

naturally occurring agent that selectively activates the NF- κ B signaling pathway. In one example, the at least one non-naturally occurring immune receptor comprises at least one antigen-binding domain and at least one transmembrane domain. In another or a further example, the at least one non-naturally occurring immune receptor is capable of recruiting at least one TCR associated signaling module. In another or a further example, the at least one non-naturally occurring immune receptor is a chimeric antigen receptor (CAR) or a recombinant TCR. In another or a further example, the at least one antigen-binding domain of the at least one non-naturally occurring immune receptor binds to an antigen selected from a group consisting of CD5; CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, MPL, 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 (gpl00); 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

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 an antigen recognized by TNT antibody. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is selected from the group consisting of vFLIP K13, K13-opt, a NEMO mutant, a NEMO-fusion protein, IKK1-S176E-S180E, IKK2-S177E-S181E, RIP, IKK α , IKK β , Tcl-1, MyD88-L265, any NF- κ B activating protein or protein fragment, any inhibitor of an inhibitor of NF- κ B pathway, any gene editing system capable of selectively activating NF- κ B, any homolog or variant thereof and any combination thereof. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is of non-viral origin. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is a gene editing system. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway induces oligomerization of NEMO/IKK γ . In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway induces activation of the IKK complex. In another or a further example, at least one the non-naturally occurring agent capable of selectively activating NF- κ B pathway does not activate the AKT pathway. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is expressed in a constitutive or inducible

manner. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is expressed transiently. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is expressed stably. In another or a further example, the activity of the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is controlled post-translationally through contacting the cell with a compound. In another or a further example, the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is expressed as a fusion construct with one or more copies of a switch domain. In another or a further example, the activity of the at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway is controlled at the post-translational level by administration of therapeutically effective amount of a compound that induces dimerization of the switch domain. In another or a further example, the switch domain comprises one or more copies of a FKBP12 domain. In another or a further example, the compound is AP20187 or Rimiducid or a homolog thereof. In another or a further example, the immune cell is a T-lymphocyte (T-cell), a CAR-T cell, a TCR-expressing T cell, a tumor infiltrating lymphocyte (TIL), a tissue resident lymphocyte, a stem cell, an induced pluripotent stem cell or a Natural Killer (NK) cell. In another or a further example, the immune cell has been engineered to lack a functional native T-Cell Receptor (TCR) signaling complex and/or β 2 microglobulin. In another or a further example, the at least one non-naturally occurring immune receptor and/or the at least one agent capable of selectively activating NF- κ B signaling pathway are cloned into an endogenous TCR gene such that the expression of the at least one non-naturally occurring immune receptor and/or the at least one agent capable of selectively activating NF- κ B signaling pathway are under control of the endogenous regulatory elements/promoter for the TCR gene. The disclosure also provides for the use of an immune cell or immune cell population as described herein that is used for the prevention and treatment of a disease selected from the group of a cancer, infectious disease, immune disease, and allergic disease. In another or a further example, at least one polynucleotide encodes the at least one non-naturally occurring immune receptor and the at least one non-naturally occurring agent capable of selectively activating NF- κ B signaling pathway are expressed from a single promoter. In another or a further example, at least one polynucleotide encoding the at least one non-naturally occurring immune receptor and the at least one non-naturally occurring agent capable of selectively activating NF- κ B signaling pathway are expressed using two or more separate promoters. In another or a further example, the at least one

polynucleotide comprises a first nucleic acid coding sequence encoding the at least one non-naturally occurring immune receptor separated from a second nucleic acid sequence encoding the non-naturally occurring agent capable of selectively activating NF- κ B such that upon expression of the first and second nucleic acid coding sequences that non-naturally occurring immune receptor and non-naturally occurring agent capable of selectively activating NF- κ B are not physically or chemically linked. In another or a further example, the at least one non-naturally occurring immune receptor and/or the at least one non-naturally occurring agent capable of selectively activating NF- κ B coding polynucleotide(s) are cloned into an endogenous TCR gene such that the at least one non-naturally occurring immune receptor and/or at least one non-naturally occurring agent capable of selectively activating NF- κ B are under control of the endogenous regulatory elements/promoter for the TCR gene. In another or a further example, one or more constant chains of the TCR genes are functionally re-expressed.

[0005a] In one aspect, the present disclosure refers to a T cell or T cell population with impaired or abolished functional expression of an endogenous TCR and expressing at least one non-naturally occurring immune receptor selected from the group of SIR, cTCR, Ab-TCR and TFP.

[0005b] In another aspect, the present disclosure refers to an induced pluripotent stem cell capable of giving rise to a T cell as disclosed herein, wherein a recombinant nucleic acid sequence encoding a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP is integrated at a site within the genome of the cell such that the non-naturally occurring immune receptor is expressed by the cell at the surface of the cell, and wherein integration of the nucleic acid encoding the non-naturally occurring immune receptor at said site reduces or prevents expression of a functional T cell receptor (TCR) complex at the surface of the cell and wherein the expression and activity of the non-naturally occurring immune receptor is optionally enhanced by expression of a sequence encoding a TCR constant chain, wherein the TCR constant chain is

- (i) a TCR alpha constant chain or fragment thereof, or
- (ii) a TCR beta constant chain or a fragment thereof, or
- (iii) a TCR gamma constant chain or fragment thereof, or
- (iv) a TCR delta constant chain or a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

[0006] The disclosure also provides at least one recombinant polynucleotide encoding at least one non-naturally occurring immune receptor, the at least one recombinant polynucleotide comprising (a) a first nucleic acid domain encoding a partial or entire transmembrane and/or cytoplasmic domain and optionally the extracellular domain of an endogenous protein, wherein the endogenous protein is expressed on the surface of lymphocytes and triggers the activation and/or proliferation of the lymphocyte; (b) optionally a polynucleotide a linker; (c) a second nucleic acid domain operably linked to the first nucleic acid domain, wherein the second nucleic acid domain encodes one or more non-natural TCR antigen binding domain(s); (d) an optional third nucleic acid domain encoding a costimulatory domain; and (e) an optional additional nucleic acid domain encoding an accessory module.

[0007] The disclosure also provides at least one recombinant polynucleotide comprising a first nucleic acid encoding a non-naturally occurring immune receptor; and a second nucleic acid encoding an accessory module comprising a selective NF- κ B activator. In one example, the first nucleic acid and the second nucleic acid are separated by an oligonucleotide linker encoding a cleavable peptide linker. In another example, the at least one comprises two recombinant polynucleotide such that the first nucleic acid and second nucleic acid are expressed from separate vectors. In another or a further example, the selective NF- κ B activator is a non-naturally occurring selective NF- κ B activator. In another or a further example, the non-naturally occurring immune receptor is selected from the group consisting of a CAR, an Ab-TCR, a TFP, a cTCR, a SIR and a recombinant

TCR. In another or a further example, the non-naturally occurring immune receptor comprises an (i) an extracellular antigen specific domain, (ii) a transmembrane domain, and (iii) an optional intracellular signaling domain comprising an immunoreceptor tyrosine-based activation motif (ITAM), wherein (iii) is located at the C-terminus of the non-naturally occurring immune receptor. In another or a further example, upon expression of the first and second nucleic acids sequences the non-naturally occurring immune receptor and selective NF- κ B activator polypeptide are not physically or chemically linked. In another or a further example, the extracellular antigen-specific domain binds to any one or more of CD5; CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, MPL, 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); AFP/MHC complex; 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

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-IGL1, 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 an antigen recognized by TNT antibody. In another or a further example, the selective NF- κ B activator is selected from the group consisting of vFLIP K13, a NEMO mutant, a NEMO-fusion protein, IKK1-S176E-S180E, IKK2-S177E-S181E, RIP, FKBPx2-RIP-ID, IKK1, FKBPx2-IKKa, IKK2, FKBPx2-IKK2, Tcl-1, MyD88-L265, any NF- κ B activating protein or protein fragment, any inhibitor of an inhibitor of NF- κ B pathway, a gene editing system capable of selectively activating NF- κ B, an RNA interference system that selectively activating NF- κ B and any combination thereof. In another or a further example, the selective NF- κ B activator is expressed as a fusion construct with one or more copies of FKBP domain. In another or a further example, the extracellular antigen specific domain is selected from the group consisting of: the variable region of the heavy chain (vH) of an antibody or a fragment thereof specific for a predefined target antigen; the variable region of the light chain (vL) of an antibody or a fragment thereof specific for a predefined target antigen; a single chain variable fragment (scFv) or a fragment thereof specific for a predefined target antigens; an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen; a single domain antibody (SDAB) fragments specific for a predefined target antigen; a camelid vHH domain specific for a predefined target

antigen; a non-immunoglobulin antigen binding scaffolds specific for a predefined target antigen; a receptors specific or a fragment thereof for a predefined target antigen; a ligands or a fragment thereof specific for a predefined target antigen; a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand specific for one or more predefined target antigens; and an autoantigen or a fragment thereof.

[0008] The disclosure also provides at least one vector comprising the at least one polynucleotide of any of the foregoing polynucleotides constructs described herein and above. In one example, the vector is selected from the group consisting of a DNA vector, an RNA vector, a plasmid, a lentivirus vector, adenoviral vector, AAV vector, a retrovirus vector, a baculovirus vector, a sleeping beauty transposon vector, and a piggybac transposon vector.

[0009] The disclosure also provides an immune effector cell or stem cell comprising at least one recombinant polynucleotide, construct or vector described herein and above. In one example the immune cell is an antigen presenting cell. In another or a further example, the immune effector cell is a human T cell, a human NKT cell or a synthetic T cell, NK cell, or a stem cell that can give rise to an immune effector cell, optionally, wherein the T cell is diacylglycerol kinase (DGK) and/or Ikaros deficient and/or Brd4 deficient.

[0010] The disclosure also provides a method to (i) extend the life span of an immune cell expressing, (ii) stimulate proliferation of an immune cell, (iii) stimulate cytokine production by an immune cell, (iv) enhance antigen presentation by an immune cell, (v) protect an immune cell from apoptosis, the method comprising transfecting or transforming the immune cells with a polynucleotide encoding a selective NF- κ B activator or a NF- κ B specific stimulatory polypeptide. In one example, the selective NF- κ B activator or a NF- κ B specific stimulatory polypeptide is selected from the group consisting of vFLIP K13, K13-opt, a NEMO mutant, a NEMO-fusion protein, IKK1-S176E-S180E, IKK2-S177E-S181E, RIP, IKK α , IKK β , Tcl-1, MyD88-L265, any NF- κ B activating protein or protein fragment, any inhibitor of an inhibitor of NF- κ B pathway, any homolog or variant thereof and any combination thereof. In another or a further example, the selective NF- κ B activator or a NF- κ B specific stimulatory polypeptide is expressed in a constitutive or inducible manner In another or a further example, the selective NF- κ B activator or a NF- κ B specific stimulatory polypeptides controlled post-translationally through contacting the T cell with a compound. In another or a further example, the selective NF- κ B activator or a NF- κ B specific stimulatory polypeptide is expressed as a fusion construct with one or more

copies of FKBP domain. In another or a further example, the activity of the selective NF- κ B activator or a NF- κ B specific stimulatory polypeptide is controlled at the post-translational level by administration of therapeutically effective amount of a compound that induces dimerization of the FKBP domain. In another or a further example, the compound is AP20187 or rimiducid.

[0011] The disclosure also provides a method of making a non-naturally occurring immune receptor-expressing immune effector cell, comprising introducing at least one vector or at least one recombinant polynucleotide construct of the disclosure into an immune effector cell or a hematopoietic stem cell or progenitor cell that can give rise to an immune effector cell, under conditions such that a non-naturally occurring immune receptor is expressed and the immune effector cell comprises (i) extended life span, (ii) improved T cell proliferation, and/or (iii) reduced apoptosis compared to a CAR-T cell lacking an NF κ B specific stimulatory polypeptide. In another or a further example, the method further comprises providing a population of immune effector cells; and removing T regulatory cells from the population, thereby providing a population of T regulatory-depleted cells; wherein the steps are performed prior to introducing the vector or recombinant polynucleotide encoding the CAR and/or NF κ B specific stimulatory polypeptide to the population. In another or a further example, the T regulatory cells are removed from the cell population using an anti-CD25 antibody, or an anti-GITR antibody. In another or a further example, the method further comprises a) providing a population of immune effector cells; and b) enriching P-glycoprotein (P-gp or Pgp; MDR1, ABCB1, CD243)-positive cells from the population, thereby providing a population of P-glycoprotein (P-gp or Pgp; MDR1, ABCB1, CD243)-enriched cells; wherein steps a) and b) are performed prior to or after introducing the vector or recombinant polynucleotide encoding the CAR and/or NF κ B specific stimulatory polypeptide. In another or a further example, the P-glycoprotein positive cells are enriched using any one or more of the methods selected from the group consisting of i) immunoselection using one or a cocktail of P-glycoprotein specific antibodies, ii) staining with one or more of fluorescent dyes that are substrates of P-glycoprotein, tetramethylrhodamine methyl ester (TMRM), Adriamycin and actinomycin-D) under conditions at which P-glycoprotein is active as a pump and enriching for cells that stain less with the dye, iii) selection of cells that are resistant to phototoxic compounds that are substrates of P-glycoprotein, such as any one or more of TH9402, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid ethyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-

imino-3H-xanthen-9-yl)-benzoic acid octyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid n-butyl ester hydrochloride, 2-(6-ethyl amino-3-ethyl imino-3H-xanthen-9-yl)-benzoic acid n-butyl ester hydrochloride, or derivatives thereof or combinations thereof, and iv) selection of cells that are resistant to cytotoxic compounds that are substrates of P-glycoprotein, such as vincristine, vinblastine, taxol, paclitaxel, mitoxantrone, etoposide, adriamycin, daunorubicin and actinomycin-D.

[0012] The disclosure also provide a method of generating a population of RNA-engineered cells comprising introducing *in vitro* transcribed RNA or RNAs or synthetic RNA or RNAs into a cell or population of cells, where the RNA or RNAs comprises a recombinant polynucleotide or polynucleotides of the disclosure.

[0012a] In another aspect, the present disclosure refers to a method of generating a T cell or a population of T cells as disclosed herein that expresses a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP and lacks a functional T cell receptor (TCR) complex, comprising:

introducing into a T cell:

(i) a nucleic acid sequence encoding a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP, and

(ii) a homologous recombination system suitable for targeted integration of the nucleic acid sequence at a site within the genome of the cell, whereby the homologous recombination system integrates the nucleic acid sequence encoding the non-naturally occurring immune receptor at said site within the genome of the cell such that integration of the non-naturally occurring immune receptor at said site reduces or prevents expression of a functional T cell receptor complex at the surface of the cell, thereby generating a T cell that expresses the non-naturally occurring immune receptor and lacks a functional TCR complex,

(iii) optionally expressing a sequence encoding a TCR constant chain, wherein the TCR constant chain is:

- (a) a TCR alpha constant chain or fragment thereof, or
- (b) a TCR beta constant chain or a fragment thereof, or
- (c) a TCR gamma constant chain or fragment thereof, or
- (d) a TCR delta constant chain or a fragment thereof, or
- (e) a combination of i) and ii) or iii) and iv),

(iv) optionally eliminating the expression of a functional HLA.

[0013] The disclosure also provides a method of providing anti-disease immunity in a subject comprising administering to the subject an effective amount of the immune effector cell or a stem cell that can give rise to an immune effector cell of the disclosure, wherein the cell is an autologous T cell or an allogeneic T cell, or an autologous NKT cell or an allogeneic NKT cell or an autologous or an allogeneic hematopoietic stem cell or an autologous or an allogeneic iPSC that can give rise to an immune effector cell. In another or a further example, the allogeneic T cell or allogeneic NKT cell or hematopoietic stem cell or iPSC lacks expression or has low expression of a functional TCR or a functional HLA.

[0014] The disclosure also provides a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising a non-naturally occurring immune receptor and a selective NFkB activator, wherein the non-naturally occurring immune receptor comprises an antigen binding domains that bind to a disease-associated antigen associated said disease-associated antigen is selected from a group consisting of: CD5, CD19; CD123; CD22; CD30; CD171; CS-1 (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); FmsLike 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

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 End products (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-IGLL1, ALK TCRgamma-delta, NKG2D, CD32 (FCGR2A), CSPG4-HMW-MAA, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, VEGFR2/KDR, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Chorionic Gonadotropin Hormone receptor (CGHR), CCR4, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), KSHV-K8.1 protein, KSHV-gH protein, auto-antibody to desmoglein 3 (Dsg3), autoantibody 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 antigen recognized by TNT antibody.

[0014a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of the T cell as disclosed herein; and a pharmaceutically acceptable carrier.

[0015] The disclosure also provides a method of treating or preventing a disease associated with expression of a disease-associated antigen in a subject, comprising

PTK7, gpNMB, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCRgamma-delta, NKG2D, CD32 (FCGR2A), CSPG4-HMW-MAA, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, VEGFR2/KDR, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Chorionic Gonadotropin Hormone receptor (CGHR), CCR4, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), KSHV-K8.1 protein, KSHV-gH protein, auto-antibody to desmoglein 3 (Dsg3), autoantibody 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 antigen recognized by TNT antibody, thereby treating the subject or preventing a disease in the subject. In another or a further example, the disease associated with expression of the disease associated antigen is selected from the group consisting of a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the disease-associated antigen. In another or a further example, the cancer is a hematologic cancer chosen from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, primary effusion lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, or pre-leukemia. In another or a further example, the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina,

carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, Merkel cell cancer, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, and metastatic lesions of said cancers. In another or a further example, the disease is associated with infection by a virus including but not limited to HIV1, HIV2, HTLV1, Epstein Barr virus (EBV), cytomegalovirus (CMV), adenovirus, adeno-associated virus, BK virus, Human Herpesvirus 6, Human Herpesvirus 8 influenza virus, parainfluenza virus, avian flu virus, MERS and SARS coronaviruses, Crimean Congo Hemorrhagic fever virus, rhino virus, enterovirus, Dengue virus, West Nile virus, Ebola virus, Marburg virus, Lassa fever virus, zika virus, RSV, measles virus, mumps virus, rhino virus, varicella virus, herpes simplex virus 1 and 2, varicella zoster virus, HIV-1, HTLV1, Hepatitis virus, enterovirus, hepatitis B virus, Hepatitis C virus, Nipah and Rift valley fever viruses, Japanese encephalitis virus, Merkel cell polyomavirus, or is associated with infection with mycobacterium tuberculosis, atypical mycobacteria species, Pneumocystis jirovecii, toxoplasmosis, rickettsia, nocardia, aspergillus, mucor, or candida. In another or a further example, the disease is an immune or degenerative disease including but not limited to diabetes mellitus, multiple sclerosis, rheumatoid arthritis, pemphigus vulgaris, ankylosing spondylitis, Hashimoto's thyroiditis, SLE, sarcoidosis, scleroderma, mixed connective tissue disease, graft versus host disease or Alzheimer's disease.

[0015a] In another aspect, the present disclosure refers to use of a T cell as disclosed herein in the manufacture of a medicament for T cell therapy.

[0016] The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **Figure 1** depicts a cartoon of current an antibody, T-cell receptor (TCR), CAR and next generation CARs and SIRS.

[0018] **Figure 2** depicts a cartoon comparing second generation CAR biological activity and structure to an embodiment of the present disclosure depicting a CAR lacking CD28 or 41BB but expressing a NF- κ B stimulatory molecule (NEMO and/or K13, or mutants thereof).

WHAT IS CLAIMED IS:

1. A T cell or T cell population with impaired or abolished functional expression of an endogenous TCR and expressing at least one non-naturally occurring immune receptor selected from the group of SIR, cTCR, Ab-TCR and TFP.
2. The T cell or T cell population of claim 1, where the at least one non-naturally occurring immune receptor is expressed from an expression cassette placed in an endogenous TRAC locus, TRBC locus, TRGC locus and/or TRDC locus of the T cell.
3. The T cell or T cell population of claim 1, where the at least one non-naturally occurring immune receptor is under the control of the promoter and/or regulatory elements for an endogenous T cell gene.
4. The T cell or T cell population of claim 1, wherein the placement of the non-naturally occurring immune receptor expression cassette disrupts or abolishes the endogenous expression of a TCR comprising an endogenous TCR α chain and/or an endogenous TCR β chain, or an endogenous TCR γ chain and/or endogenous TCR δ chain in the T cell.
5. The T cell or T cell population of claim 1, wherein the disruption or abolished expression of an endogenous TCR results in enhanced expression and/or activity of the non-naturally occurring immune receptor as compared to its expression and/or activity in T cells with wild-type endogenous TCR.
6. The T cell or T cell population of claim 5, wherein the non-naturally occurring immune receptor is one or more of a SIR, a cTCR and/or an Ab-TCR or a combination thereof.
7. The T cell or T cell population of claim 1, wherein the non-naturally occurring immune receptor is a TFP and the disruption or abolished expression of an endogenous TCR results in impaired expression and/or activity of the TFP as compared to its expression and/or activity in T cells with wild-type endogenous TCR.

8. The T cell or T cell population of claim 1, wherein the non-naturally occurring immune receptor is a TFP and the T cell or T cell population further expresses a sequence encoding a TCR constant chain, wherein the TCR constant chain is

- (i) a TCR alpha constant chain or fragment thereof, or
- (ii) a TCR beta constant chain or a fragment thereof, or
- (iii) a TCR gamma constant chain or fragment thereof, or
- (iv) a TCR delta constant chain or a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

9. The T cell or T cell population of claim 7, wherein the expression of a sequence encoding a TCR constant chain restores the expression and/or activity of the TFP.

10. The T cell or T cell population of claim 8, wherein the TFP is one or more of CD3 ϵ -TFP (or TFP ϵ), CD3 γ -TFP (or TFP γ) or CD3 δ -TFP (or TFP δ).

11. The T cell or T cell population of claim 1, wherein a promotor-less recombinant nucleic acid sequence encoding a non-naturally occurring immune receptor is integrated at a site in the genome of the cell, said site being the first exon of the TCR alpha chain, such that the non-naturally occurring immune receptor is expressed under control of the endogenous TCR alpha chain promoter, to produce said non-naturally occurring immune receptor at the surface of the cell, and wherein integration of the non-naturally occurring immune receptor at said site reduces or prevents expression of a functional TCR alpha chain and wherein the expression and activity of the non-naturally occurring immune receptor is optionally enhanced by expression of a sequence encoding a TCR constant chain, wherein the TCR constant chain is

- (i) a TCR alpha constant chain or fragment thereof, or
- (ii) a TCR beta constant chain or a fragment thereof, or
- (iii) a TCR gamma constant chain or fragment thereof, or
- (iv) a TCR delta constant chain or a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

12. An induced pluripotent stem cell capable of giving rise to a T cell of claim 1, wherein a recombinant nucleic acid sequence encoding a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP is integrated at a site within the

genome of the cell such that the non-naturally occurring immune receptor is expressed by the cell at the surface of the cell, and wherein integration of the nucleic acid encoding the non-naturally occurring immune receptor at said site reduces or prevents expression of a functional T cell receptor (TCR) complex at the surface of the cell and wherein the expression and activity of the non-naturally occurring immune receptor is optionally enhanced by expression of a sequence encoding a TCR constant chain, wherein the TCR constant chain is

- (i) a TCR alpha constant chain or fragment thereof, or
- (ii) a TCR beta constant chain or a fragment thereof, or
- (iii) a TCR gamma constant chain or fragment thereof, or
- (iv) a TCR delta constant chain or a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

13. The T cell or T cell population of claim 1, wherein the T cell further lacks the expression of a functional HLA.

14. The T cell or T cell population of claim 1, wherein the T cell is not alloreactive.

15. The T cell or T cell population of claim 1, wherein the cell further expresses at least one non-naturally occurring agent capable of selectively activating NF- κ B pathway selected from the group consisting of vFLIP K13, K13-opt, a NEMO mutant, a NEMO-fusion protein, IKK1-S176E-S180E, IKK2-S177E-S181E, RIP, IKK α , IKK β , Tc1-1, MyD88-L265, any NF- κ B activating protein or protein fragment, any inhibitor of an inhibitor of NF- κ B pathway, any gene editing system capable of selectively activating NF- κ B, any homolog or variant thereof and any combination thereof.

16. The T cell or T cell population of claim 1, wherein the at least one non-naturally occurring immune receptor binds to an antigen selected from a group consisting of CD5; CD19; CD123; CD22; CD30; CD171; CS1 (also referred to as CD2 subset 1, CRACC, MPL, 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-ESO-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 IB 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 an antigen recognized by TNT antibody.

17. A method of generating a T cell or a population of T cells of claim 1 that expresses a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP and lacks a functional T cell receptor (TCR) complex, comprising:

introducing into a T cell:

(i) a nucleic acid sequence encoding a non-naturally occurring immune receptor selected from the group of a SIR, cTCR, Ab-TCR and TFP, and

(ii) a homologous recombination system suitable for targeted integration of the nucleic acid sequence at a site within the genome of the cell, whereby the homologous recombination system integrates the nucleic acid sequence encoding the non-naturally occurring immune receptor at said site within the genome of the cell such that integration of the non-naturally occurring immune receptor at said site reduces or prevents expression of a functional T cell receptor complex at the surface of the cell, thereby generating a T cell that expresses the non-naturally occurring immune receptor and lacks a functional TCR complex,

(iii) optionally expressing a sequence encoding a TCR constant chain, wherein the TCR constant chain is:

- (a) a TCR alpha constant chain or fragment thereof, or
- (b) a TCR beta constant chain or a fragment thereof, or
- (c) a TCR gamma constant chain or fragment thereof, or
- (d) a TCR delta constant chain or a fragment thereof, or
- (e) a combination of i) and ii) or iii) and iv),

(iv) optionally eliminating the expression of a functional HLA.

18. The T cell of claim 1, where the T cell is an autologous T cell, an allogeneic T cell, an induced pluripotent stem cell derived T cell, a stem cell derived T cell, a cytotoxic T-cell, regulatory T cell, immunoinhibitory T cell, CD4⁺ T cell, CD8⁺ cell, central memory T cell (TCM), stem memory T cell (TSCM), effector memory T cell, effector T cell, helper T-cell.

19. A pharmaceutical composition comprising a therapeutically effective amount of the T cell of claim 1; and a pharmaceutically acceptable carrier.

20. Use of a T cell of claim 1 in the manufacture of a medicament for T cell therapy.