

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 an immune cell, an immune effector cell or a stem cell that gives rise to an immune cell or immune effector cell with impaired or abolished functional expression of one or more endogenously expressed TCR chains selected from the group consisting of TCR α (or C α), TCR β 1 (C β 1), TCR β 2 (C β 2), TCR γ (C γ) and/or TCR δ (C δ) and expressing at least one non-naturally occurring immune receptor wherein the at least one non-naturally occurring immune receptor comprises of more than one TCR constant chains or can form a multimer with an endogenous TCR chain and/or CD3 γ , CD3 δ and CD3 ϵ chains and wherein the at least one non-naturally occurring immune receptor comprises one or more non-naturally occurring TCR antigen binding domains selected from the group of (i) an antibody or an antibody fragment thereof, (ii) an Fv, an Fab, or an (Fab')₂, (iii) a heavy chain variable region of an antibody (vH domain) or a fragment thereof, (iv) a light chain variable region of an antibody (vL domain) or a fragment thereof, (v) a single chain variable fragment (scFv) or a fragment thereof, (vi) a single domain antibody (SDAB) or a fragment thereof, (vii) a camelid vHH domain or a fragment thereof, (viii) a non-immunoglobulin antigen binding scaffold or a fragment thereof, (ix) a receptor or a fragment thereof, (x) a ligand or a fragment thereof, or (xi) an autoantigen or a fragment thereof, operatively linked via optional linker domains to: a) at least one exogenously expressed TCR constant chain selected from the group of constant chain of TCR α (or C α), TCR β 1 (or C β 1), TCR β 2 (or C β 2), TCR γ (or C γ) and TCR δ (or C δ) or a functional fragment or a variant thereof and where the at least one exogenously expressed TCR constant chain is expressed from an expression cassette placed in an endogenous gene locus; and/or b) at least one exogenously expressed CD3 chain selected from the group of CD3 γ , CD3 δ and CD3 ϵ chain or a functional fragment or a variant thereof and where the CD3 chain is co-expressed with at least one exogenously expressed TCR constant chain selected from the group of constant chain of TCR α (or C α), TCR β 1 (or C β 1), TCR β 2 (or C β 2), TCR γ (or C γ) and TCR δ (or C δ) or a functional fragment or a variant thereof.

[0005b] In another example, 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).

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 method of generating a cell as disclosed herein that expresses a non-naturally occurring immune receptor comprising: introducing into the cell: (i) a nucleic acid sequence encoding a non-naturally occurring immune receptor, 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, variant thereof or functional fragment thereof, or (b) a TCR beta constant chain, variant thereof or a functional fragment thereof, or (c) a TCR gamma constant chain, variant thereof or functional fragment thereof, or (d) a TCR delta constant chain, variant thereof or functional a fragment thereof, or (e) a combination of (a) and (b) or (c) and (d), (iv) optionally eliminating the expression of a functional HLA; (v) optionally expressing a non-naturally occurring agent that selectively activates that NF-kB pathway.

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-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.

[0014a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of the 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

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 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 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. An immune cell, an immune effector cell or a stem cell that gives rise to an immune cell or immune effector cell with impaired or abolished functional expression of one or more endogenously expressed TCR chains selected from the group consisting of TCR α (or C α), TCR β 1 (C β 1), TCR β 2 (C β 2), TCR γ (C γ) and/or TCR δ (C δ) and expressing at least one non-naturally occurring immune receptor wherein the at least one non-naturally occurring immune receptor comprises of more than one TCR constant chains or can form a multimer with an endogenous TCR chain and/or CD3 γ , CD3 δ and CD3 ϵ chains and wherein the at least one non-naturally occurring immune receptor comprises one or more non-naturally occurring TCR antigen binding domains selected from the group of

- (i) an antibody or an antibody fragment thereof,
- (ii) an Fv, an Fab, or an (Fab')₂,
- (iii) a heavy chain variable region of an antibody (vH domain) or a fragment thereof,
- (iv) a light chain variable region of an antibody (vL domain) or a fragment thereof,
- (v) a single chain variable fragment (scFv) or a fragment thereof,
- (vi) a single domain antibody (SDAB) or a fragment thereof,
- (vii) a camelid vHH domain or a fragment thereof
- (viii) a non-immunoglobulin antigen binding scaffold or a fragment thereof,
- (ix) a receptor or a fragment thereof,
- (x) a ligand or a fragment thereof, or
- (xi) an autoantigen or a fragment thereof,

operatively linked via optional linker domains to:

- a) at least one exogenously expressed TCR constant chain selected from the group of constant chain of TCR α (or C α), TCR β 1 (or C β 1), TCR β 2 (or C β 2), TCR γ (or C γ) and TCR δ (or C δ) or a functional fragment or a variant thereof and where the at least one exogenously expressed TCR constant chain is expressed from an expression cassette placed in an endogenous gene locus; and/or
- b) at least one exogenously expressed CD3 chain selected from the group of CD3 γ , CD3 δ and CD3 ϵ chain or a functional fragment or a variant thereof and where the CD3 chain is co-expressed with at least one exogenously expressed TCR constant chain selected from the group of constant chain of TCR α (or C α), TCR β 1 (or C β 1), TCR β 2 (or C β 2), TCR γ (or C γ) and TCR δ (or C δ) or a functional fragment or a variant thereof.

2. The cell of claim 1, where the endogenous gene locus is selected from the group consisting of TRAC locus, TRBC locus, TRGC locus and/or TRDC locus.
3. The cell 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 cell of claim 1, where the non-naturally occurring immune receptor comprises at least one exogenously expressed CD3 chain that is expressed from an expression cassette placed in an endogenous gene locus and where the expression cassette optionally co-expresses the at least one exogenously expressed TCR constant chain.
5. A cell of claim 1, wherein the endogenous gene locus is a first endogenous TCR locus, and a second endogenous TCR locus that is different from the first endogenous TCR locus is modified to eliminate the expression of an endogenous TCR chain encoded by the second endogenous TCR locus wherein the second endogenous TCR locus is optionally modified to express a gene.
6. The cell of claim 1, where the at least one non-naturally occurring immune receptor comprises one or more TCR constant chains and/or CD3 chains selected from the group consisting of:
 - (i) a T cell receptor alpha (TCR α) constant chain (C α) having an amino acid sequence represented by SEQ ID NO: 15041-15048 and 15133 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 15041-15048 and 15133 or a sequence that is at least 85% identical to SEQ ID NO:15041 and comprises one or more of the following position-amino acids 10C, 15C, 45C, 48C, 61R, 91S, 92D, 93V, and/or 94P or the equivalent residues from a non-human species;
 - (ii) a T cell receptor beta (TCR β) constant chain (C β) having an amino acid sequence represented by SEQ ID NO: 15051-15056, 15068 and 15134 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 15051-15056, 15068 and 15134 or an amino acid sequence that is at least 85% identical to SEQ ID NO:15051 or 15052 and comprises one or more of the following position-amino acids 15C, 17C, 18K or R, 22A, 57C, 59C, 77C, 79G, 133I, 136A and/or 139H or the equivalent residues from a non-human species;

(iii) a T cell receptor gamma (TCR γ) constant chain (C γ) having an amino acid sequence represented by SEQ ID NO: 15068 and 15135 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 15068 and 15135 or the equivalent residues from a non-human species;

(iv) a T cell receptor delta (TCR δ) constant chain (C δ) having an amino acid sequence represented by SEQ ID NO: 15069 and 15136 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 15069 and 15136 or the equivalent residues from a non-human species;

(v) a CD3 epsilon (CD3 ϵ) chain having an amino acid sequence represented by SEQ ID NO: 4861 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 4861 or the equivalent residues from a non-human species;

(vi) a CD3 gamma (CD3 γ) chain having an amino acid sequence represented by SEQ ID NO: 4862 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 4862 or the equivalent residues from a non-human species;

(vii) a CD3 delta (CD3 δ) chain having an amino acid sequence represented by SEQ ID NO: 4857 or a functional fragment or variant thereof or an amino acid sequence with at least 85% identity to SEQ ID NO: 4857 or the equivalent residues from a non-human species;

(viii) a combination of two T cell receptor chains selected from (i) and (ii) or (iii) and (iv).

7. The cell of claim 1 or 2, wherein the one or more exogenous TCR constant chains or functional fragments or variants thereof comprising the non-naturally occurring immune receptor comprise one or more mutations that a) enhance the expression of the exogenous TCR chains or functional fragments or variants thereof; b) enhance the pairing of the exogenous TCR chains or functional fragments or variants thereof; c) reduce the pairing of the exogenous TCR chains with the endogenous TCR chains or functional fragments or variants thereof; d) results in formation of an extra disulfide bond between the exogenous TCR chains or functional fragments or variants thereof.

8. The cell of claim 1, wherein the non-naturally occurring immune receptor comprises
a) the variable regions of heavy and light chains of an antibody or functional fragments thereof specific for a predefined target antigen, such that, when expressed, one of

said heavy and light chains of the antibody or fragments thereof is attached to one of said two T-cell receptor constant chains or functional fragments or variants thereof via an optional linker and the other of said heavy and light chains of the antibody or functional fragments thereof is attached to the other of said two T cell receptor constant chains or functional fragments or variants thereof via an optional linker; or

b) an scFv specific for a predefined target antigen attached to one of the two T cell receptor chains or functional fragments or variants thereof via an optional linker; or

c) one or two single domain antibody (SDAB) fragments specific for one or more predefined target antigens, such that, when expressed, one of said SDAB fragments is attached to one of said two T cell receptor chains or functional fragments or variants thereof via an optional linker and the other of said SDAB fragments is attached to the other of said two chains of said T-cell constant regions or functional fragments or variants thereof via an optional linker; or

d) one or two camelid vHH domains specific for one or more predefined target antigens, such that, when expressed, one of said vHH domains is attached to one of said two T cell receptor chains or functional fragments or variants thereof via an optional linker and the other of said vHH domains is attached to the other of said two chains of said T-cell constant regions or functional fragments or variants thereof via an optional linker; or

e) one or two non-immunoglobulin antigen binding scaffolds specific for one or more predefined target antigens, such that, when expressed, one of said non-immunoglobulin antigen binding scaffold is attached to one of said two T cell receptor chains or functional fragments or variants thereof via an optional linker and the other of said non-immunoglobulin antigen binding scaffold is attached to the other of said two chains of said T-cell constant regions or functional fragments or variants thereof via an optional linker.

9. A cell of claim 1, wherein the non-naturally occurring immune receptor comprises:

i) a first antigen-binding chain comprising a non TCR antigen binding domain comprising a heavy chain variable region of an antibody (vH domain) or a functional fragment thereof; and

ii) a second antigen-binding chain comprising a non TCR antigen binding domain comprising a light chain variable region of the antibody (vL domain) or a functional fragment thereof;

wherein the first and second antigen-binding chains each comprise a TCR α constant chain (TRAC) polypeptide or a TCR β constant chain (TRBC) polypeptide, wherein at least

one of the TRAC polypeptide and the TRBC polypeptide is endogenous, and the first and the second antigen-binding chains bind to an antigen, and the cell is a T cell or a pluripotent stem cell from which a T cell may be differentiated.

10. The cell of claim 9, wherein a) the first antigen-binding chain comprises an antigen-binding fragment of a vH domain of an antibody and an endogenous TRAC polypeptide; and the second antigen-binding chain comprising an antigen-binding fragment of a vL domain of an antibody and an exogenous TRBC polypeptide or b) the first antigen-binding chain comprises an antigen-binding fragment of a vL domain of an antibody and an endogenous TRAC polypeptide; and the second antigen-binding chain comprising an antigen-binding fragment of a vH domain of an antibody and an exogenous TRBC.

11. A cell of claim 1, where the at least one non-naturally occurring immune receptor binds to an antigen in an HLA-dependent or an HLA-independent manner.

12. The cell 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 a CD3 γ , CD3 δ or CD3 ϵ chain 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, variant thereof or functional fragment thereof, or
- (ii) a TCR beta constant chain, variant thereof or functional a fragment thereof, or
- (iii) a TCR gamma constant chain, variant thereof or functional fragment thereof, or
- (iv) a TCR delta constant chain, variant thereof or functional a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

13. The cell of claim 1, wherein a recombinant nucleic acid sequence encoding a non-naturally occurring immune receptor is integrated at a site within the genome of the cell such that the non-naturally occurring immune receptor is expressed under control of an endogenous gene promoter to produce said non-naturally occurring immune receptor 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 comprising a CD3 γ , CD3 δ or CD3 ϵ chain 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, variant thereof or functional fragment thereof, or
- (ii) a TCR beta constant chain, variant thereof or functional a fragment thereof, or
- (iii) a TCR gamma constant chain, variant thereof or functional fragment thereof, or
- (iv) a TCR delta constant chain, variant thereof or functional a fragment thereof, or
- (v) a combination of i) and ii) or iii) and iv).

14. 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; prostatein; 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 IB 1 (CYPIB 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 an antigen recognized by TNT antibody.

15. A method of generating a cell of claim 1 that expresses a non-naturally occurring immune receptor comprising:

introducing into the cell:

- (i) a nucleic acid sequence encoding a non-naturally occurring immune receptor, 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, variant thereof or functional fragment thereof, or
 - (b) a TCR beta constant chain, variant thereof or a functional fragment thereof, or
 - (c) a TCR gamma constant chain, variant thereof or functional fragment thereof, or
 - (d) a TCR delta constant chain, variant thereof or functional a fragment thereof, or
 - (e) a combination of (a) and (b) or (c) and (d),
- (iv) optionally eliminating the expression of a functional HLA;
- (v) optionally expressing a non-naturally occurring agent that selectively activates that NF-kB pathway.

16. The cell 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 and wherein

a) the non-naturally occurring immune receptor comprises constant chains of TCR α , TCR β 1, TCR β 2, TCR γ and/or TCR δ or fragments or variants thereof and 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 a cell with wild-type endogenous TCR; and/or

b) the non-naturally occurring immune receptor comprises a CD3 γ , CD3 δ or CD3 ϵ chain or fragments or variants thereof and the disruption or abolished expression of an endogenous TCR results in impaired expression and/or activity of the non-naturally occurring immune receptor as compared to its expression and/or activity in a cell with wild-type endogenous TCR and wherein the cell further expresses a sequence encoding an exogenous TCR constant chain, wherein the TCR constant chain is

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

wherein the expression of a sequence encoding a TCR constant chain restores the expression and/or activity of the non-naturally occurring immune receptor comprising a CD3 γ , CD3 δ or CD3 ϵ chain.

17. The cell 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 a) a mutant of NEMO/IKK γ that selectively and constitutively activates the NF- κ B pathway, b) a fusion protein comprising NEMO/IKK γ or a mutant thereof that allows drug-inducible selective activation of the NF- κ B pathway.

18. The cell of claim 1, wherein

(a) the immune cell and/or an immune effector cells is selected from the group consisting of alpha/beta T cell, gamma/delta T cell, cytotoxic T cell, helper T cell, an autologous T cell, an allogeneic 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, synthetic T cell, tumor infiltrating lymphocyte (TIL), a tissue resident lymphocyte, natural killer (NK) cell, natural killer T (NKT) cell, helper T-cell or combinations thereof; and

b) the stem cell that can give rise to an immune cell and/or an immune effector cell is selected from the group of hematopoietic stem cell, induced pluripotent stem cells (iPSC), pluripotent embryonic stem cells or embryonic stem cells.

19. A pharmaceutical composition comprising a therapeutically effective amount of the cell of claim 1; and a pharmaceutically acceptable carrier.
20. Use of a cell of claim 1 in the manufacture of a medicament for T cell therapy.