

CLAIMS

1. A lentiviral vector comprising a polynucleotide encoding a fusion polypeptide comprising:

I) (a) a TGF β R2 polypeptide comprising:

- (i) an extracellular TGF β 1-binding domain of TGF β R2;
- (ii) an IL-12R β 2 transmembrane domain; and
- (iii) an IL-12R β 2 intracellular signaling domain;

(b) a viral self-cleaving 2A peptide; and

(c) a TGF β R1 polypeptide comprising:

- (i) an extracellular TGF β 1-binding domain of TGF β R1;
- (ii) an IL-12R β 1 transmembrane domain; and
- (iii) an IL-12R β 1 intracellular signaling domain; or

II) (a) a TGF β R2 polypeptide comprising:

- (i) an extracellular TGF β 1-binding domain of TGF β R2;
- (ii) an IL-12R β 1 transmembrane domain; and
- (iii) an IL-12R β 1 intracellular signaling domain;

(b) a viral self-cleaving 2A peptide; and

(c) a TGF β R1 polypeptide comprising:

- (i) an extracellular TGF β 1-binding domain of TGF β R1;
- (ii) an IL-12R β 2 transmembrane domain; and
- (iii) an IL-12R β 2 intracellular signaling domain.

2. The lentiviral vector of claim 1, further comprising an engineered antigen receptor and a second viral self-cleaving 2A polypeptide.

3. The lentiviral vector of claim 2, wherein the engineered antigen receptor is selected from the group consisting of: an engineered T cell receptor (TCR), a chimeric antigen

receptor (CAR), a DARIC receptor or components thereof, and a chimeric cytokine receptor; optionally, wherein the engineered antigen receptor recognizes an antigen selected from the group consisting of: alpha folate receptor, 5T4, $\alpha\beta6$ integrin, BCMA, B7-H3, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD138, CD171, CEA, CSPG4, EGFR, EGFR family including ErbB2 (HER2), EGFRvIII, EGP2, EGP40, EphA2, EpCAM, FAP, fetal AchR, GD2, GD3, Glypican-3 (GPC3), HLA-A1+MAGE1, HLA-A2+MAGE1, HLA-A3+MAGE1, HLA-A1+NY-ESO-1, HLA-A2+NY-ESO-1, HLA-A3+NY-ESO-1, IL-11R α , IL-13R α 2, Lambda, Lewis-Y, Kappa, Mesothelin, Muc1, Muc16, NCAM, NKG2D Ligands, NY-ESO-1, PRAME, PSCA, PSMA, ROR1, SSX, Survivin, TAG72, TEMs, VEGFR2, and WT-1.

4. A cell comprising the lentiviral vector of any one of claims 1 to 3.

5. The cell of claim 4, wherein the cell is:

- (a) a hematopoietic cell;
- (b) a T cell;
- (c) a CD3⁺, CD4⁺, and/or CD8⁺ cell;
- (d) an immune effector cell;
- (e) a cytotoxic T lymphocyte (CTL), a tumor infiltrating lymphocyte (TIL), or a helper T cell; or
- (f) a natural killer (NK) cell or natural killer T (NKT) cell.

6. A composition comprising the lentiviral vector of any one of claims 1 to 3, or the cell of claim 4 or claim 5.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the lentiviral vector of any one of claims 1 to 3, or the cell of claim 4 or claim 5.

8. Use of the cell of claim 4 or a composition comprising the cell of claim 4 in the manufacture of a medicament for treating a cancer, solid cancer, or hematological malignancy, wherein the cell is a T cell, an immune effector cell, or an NK cell.