low levels on the surface of skin and oral mucosa; otherwise TROP-2 is not expressed on normal tissue.

[0006] There exists a need in the field of cancer biology for methods and compositions concerning genetic engineering of cells, including human NK cells, for cell therapy to target cancers including TROP-2-positive tumors.

SUMMARY

[0006a] In one aspect, provided herein is a polynucleotide that encodes an anti-TROP-2 chimeric antigen receptor (CAR), the CAR comprising (i) an anti-TROP-2 antigen binding region of a TROP-2 specific antibody, (ii) a transmembrane domain, and (iii) an intracellular region.

[0006b] In another aspect, provided herein is a vector comprising the polynucleotide as described herein, optionally wherein the vector is: (a) a viral vector, optionally wherein the viral vector is an adenoviral vector, adeno-associated viral vector, lentiviral vector, or retroviral vector; or (b) a non-viral vector, optionally wherein the non-viral vector is a plasmid.

[0006c] In another aspect, provided herein is an immune cell comprising the polynucleotide as described herein or the vector as described herein, optionally wherein: (a) the immune cell is a natural killer (NK) cell, T cell, gamma delta T cell, alpha beta T cell, invariant NKT (iNKT) cell, B cell, macrophage, mesenchymal stromal cell, or dendritic cell, optionally wherein the immune cell is a NK cell, further optionally wherein: (i) the NK cell is derived from cord blood, peripheral blood, induced pluripotent stem cells, hematopoietic stem cells, bone marrow, or from a cell line, optionally wherein the NK cell is derived from: (A) a cell line, wherein the NK cell line is NK-92; or (B) a cord blood mononuclear cell; and/or (ii) the NK cell is a $CD56^+$ NK cell; and/or (iii) the NK cell expresses a recombinant cytokine, optionally wherein the cytokine is IL-15, IL-2, IL-12, IL-18, IL-21, IL-7, or IL-23, further optionally wherein the cytokine is IL-15; and/or (b) expression of one or more endogenous genes in the immune cell has been modified, optionally, wherein the one or more genes comprise NKG2A, SIGLEC-7, LAG3, TIM3, CISH, FOXO1, TGFBR2, TIGIT, CD96, ADORA2, NR3C1, PD1, PDL-1, PDL-2, CD47, SIRPA, SHIP1, ADAM17, RPS6, 4EBP1, CD25, CD40, IL21R, ICAM1, CD95, CD80, CD86, IL10R, CD5, CD7, CTLA-4, TDAG8, CD38, or a combination thereof.

[0006d] In another aspect, provided herein is a population of immune cells comprising the immune cell as described herein.

[0006e] In another aspect, provided herein is use of cells harboring the polynucleotide as described herein in the manufacture of a medicament for killing TROP-2-positive cells in an individual, wherein said cells are to be administered to the individual.

[0006f] In another aspect, provided herein is a polynucleotide that encodes: (a) an anti-TROP-2 chimeric antigen receptor (CAR), the CAR comprising (i) an anti-TROP-2 antigen binding region of an RS7 antibody, (ii) a transmembrane domain, and (iii) an intracellular region; (b) IL-15; and (c) Caspase 9; optionally wherein the RS7 antibody is a: (i) humanized RS7 antibody; or (ii) murine RS7 antibody.

[0006g] In another aspect, provided herein is a polynucleotide that encodes: (a) an anti-TROP-2 chimeric antigen receptor (CAR), the CAR comprising (i) an anti-TROP-2 antigen binding region of a 2G10 antibody, (ii) a transmembrane domain, and (iii) an intracellular region; (b) IL-15; and (c) Caspase 9; optionally wherein the 2G10 antibody is: (i) a murine 2G10 antibody; or (ii) a humanized 2G10 antibody.

[0006h] In another aspect, provided herein is an NK cell comprising the polynucleotide as described herein.

[0006i] In another aspect, provided herein is a natural killer cell comprising: (a) a first polynucleotide encoding an anti-TROP-2 chimeric antigen receptor; (b) a second polynucleotide encoding IL-15; and (c) a third polynucleotide encoding Caspase 9, optionally wherein the first polynucleotide, the second polynucleotide, and the third polynucleotide are: (i) present on the same nucleic acid molecule; or (ii) present on two different nucleic acid molecules; or (iii) present on three different nucleic acid molecules.

[0006j] In another aspect, provided herein is a polynucleotide that encodes for SEQ ID NO:2, optionally wherein the polynucleotide comprises a sequence having at least 90% identity with SEQ ID NO:1, further optionally wherein the polynucleotide comprises SEQ ID NO:1.

[0006k] In another aspect, provided herein is a polynucleotide that encodes for SEQ ID NO:4, optionally wherein the polynucleotide comprises a sequence having at least 90% identity with SEQ ID NO:3, further optionally wherein the polynucleotide comprises SEQ ID NO:3.

[0006l] In another aspect, provided herein is a polynucleotide that encodes for SEQ ID NO:6, optionally wherein the polynucleotide comprises a sequence having at least 90% identity with SEQ ID NO:5, further optionally wherein the polynucleotide comprises SEQ ID NO:5.

[0006m] In another aspect, provided herein is a polynucleotide that encodes for SEQ ID NO:8, optionally wherein the polynucleotide comprises a sequence having at least 90% identity with SEQ ID NO:7, further optionally wherein the polynucleotide comprises SEQ ID NO:7.

[0006n] In another aspect, provided herein is cells harboring the polynucleotide as described herein for use in therapy.

[0007] Embodiments of the disclosure encompass methods and compositions related to engineered cellular receptors, including chimeric antigen receptors (CARs) that target TROP-2 (also known as tumor-associated calcium signal transducer 2, trophoblast cell surface antigen 2, or EGP-1, for example). In specific embodiments, the engineered receptors that target TROP-2 are in the form of polynucleotides, polypeptides, and/or are comprised on the surface of cells of any kind, including immune cells. In specific cases, the cells are immune cells, and in certain embodiments the immune cells are NK cells, NK T cells, invariant NKT cells, gamma delta T cells, alpha beta T cells, regulatory T cells, B cells, macrophages, mesenchymal stromal cells (MSCs), dendritic cells, and so forth, from any source. In some embodiments, the immune cells are NK cells. In certain embodiments, reprogrammed NK cells from cord blood (CB-NK) are encompassed for targeting cancers expressing TROP-2 molecules.

[0008] TROP-2 (also "TROP2" or "Trop2") is utilized as a target antigen for aspects of the disclosed methods and compositions at least in part because it is expressed on multiple cancers, including breast, lung, urothelial, gastric, colorectal, pancreatic, prostatic, cervical, head and neck, and ovarian carcinomas.

[0009] The present disclosure includes a number of novel CAR molecules including fusion of an scFv targeting human TROP-2 (including, for example, an scFv from an antibody such as an RS7 antibody (e.g., mRS7, hRS7), Pr1E11, TrMab-29, datopotamab, 2G10, 2EF, etc.), including in some cases that incorporate either CD3ζ alone or in combination with costimulatory or adaptor signaling domains, such as from NKG2D, OX-40, CD27, 41BB, CD28, DAP10, DAP12, and/or 2B4. In specific cases, allogeneic CB-NK cells are retrovirally transduced to express a TROP-2 CAR. In particular embodiments, immune cells of the disclosure encompassing TROP-2 CAR molecules also express one or more proteins that support their survival and proliferation. In specific cases, the immune cells are engineered to express one or more cytokines that facilitate the cells' expansion and persistence. In specific cases, the one or more cytokines are interleukin 15 (IL-15), IL-2, IL-7, IL-12, IL-18, IL-21,