

the need in most cases to create “room” for successful eventual re-implantation by ablation of existing cell populations in the patient (*e.g.*, S.L. Maude *et al.*, N Engl J Med., 378:439-448, 2018; doi: 10.1056/NEJMoa1709866). The use of engineered allogeneic T cells has been proposed as a solution and clinical trials have started, but there are several issues attached to this stop-gap methodology. Firstly, there are essentially no perfect HLA matches except between identical twins, so the CAR T cells will likely be short-lived and eliminated by an allogeneic response; attempts to use cells where the HLA has been removed increases the risk of a leukemia derived from CAR T cells. Secondly, although this approach potentially allows treatment of more than a single patient with a particular preparation of allogeneic CAR T cells, the maximum number of patients that can be treated is estimated as about 100; then a fresh preparation of unknown potency will need to be made and tested *in vitro*, which can be quite misleading for *in vivo* potency prediction.

SUMMARY

[0006] The disclosure provides a way around at least some of these difficulties by using direct administration of integrating gene transfer vectors encoding therapeutic gene(s) that transduce patient's cells directly. In one aspect, the present disclosure refers to a pharmaceutical composition for administration to a subject, the pharmaceutical composition comprising: a non-replicating viral vector containing a heterologous polynucleotide encoding a product having an immune activating effect, wherein the non-replicating viral vector transduces or integrates into blood cells of the subject. In another aspect, the present disclosure refers to a non-replicating viral vector comprising: an envelope comprising envelope proteins and lipid membrane; a nucleic acid contained within the envelope, the nucleic acid comprising a sequence from 5' to 3' comprising: SEQ ID NO:12 from nucleotide 1 to 1050 or a sequence that is at least 85% identical thereto; an RNA sequence encoding a chimeric antigen receptor (CAR); and SEQ ID NO:12 from nucleotide 1101 to 1662 or a sequence that is at least 85% identical thereto, wherein the RNV can infect dividing cells and wherein the RNA sequence encoding the chimeric antigen receptor is integrated into the dividing cell. In another aspect, the present disclosure refers to the use of the pharmaceutical composition as disclosed herein or an RNV CAR as disclosed herein in the manufacture of a medicament for providing adoptive cell therapy to a subject. In one example the vector is a retroviral vector, the target is a T cell and the transgene is a CAR or similar artificial receptor construct (*e.g.*, 1st, 2nd, 3rd *etc.* generation CAR constructs). In another example, the vector is retroviral vector, the target is a cell that has been activated by administration of an external agent and the transgene encodes a therapeutic activity. In this and other examples a retroviral

vector can be replicating (RRV) or non-replicating (RNV) and can be derived from any integrating virus such as a foamy virus, a lentivirus, an alpha, beta or gamma retrovirus or CRISPR elements and also includes non-viral integrating vector such as those based on transposons such as “Piggy-bac” (Saito *et al.*, Cytother. 16:1257-1269, 2014) or “Sleeping Beauty”. In another example, the vector is a retroviral vector, the activating agent is granulocyte colony stimulating factor (GCSF) and the target is CD34⁺ cells. In a further example, the vector is a gamma retroviral non-replicating vector, the target population is naturally activated T cells, and the transgene is a T cell receptor. In a further example, the vector is a gamma retroviral vector, the target cell population is a naturally activated cell population and the transgene encodes an immune activating agent. In yet another example, the vector is a gamma retroviral vector, the target population is naturally activated T cells, and the transgene is a CAR (*e.g.*, 1st, 2nd, 3rd generation CAR). In a further example, the CAR comprises a binding domain that targets one or more of: CD5; CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha (FRa or FR1); Folate receptor beta (FRb); Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint

cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycosphingolipid (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; survivin; telomerase; prostate carcinoma tumor antigen-1 (PCT A-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B 1 (CYP1B 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RUI1); renal ubiquitous 2 (RUI2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein

70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1), MPL, Biotin, c-MYC epitope Tag, CD34, LAMP1 TROP2, GFRalpha4, CDH17, CDH6, NYBR1, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen); Fucosyl-GM1, PTK7, gpNMB, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, TCRgamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Gonadotropin Hormone receptor (CGHR or GR), CCR4, GD3, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, KSHV K8.1, KSHV-gH, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), auto antibody to desmoglein 3 (Dsg3), auto antibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IgE, CD99, Ras G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, Claudin18.2 (CLD18A2 or CLDN18A.2)), P-glycoprotein, STEAP1, Liv1, Nectin-4, Cripto, gpA33, BST1/CD157, low conductance chloride channel, and the antigen recognized by TNT antibody.

BRIEF DESCRIPTION OF THE FIGURES

[0007] **FIG. 1** shows the sequence and annotation of the sequence of a plasmid construct of the disclosure.

[0008] **FIG. 2** shows the viral RNA (vRNA) sequence with the multiple cloning site highlighted/bold/underlined. A CAR coding sequence (RNA) can be cloned into the multiple cloning site (MCS) to form the RNVCAR viral sequence.

[0009] **FIG. 3** shows various DNA sequences encoding CARs used to exemplify the invention. Note that the corresponding RNA sequence is contemplated wherein T is replaced with U in the sequences.

[0010] **FIG. 4** shows various plasmid sequences containing an scFv sequence that binds to CD19 for the production of an CD19-RNVCAR.

- [0011]** **FIG. 5A-B** schematically depicts exemplary RNV vectors of the disclosure.
- [0012]** **FIG. 6** a plot of Infection level in PBMC in Balb/c mice with RNV-GFP determined in peripheral blood mononuclear cells (PBMC) at 7 days after the first IV dose of RNV-GFP.
- [0013]** **FIG. 7** shows a plot of RNV-GFP infection evaluated in a subset of PBMC populations: CD11b⁺, CD4⁺, CD8⁺, and CD19⁺ in parallel samples to those taken to generate the data for FIG. 6.
- [0014]** **FIG. 8** shows the results of an experiment in the A20 B-cell lymphoma animal model where tumor-bearing mice injected IV with the vector, RNV-1D3CAR, at a dose of 1E7 or 1E8 TU per day for five consecutive days, starting at day 5 after A20 implantation. Mice were monitored for 37 days and survival assessed. The higher dose of RNV-1D3CAR (5E8 TU) led to an improvement in survival in A20 lymphoma tumor bearing mice compared to a vehicle treated control group (no RNV) or the lower dose of RNV-1D3CAR (5E7).

DETAILED DESCRIPTION

aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within a CAR of the disclosure can be replaced with other amino acid residues from the same side chain family and the altered CAR can be tested using the binding and/or functional assays described herein.

[0049] "Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connote or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an antigen binding domain that is derived from an antibody molecule, the antigen binding domain retains sufficient antibody structure such that it has the required function, namely, the ability to bind to an antigen. It does not connote or include a limitation to a particular process of producing the antibody, *e.g.*, it does not mean that, to provide the antigen binding domain, one must start with an antibody sequence and delete unwanted sequence, or impose mutations, to arrive at the antigen binding domain.

[0050] An "intracellular signaling domain," as the term is used herein, refers to an intracellular signaling portion of a molecule. The intracellular signaling domain generates a signal that promotes an immune effector function of an immune cells. Examples of immune effector function include cytolytic activity and helper activity, including the secretion of cytokines.

[0051] In another embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent stimulation. In another embodiment, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For example, a primary intracellular signaling domain can comprise a cytoplasmic sequence of CD3z, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule, such as CD28 or 41BB.

[0052] A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, common γ (FCER1G), γ (Fc γ RIIa), β (Fc ϵ R1b), CD3 γ , CD3 δ , CD3 ϵ , CD79a, CD79b, DAP10, and DAP12.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for administration to a subject, the pharmaceutical composition comprising:
 - a non-replicating viral vector containing a heterologous polynucleotide encoding a product having an immune activating effect
 - wherein the non-replicating viral vector transduces or integrates into blood cells of the subject.
2. The pharmaceutical composition of claim 1, wherein the subject is a mammal.
3. The pharmaceutical composition of claim 2, wherein the mammal is a human.
4. The pharmaceutical composition of claim 1, wherein the composition is to be administered intraperitoneally or intravascularly.
5. The pharmaceutical composition of claim 1, wherein the viral vector is a retroviral vector selected from the group consisting of a gammaretroviral vector, a betaretroviral vector, an alpharetroviral vector, a lentiviral vector and a foamy viral vector.
6. The pharmaceutical composition of claim 5, wherein the RNV comprises:
 - an envelope comprising envelope proteins and lipid membrane;
 - a nucleic acid contained within the envelope, the nucleic acid comprising a sequence from 5' to 3' comprising:
 - SEQ ID NO:12 from nucleotide 1 to 1050 or a sequence that is at least 85% identical thereto;
 - an RNA sequence encoding the product having the immune activating effect; and
 - SEQ ID NO:12 from nucleotide 1101 to 1662 or a sequence that is at least 85% identical thereto,
 - wherein the RNV can infect dividing cells and wherein the RNA sequence encoding the product having immune activating effect is integrated into the dividing cell.
7. The pharmaceutical composition of any one of the foregoing claims wherein the immune activating effect is an immune mediated activity.

8. The pharmaceutical composition of any one of claims 1-6, wherein the blood cells are T-cells or T-cell precursors.
9. The pharmaceutical composition of any one of claims 1-6, wherein the heterologous polynucleotide encodes a chimeric antigen receptor (CAR) or CAR-like molecule.
10. The pharmaceutical composition of claim 9, wherein the CAR or CAR-like molecule comprises an antigen binding domain, an optional spacer, a transmembrane domain and an optional intracellular domain.
11. The pharmaceutical composition of claim 10, wherein the antigen binding domain is a non-immunoglobulin binding domain.
12. The pharmaceutical composition of claim 11, wherein the non-immunoglobulin binding domain comprises a scaffold protein.
13. The pharmaceutical composition of claim 10, wherein the transmembrane domain is a CD28 transmembrane domain or a CD8 transmembrane domain.
14. The pharmaceutical composition of claim 13, wherein the CD8 transmembrane domain is encoded by a sequence that is 98% to 100% identical to SEQ ID NO:1.
15. The pharmaceutical composition of claim 10, wherein the antigen binding domains comprises an scFv or antibody fragment.
16. The pharmaceutical composition of claim 10, wherein the optional spacer is encoded by a sequence that is at least 98% identical to SEQ ID NO:2.
17. The pharmaceutical composition of claim 10, wherein the optional intracellular domain comprises a CD3 ζ domain.
18. The pharmaceutical composition of claim 10, wherein the optional intracellular domain comprises a 41BB or CD28 intracellular domain.

19. The pharmaceutical composition of claim 18, wherein the 41BB domain is encoded by a sequence that is 98% to 100% identical to SEQ ID NO:5.
20. The pharmaceutical composition of claim 17, wherein the CD3 ζ domain is encoded by a sequence that is at least 98% identical to SEQ ID NO:4.
21. The pharmaceutical composition of claim 10, wherein the antigen-binding domains specifically binds to an antigen selected from the group consisting of:
 CD5, CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha (FRa or FR1); Folate receptor beta (FRb); Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); tumor endothelial marker 1

(TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycosphingolipid (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; survivin; telomerase; prostate carcinoma tumor antigen-1 (PCT A-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B 1 (CYP1B 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-

containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1), MPL, Biotin, c-MYC epitope Tag, CD34, LAMP1 TROP2, GFRalpha4, CDH17, CDH6, NYBR1, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen); Fucosyl-GM1, PTK7, gpNMB, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, TCRgamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Gonadotropin Hormone receptor (CGHR or GR), CCR4, GD3, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, KSHV K8.1, KSHV-gH, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), auto antibody to desmoglein 3 (Dsg3), auto antibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IgE, CD99, Ras G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, Claudin18.2 (CLD18A2 or CLDN18A.2)), P-glycoprotein, STEAP1, Liv1, Nectin-4, Cripto, gpA33, BST1/CD157, low conductance chloride channel, and the antigen recognized by TNT antibody.

22. The pharmaceutical composition of claim 1, wherein the viral vector comprises a self-inactivating nucleic acid sequence (SIN).

23. The pharmaceutical composition of claim 1, wherein the viral vector is produced by expression of a sequence selected from the group consisting of SEQ ID NO:18, 19, 20, 21, and 22.

24. A non-replicating viral vector comprising:
an envelope comprising envelope proteins and lipid membrane;
a nucleic acid contained within the envelope, the nucleic acid comprising a sequence from 5' to 3' comprising:
SEQ ID NO:12 from nucleotide 1 to 1050 or a sequence that is at least 85% identical thereto;
an RNA sequence encoding a chimeric antigen receptor (CAR); and
SEQ ID NO:12 from nucleotide 1101 to 1662 or a sequence that is at least 85% identical thereto,

wherein the RNV can infect dividing cells and wherein the RNA sequence encoding the chimeric antigen receptor is integrated into the dividing cell.

25. The RNVCAR of claim 24, wherein the CAR comprises an antigen binding domain, an optional spacer, a transmembrane domain and an optional intracellular domain.

26. The RNVCAR of claim 25, wherein the transmembrane domain is a CD28 transmembrane domain.

27. The RNVCAR of claim 25, wherein the transmembrane domain is a CD8 transmembrane domain.

28. The RNVCAR of claim 27, wherein the CD8 transmembrane domain is encoded by a sequence that is 98% to 100% identical to SEQ ID NO:1.

29. The RNVCAR of claim 25, wherein the antigen binding domains comprises an scFv or antibody fragment or non-immunoglobulin binding domain.

30. The RNVCAR of claim 25, wherein the optional spacer is encoded by a sequence that is at least 98% identical to SEQ ID NO:2.

31. The RNVCAR of claim 25, wherein the intracellular domain comprises a CD3 ζ domain.

32. The RNVCAR of claim 25, wherein the intracellular domain comprises a 41BB or CD28 intracellular domain.

33. The RNVCAR of claim 32, wherein the 41BB domain is encoded by a sequence that is 85% to 100% identical to SEQ ID NO:5.

34. The RNVCAR of claim 31, wherein the CD3 ζ domain is encoded by a sequence that is at least 98% identical to SEQ ID NO:4.

35. The RNVCAR of claim 24, wherein the RNA sequence encoding the chimeric antigen receptor comprises any one of SEQ ID NOs: 13 to 17 wherein T is U.

36. The RNVCAR of claim 25, wherein the antigen-binding domains specifically binds to an antigen selected from the group consisting of:

CD5, CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha (FRa or FR1); Folate receptor beta (FRb); Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein coupled receptor class C group 5, member D (GPC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a;

anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1);
 hexasaccharide portion of globoH glycosphingolipid (GloboH); mammary gland differentiation
 antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1);
 adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20
 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); Olfactory receptor 51E2
 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein
 (WT1); Cancer/testis antigen 1 (NY-ES0-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-
 associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome
 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1);
 angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1
 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor
 protein p53 (p53); p53 mutant; prostein; survivin; telomerase; prostate carcinoma tumor
 antigen-1 (PCT A-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or
 MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT);
 sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG
 (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-
 transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-
 myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras
 Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome
 P450 1B 1 (CYP1B 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother
 of the Regulator of Imprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T
 Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-
 TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4
 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation
 Endproducts (RAGE-1); renal ubiquitous 1 (RUI); renal ubiquitous 2 (RU2); legumain;
 human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal
 carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72;
 Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor
 (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2
 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family
 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-
 containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75);
 Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like
 polypeptide 1 (IGLL1), MPL, Biotin, c-MYC epitope Tag, CD34, LAMP1 TROP2,

GFRalpha4, CDH17, CDH6, NYBR1, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen); Fucosyl-GM1, PTK7, gpNMB, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, TCRgamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Gonadotropin Hormone receptor (CGHR or GR), CCR4, GD3, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, KSHV K8.1, KSHV-gH, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), auto antibody to desmoglein 3 (Dsg3), auto antibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IgE, CD99, Ras G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, Claudin18.2 (CLD18A2 or CLDN18A.2)), P-glycoprotein, STEAP1, Liv1, Nectin-4, Cripto, gpA33, BST1/CD157, low conductance chloride channel, and the antigen recognized by TNT antibody.

37. The RNVCAR of claim 24, further comprising an IRES or 2A peptide cassette operably linked to a heterologous polynucleotide.

38. The RNVCAR of claim 37, wherein the heterologous polynucleotide encodes a prodrug activator enzyme.

39. The RNVCAR of claim 38, wherein the prodrug activator enzyme is cytosine deaminase or thymidine kinase.

40. The RNVCAR of any one of claims 24-36, produced by transfecting a packaging cell line with a plasmid comprising SEQ ID NO:3 containing a chimeric antigen receptor coding sequence, culturing the packaging cell to produce the RNVCAR and isolating the RNVCAR.

41. The RNVCAR of claim 40, wherein the plasmid comprises a sequence selected from the group consisting of SEQ ID NO:18 to 22.

42. Use of the pharmaceutical composition of any one of claims 1-6 or an RNVCAR of any one of claims 24-36 in the manufacture of a medicament for providing adoptive cell therapy to a subject.

43. The use of claim 42, wherein the subject is to be treated with an agent to activate T-cells prior to or simultaneously with the administration of the RNVCAR.