CONSTITUTIVELY ACTIVE CYTOKINE RECEPTORS FOR CELL THERAPY

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 62/380,021, filed August 26, 2016, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] Embodiments of the disclosure include at least the fields of cell biology, molecular biology, immunology, and medicine, including at least cancer medicine.

BACKGROUND

[0003] Cell therapy with antigen-specific T-cells has shown promise in preclinical models and early phase clinical trials, however few patients with bulky disease have been cured. This lack of efficacy is because of several factors, including limited *in vivo* T-cell expansion post-infusion. Lymphodepleting patients prior to T-cell transfer with chemotherapy and/or radiation greatly enhances *in vivo* T-cell expansion, however these agents have unwanted side effects. There is needed a means for enabling T-cell expansion without such toxic agents.

[0004] The present disclosure satisfies a need in the art to provide methods and compositions for safely enhancing T-cell expansion *in vivo*.

SUMMARY

[0005] Examples of the disclosure concern methods and compositions for enhancing immune cell expansion and/or proliferation, including *in vivo* following infusion. In specific cases, T-cells express a particular constitutively active cytokine receptor molecule to facilitate expansion of the T-cells *in vivo* for use as a therapy for a medical condition, including cancer. The constitutively active cytokine receptor comprises at least one endodomain, a transmembrane domain, and at least one exodomain, in specific examples.

[0006] Disclosed are engineered cytokine receptor polypeptides that homodimerize and facilitate downstream signaling without need for binding of the relevant cytokine. A common feature of such engineered cytokine receptors is that they are engineered to comprise one or more mutations, *e.g.*, in the transmembrane domain, that cause or facilitate homodimerization, and therefore signaling, in the absence of binding of the cognate cytokine.

As such, with respect to cytokine signaling, they are constitutively active (that is, the mutations are "gain-of-function" mutations).

[0007] In particular cases, the engineered cytokine receptor polypeptide is constitutively active because the transmembrane domain of the receptor comprises one or more mutations that permit the receptor to homodimerize such that an external signal, *e.g.*, a cytokine, is not required to activate the transmembrane domain and endodomains. In at least some cases, the one or more mutations in the transmembrane domain impart a structural configuration to the transmembrane domain/endodomain that positions the molecule in closer proximity to a desired target molecule through which their signal acts. In specific examples, the mutation in the transmembrane domain is or comprises insertion of at least one cysteine in the transmembrane domain amino acid sequence to allow a disulfide bridge to form (thereby facilitating homodimerization of the polypeptide) and/or includes insertion of at least one proline to induce a conformational change (for example, to cause the molecule to kink or twist or rotate about an axis through the receptor molecule), both of which mutations would structurally impact the nature of the molecule and therefore its signaling.

[0008] In specific examples, the transmembrane domain is a IL-7 cytokine receptor alpha transmembrane domain comprising one or more mutations compared to the corresponding wildtype IL-7 cytokine receptor alpha transmembrane domain. In a specific example, when the transmembrane domain is from IL-7 cytokine receptor alpha, the mutation is in the sequence LLTISILSFFSVALLVILACVLW (SEQ ID NO:25). In specific examples, the mutation introduces at least one cysteine into the transmembrane domain and/or the mutation introduces a proline into the transmembrane domain. The transmembrane domain is 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33 amino acids in length, in some cases.

[0009] In particular examples of the transmembrane domain, the domain is self-dimerizing, and in specific cases the transmembrane domain is the endogenous transmembrane domain of the one or more cytokine receptor endodomains of the disclosure or that is a self-activating derivative thereof. A self-activating derivative may comprise one or more mutations compared to the corresponding wildtype transmembrane domain, and the one or more mutations renders the receptor able to homodimerize. In specific cases the mutation(s) render the receptor able to homodimerize through the transmembrane and endodomain components. In specific examples, the one or more mutations renders the transmembrane and endodomain able to

structurally orient (such as twist) such that janus kinases are able to phosphorylate and activate the endodomains/polypeptides, for example. In specific examples, the one or more mutations renders the transmembrane and endodomain able to structurally twist collectively in a helical manner.

[0010] In certain examples, the engineered cytokine receptor polypeptide comprises at least one endodomain, at least one transmembrane domain and at least one exodomain, and optionally comprises one or more exodomains. In some examples, the endodomain is wild-type, that is, is functionally active with respect to cytokine signaling. In a specific example, the engineered cytokine receptor polypeptide comprises a normal (wild-type) exodomain; in this example, the polypeptide homodimerizes, and transmits a signal, in the presence or absence of the cognate cytokine. In another specific example, the engineered cytokine receptor polypeptide comprises an exodomain that is not a wild-type exodomain for such a receptor. In more specific examples, the exodomain binds a ligand that would normally be deleterious to the cell in which the receptor resides (for example, a ligand that normally would downregulate the cell or cause anergy of the cell or cause apoptosis of the cell). For example, such a non-wild-type exodomain can be, or can serve as, a decoy receptor for, *e.g.*, a checkpoint protein; *e.g.*, the exodomain comprises a receptor for the checkpoint protein PD-1. In some cases, the non-wild-type exodomain is a target for an antibody that, when bound to the exodomain, targets a cell comprising the engineered cytokine receptor polypeptide for destruction. In another specific example, the engineered cytokine receptor polypeptide lacks an exodomain. In certain examples, the cytokine is an interleukin, such as IL-7, IL-21, IL-23, or IL-12.

[0011] In specific examples of the disclosure, a constitutively active cytokine receptor induces constitutive IL-7 receptor activity. In certain examples, one or more mutations or alterations in the transmembrane domain of IL-7Rα renders the receptor able to induce signaling in a homo-dimerization state. In a specific example, the interleukin is IL-7. In a specific example, the engineered cytokine receptor polypeptide is an engineered IL-7 receptor polypeptide.

[0012] In other examples, provided herein are polynucleotides that encode such engineered cytokine receptor polypeptides, cells that comprise such polynucleotides, cells that express such polypeptides, *e.g.*, cells that additionally express a chimeric antigen receptor, and the uses of such cells to treat disease, *e.g.*, cancer (*e.g.*, a blood cancer or a solid tumor).

[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 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 a cytokine 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.

[0015] In one example, an extracellular domain is globular in form. The extracellular domain may be a decoy receptor that lacks signal transmission activity. The extracellular domain may be the target of a cytotoxic antibody. In specific cases, the extracellular domain is at least 70 amino acids and/or no more than 2000 amino acids. The length of the extracellular domain may be 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. In some cases, the extracellular domain is the extracellular domain of CD34. In certain examples, the extracellular domain is from CD30, HER2, EGFR, CD19, CD34, TGF-beta receptor, IL-4 receptor, IL-13 receptor alpha1 and alpha 2, IL-8 receptor, IL-10 receptor, PD-1, LAG3, TIGIT, CTLA4, FAS, CD19, CD27, CD28, CD52, CD134, CD137, HER2, EGFR, NGFR, or a combination thereof.

[0016] In particular examples, a cell(s) expressing a constitutively active cytokine receptor is an immune cell. The cell may be a T-cell, a NK cell, a NK T-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. In specific examples, the cell comprises a non-natural molecule that confers antigen specificity for the cell. The cell may further comprise at least one additional engineered receptor, for example another 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.

[0016a] In another aspect, the present disclosure refers to a cell comprising the polynucleotide as described herein.

[0017] In some examples related to cells expressing the constitutively active cytokine receptor, the cell harbors a polynucleotide that expresses a receptor polypeptide. The polynucleotide may be further defined as an expression vector, such as a viral vector or a non-viral vector. A viral vector may be a retroviral, lentiviral, adenoviral, or adeno-associated viral vector. A non-viral vector may be a plasmid, for example.

[0018] In an example, there is a plurality of cells of the disclosure that express a constitutively active cytokine receptor, wherein the cells comprise a mixture of one or more of a T-cell, a NK cell, a NK T-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.

[0018a] In another aspect, the present disclosure refers to a plurality of cells as described herein, 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.

[0019] In one example, there is a method of expanding a population of cells, comprising the step of expressing the polynucleotide in a cell encompassed by the disclosure. The cell may be *in vitro* or *in vivo*, such as in a mammal, including a human. In specific examples, the human is provided an effective amount of one or more inhibitors of the extracellular domain that upon binding to the extracellular domain target the cell for destruction. The inhibitor may be one or more antibodies of any kind. In certain examples, the human is in need of therapy and a therapeutically effective amount of cells is provided to the human. In specific examples, the human has cancer, an infectious disease, an autoimmune disease, an immunodeficiency, or is pre- or post-solid organ transplantation or stem cell transplantation.

[0019a] In another aspect, the present disclosure refers to an in vitro method of expanding a population of cells, comprising the step of expressing the polynucleotide in the cell as described herein.

[0020] In certain examples, the constitutively active cytokine receptor utilizes an exodomain that is utilized as a sink or ligand trap, such as by binding up one or more molecules that would be detrimental to the cells expressing the constitutively active cytokine receptor. Such a ligand may be immunosuppressive, for example, because it would normally activate signaling pathways to turn off the T-cell, as in immunosuppression. In some such cases the exodomain binds the harmful ligand as a decoy receptor yet the transmembrane/endodomains are still able to independently give a positive cytokine signal. In some examples, a decoy receptor prevents a corresponding ligand from suppressing the T-cell as it would under normal circumstances. Exodomains of the decoy receptor may bind inhibitory cytokines, for example. Examples of harmful ligands to which the decoy receptor may bind include TGF-beta, PD-L1, IL-4, IL-13, IL-8, and IL-10. In some examples, the decoy receptor exodomain is one of an inhibitory receptor normally expressed by T-cells such as, but not limited to, LAG3, TIGIT, CTLA4, FAS.

[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.

[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 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 the one or more cytokine receptor endodomains of component a) 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.

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 l , 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.