extracellular domain for the corresponding one or more cytokine receptor endodomains in component a), wherein the extracellular domain is not derived from an interleukin receptor, wherein the extracellular domain provides protein stabilization, permits identification, or a combination thereof; wherein the transmembrane domain facilitates signaling regardless of the extracellular domain binding to a ligand.

[0013b] In another aspect, the present disclosure refers to a polynucleotide that encodes an engineered cytokine receptor polypeptide, said polypeptide comprising the following components: a) one or more cytokine receptor endodomains; b) a transmembrane domain that comprises one or more mutations that promote homodimerization of the receptor polypeptide; and c) one or more extracellular domains that are not an endogenous extracellular domain for the corresponding one or more cytokine receptor endodomains in component a), wherein the extracellular domain is not derived from an interleukin receptor, and wherein the extracellular domain is a decoy receptor that lacks signal transmission activity, and wherein the transmembrane domain comprises the sequence selected from the group consisting of SEQ ID NO:2 through SEQ ID NO:24.

[0013c] In another aspect, the present disclosure refers to a polypeptide encoded by the polynucleotide as described herein.

[0014] In certain examples, one or more cytokine receptor endodomains elicits signaling through a STAT5 pathway in the cell or a STAT3 pathway in the cell. In specific cases, a cytokine receptor endodomain is from IL-7 receptor alpha, IL-21 receptor alpha, CD122, IL-23 receptor alpha, IL-12 receptor alpha, or a combination thereof.

[0020a] In another aspect, the present disclosure refers to use of an immune cell expressing (1) a chimeric antigen receptor that targets said tumor antigen; and (2) a constitutively-active cytokine receptor in the manufacture of a medicament for treating cancer in an individual, wherein the cancer expresses a tumor antigen, wherein the constitutively-active cytokine receptor comprises a transmembrane domain that comprises one or more mutations that promote homodimerization of the receptor polypeptide, wherein the mutations comprise at least the introduction of one cysteine into the transmembrane domain, or the introduction of one proline into the transmembrane domain, or both, wherein the transmembrane domain is derived from IL-7 cytokine receptor alpha.

[0021] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description of the disclosure that follows may be better understood. Additional features and advantages of the disclosure will be described hereinafter which form the subject of the claims of the disclosure. It should be appreciated by those skilled in the art that the conception and specific example disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present disclosure. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the disclosure as set forth in the appended claims. The novel features which are believed to be characteristic of the disclosure, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] For a more complete understanding of the present invention, reference is now made to the following descriptions taken in conjunction with the accompanying drawings.

[0023] FIG. 1: Scheme of normal IL-7 cytokine/receptor signaling.

[0024] FIG. 2: Scheme of signaling at the IL7RP2 receptor.

[0025] FIG. 3: Scheme of signaling in the Δ34.IL7RP2 protein.

[0026] FIGS. 4A and 4B: STAT5 is constitutively active in IL7RP2-transduced T-cells. FIG. 4A is data from a representative donor, and FIG. 4B is the average results of three donors.

[0027] FIG. 5: IL7RP2-transduced, antigen-specific T-cells have greater proliferative potential then unmodified, antigen-specific T-cells after antigen-specific stimulation.

[0028] FIGS. 6A, 6B, and 6C: GD2.CAR T-cells co-expressing Δ34.IL7RP2 have greater expansion and anti-tumor efficacy then GD2.CAR T-cells *in vivo*. GD2.CAR- Δ34.IL7RP2 T-cells significantly expanded *in vivo* and demonstrated prolonged T-cell persistence at the tumor site in comparison to GD2.CAR T-cells (FIG. 6A). LAN-1 tumors outgrew in mice receiving

CLAIMS

What is claimed is:

1. A polynucleotide that encodes an engineered cytokine receptor polypeptide, said polypeptide comprising the following components:

   a) one or more cytokine receptor endodomains;

   b) a transmembrane domain derived from the transmembrane domain of interleukin-7 (IL-7) cytokine receptor alpha that comprises one or more mutations that promote homodimerization of the receptor polypeptide, wherein the mutations comprise at least the introduction of one cysteine into the transmembrane domain, or the introduction of one proline into the transmembrane domain, or both; and

   c) one or more extracellular domains that are not an endogenous extracellular domain for the corresponding one or more cytokine receptor endodomains in component a), wherein the extracellular domain is not derived from an interleukin receptor, wherein the extracellular domain provides protein stabilization, permits identification, or a combination thereof;

   wherein the transmembrane domain facilitates signaling regardless of the extracellular domain binding to a ligand.

2. A cell comprising the polynucleotide of claim 1.

3. The cell of claim 2, wherein the one or more cytokine receptor endodomains elicits signaling through a STAT5 pathway in the cell.

4. The cell of claim 2, wherein the one or more cytokine receptor endodomains elicits signaling through a STAT3 pathway in the cell.

5. The cell of any one of claims 2-4, wherein the cytokine receptor endodomain is from IL-7 cytokine receptor alpha, IL-21 cytokine receptor alpha, CD122, IL-23 cytokine receptor alpha, IL-12 cytokine receptor alpha, or a combination thereof.

6. The cell of any one of claims 2-5, wherein the transmembrane domain is self-oligomerizing.

7. The cell of any one of claims 2-6, wherein the transmembrane domain is the endogenous transmembrane domain of IL-7 cytokine receptor alpha or that is a self-activating derivative thereof.

8. The cell of claim 7, wherein the self-activating derivative comprises one or more mutations compared to the corresponding wildtype transmembrane domain.

9. The cell of claim 8, wherein the one or more mutations renders the receptor able to homodimerize through the transmembrane and endodomain components.

10. The cell of claim 8, wherein the one or more mutations renders the transmembrane and endodomain able to structurally twist such that janus kinases associated with the endodomains are oriented to permit cross phosphorylation and activation.

11. The cell of claim 8, wherein the one or more mutations renders the transmembrane and endodomain able to structurally twist collectively in a helical manner.

12. The cell of any one of claims 8-11, wherein the transmembrane domain is the IL-7 cytokine receptor alpha transmembrane domain comprising one or more mutations compared to the corresponding IL-7 cytokine receptor alpha transmembrane domain.

13. The cell of any one of claims 8-12, wherein when the transmembrane domain is from IL-7 cytokine receptor alpha, the mutation is in the sequence PILLTISILSFFSVALLVILACVLW (SEQ ID NO:1).

14. The cell of any one of claims 6-13, wherein the transmembrane domain is 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 amino acids in length.

15. The cell of any one of claims 2-14, wherein the extracellular domain is globular in form.

16. The cell of any one of claims 2-15, wherein the extracellular domain is a decoy receptor that lacks signal transmission activity.

17. The cell of claim 16, wherein the decoy receptor comprises a constitutively-active cytokine receptor in which the extracellular domain is or comprises an extracellular domain from PD-1 or B7.

18. The cell of any one of claims 2-17, wherein the extracellular domain is the extracellular domain of CD34.

19. The cell of any one of claims 2-10, wherein the length of the extracellular domain is at least 70 amino acids.

20. The cell of any one of claims 2-19, wherein the length of the extracellular domain is no more than 2000 amino acids.

21. The cell of any one of claims 2-20, wherein the length of the extracellular domain is between 70-2000 amino acids, 100-1000 amino acids, 500-2000 amino acids, 50-500 amino acids, 100-750 amino acids, 200-2000 amino acids, or 500-2000 amino acids.

22. The cell of any one of claims 2-21, wherein the extracellular domain is from PD-1 CD30, HER2, EGFR, CD19, CD34, TGF-beta receptor, LAG3, TIGIT, CTLA4, FAS, CD19, CD27, CD28, CD52, CD134, CD137, HER2, EGFR, or NGFR.

23. The cell of any one of claims 2-22, wherein the cell is an immune cell.

24. The cell of any one of claims 2-22, wherein the cell is a T-cell, a NK cell, a NKT cell, αβ cell, γδ T-cell, a Mucosa Associated Invariant T-cell (MAIT T-cell), innate lymphoid cell, a stem cell, or a progenitor cell.

25. The cell of any one of claims 2-24, wherein the cell comprises a non-natural molecule that confers antigen specificity for the cell.

26. The cell of any one of claims 2-25, wherein the cell further comprises at least one additional engineered receptor.

27. The cell of claim 26, wherein the additional engineered receptor is a constitutively active cytokine receptor, a chimeric antigen receptor, a recombinant T-cell receptor, a bispecific T-cell engager (BiTE or T-cell ENG), Dual-Affinity Re-Targeting (DART) protein, or a combination thereof.

28. The cell of any one of claims 2-27, wherein the cell is a T-cell that comprises at least one chimeric antigen receptor.

29. The cell of any one of claims 2-28, wherein the polynucleotide is further defined as an expression vector.

30. The cell of claim 29, wherein the expression vector is a viral vector or a non-viral vector.

31. The cell of claim 30, wherein the viral vector is a retroviral, lentiviral, adenoviral, or adeno-associated viral vector.

32. The cell of any one of claims 1-31, wherein the transmembrane domain comprises the sequence selected from the group consisting of SEQ ID NO:2 through SEQ ID NO:24.

33. A plurality of cells of any one of claims 2-32, wherein the cells comprise a mixture of one or more of a T-cell, a NK cell, a NKT cell, an αβ T-cell, a γδ T-cell, a Mucosa Associated Invariant T-cell (MAIT T-cell), innate lymphoid cell, a stem cell, a progenitor cell, or an immune effector cell.

34. An in vitro method of expanding a population of cells, comprising the step of expressing the polynucleotide in the cell of any one of claims 2-32.

35. A polynucleotide that encodes an engineered cytokine receptor polypeptide, said polypeptide comprising the following components:

a) one or more cytokine receptor endodomains;

b) a transmembrane domain that comprises one or more mutations that promote homodimerization of the receptor polypeptide; and

c) one or more extracellular domains that are not an endogenous extracellular domain for the corresponding one or more cytokine receptor endodomains in component a), wherein the extracellular domain is not derived from an interleukin receptor, and wherein the extracellular domain is a decoy receptor that lacks signal transmission activity, and

wherein the transmembrane domain comprises the sequence selected from the group consisting of SEQ ID NO:2 through SEQ ID NO:24.

36. The polynucleotide of claim 35, wherein the extracellular domain is or comprises an extracellular domain from PD-1 or B7.

37. A polypeptide encoded by the polynucleotide of claim 35 or 36.

38. A cell comprising the polynucleotide of claim 35 or 36.

39. Use of an immune cell expressing (1) a chimeric antigen receptor that targets said tumor antigen; and (2) a constitutively-active cytokine receptor in the manufacture of a medicament for treating cancer in an individual, wherein the cancer expresses a tumor antigen, wherein the constitutively-active cytokine receptor comprises a transmembrane domain that comprises one or more mutations that promote homodimerization of the receptor polypeptide, wherein the mutations comprise at least the introduction of one cysteine into the transmembrane domain, or the introduction of one proline into the transmembrane domain, or both, wherein the transmembrane domain is derived from IL-7 cytokine receptor alpha.
40. The use of claim 39, wherein said constitutively-active cytokine receptor comprises an interleukin-7 (IL-7) receptor endodomain and a transmembrane domain that promotes homodimerization of the cytokine receptor such that said cytokine receptor is constitutively active.
41. The use of claim 40, wherein said transmembrane domain comprises the sequence of any of SEQ ID NOS:2-24.
42. The use of any of claims 39-41, wherein said constitutively-active cytokine receptor comprises an extracellular domain that does not transmit a signal when the cognate cytokine binds to said extracellular domain.
43. The use of claim 42, wherein said constitutively-active cytokine receptor comprises an IL-7 receptor endodomain, and the cognate cytokine is IL-7.
44. The use of claim 42 or claim 43, wherein the extracellular domain is an extracellular domain from CD34.
45. The use of claim 42 or claim 43, wherein the extracellular domain is an extracellular domain from PD-1 or B7.
46. The use of any of claims 39-45, wherein the cancer is glioblastoma.
47. The use of any of claims 39-46, wherein said tumor antigen is GD2.
48. The use of any of claims 39-46, wherein said tumor antigen is EphA2.

49. The use of any of claims 39-46, wherein said tumor antigen is EphA3, HER2 (ERBB2), GD2, Glypican-3, 5T4, 8H9, αvβ6 integrin, B cell maturation antigen (BCMA) B7-H3, B7-H6, CAIX, CA9, CD19, CD20, CD22, kappa light chain, CD30, CD33, CD38, CD44, CD44v6, CD44v7/8, CD70, CD96, CD123, CD138, CD171, CEA, CLL-1, CSPG4, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, ERBB3, ERBB4, ErbB3/4, FAP, FAR, FBP, fetal AchR, Folate Receptor α, GD2, GD3, HLA-AI MAGE A1, HLA-A2, IL13Ra2, KDR, Lambda, Lewis-Y, MCSP, Mesothelin, Muc1, Muc16, NCAM, NKG2D ligands, NY-ESO-1, PRAME, PSCA, PSC1, ROR1, Sp17, TAG72, TEM8, Tn-O-glycopeptide, VEGFR2, carcinoembryonic antigen, HMW-MAA, VEGF receptors, TSHR, CS- 1, CMA, Tn Ag, prostate specific membrane antigen (PSMA), FLT3, CD44v6, KIT, interleukin- 11 receptor a (IL-l lRa), PRSS21, VEGFR2, CD24, platelet-derived growth factor receptor- beta (PDGFR-beta), SSEA-4, ERBB2 (Her2/neu), Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gplOO, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, GPRC5D, CXORF61 , CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1 , UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, LAGE-la, MAGE-Al, legumain, HPV E6,E7, MAGE Al, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1 , p53, p53 mutant, prostein, survivin and telomerase, PCTA-l/Galectin 8, MelanA/MARTl, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B 1 , MYCN, RhoC, TRP-2, CYP1B 1, BORIS, SART3, PAX5, OY-TES 1 , LCK, AKAP-4, SSX2, RAGE-1 , human telomerase reverse transcriptase, RUl, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, or lGLL1.

50. The use of any of claims 39-45 or 49, wherein the cancer is breast cancer, prostate cancer, lung cancer, brain cancer, colon cancer, head and neck cancer, skin cancer, ovarian cancer, endometrial cancer, cervix cancer, kidney cancer, lung cancer, gastric cancer, cancer of the small intestine, liver cancer, pancreatic cancer, gall bladder cancer, a cancer of the bile duct, esophageal cancer, cancer of the salivary glands or cancer of the thyroid gland.