

including Ab-TCR (WO 2017/070608 A1 incorporated herein by reference), TCR receptor fusion proteins or TFP (WO 2016/187349 A1 incorporated herein by reference), Synthetic Immune Receptors (SIRs) (see, WO 2018/102795 A1, incorporated herein by reference), Tri-functional T cell antigen coupler (Tri-TAC) (see, WO 2015/117229 A1, incorporated herein by reference). These alternative CAR designs, in general, lack a co-stimulatory domain.

SUMMARY

[0007] The following examples and aspects thereof are described and illustrated in conjunction with systems, compositions and methods which are meant to be exemplary and illustrative, not limiting in scope.

[0008] In one aspect, the present disclosure refers to at least one recombinant polynucleotide encoding a synthetic immune receptor-CD3z (zSIR) comprising two polypeptide chains ~~where,~~ wherein each chain comprises one or more non-natural TCR antigen binding domains operably linked via linkers to a CD3z chain or ~~fragment~~ a functional portion thereof, wherein the non-natural TCR antigen binding domain(s) are selected from the group consisting of: a) an antibody; b) an antibody fragment selected from a Fv, a Fab, or an (Fab')₂; c) a single chain variable fragment (scFv) or a fragment thereof; d) a single domain antibody (SDAB) or a fragment thereof; e) a camelid VHH domain or a fragment thereof; f) a monomeric variable region of an antibody; g) a non-immunoglobulin antigen binding scaffold or a fragment thereof; h) a receptor or a fragment thereof; i) a ligand or a fragment thereof; and wherein the linkers (1) are derived from antibodies; or (2) are longer than 100 amino acids in length; or (3) are between 5-20 amino acids in length; or (4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or (5) differ in length by no more than 20 amino acids; or comprises a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof ~~CD3z chain or fragment thereof comprises the partial or entire transmembrane, cytosolic and optionally the extracellular domain of CD3z or a variant thereof.~~ In another aspect, the present disclosure refers to at least one recombinant polynucleotide encoding a synthetic immune receptor-CD3z (zSIR) comprising two polypeptide chains wherein the first polypeptide chain comprises the vL fragment of an antibody operably linked to a first CD3z chain or a functional portion thereof and second polypeptide chain comprises the vH fragment of an antibody operably linked to a second CD3z chain or functional portion thereof, wherein when expressed in a cell, the vL and vH fragment can associate to bind to their cognate antigen in an MHC-dependent and/or MHC-independent manner, and wherein: (a) the vL and vH fragments are operably linked directly to one or both CD3z chains or functional portions thereof; and/or (b) the vL and vH fragments are operably linked to one or both CD3z chains or functional portions thereof via linker(s), where the linker(s) (1) are derived from antibodies; or (2) are longer than 100 amino acids in length; or (3) are between 5-20 amino acids in length; or (4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or (5) differ in length by no more than 20 amino acids; or comprise a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof. In one example, the present disclosure refers to a synthetic immune receptor-CD3z (zSIR) polypeptide or polypeptide dimer comprising two chains encoded by the at least one recombinant polynucleotide as disclosed herein, wherein each chain comprises one or more non-natural TCR antigen binding domains operably linked to a partial or entire transmembrane, cytosolic and optional extracellular domain of a CD3z chain or a variant thereof.

[0008a] In another aspect, the present disclosure refers to a recombinant polynucleotide as disclosed herein, comprising a polynucleotide encoding the vL and vH fragments whose SEQ ID NOs and target antigens are listed in Table 3 and whose complementarity determining region 1 (CDR1), 2 (CDR2) and 3 (CDR3) SEQ ID NOs are listed in Table 4, wherein a) the vL fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, the CDR2 amino acid sequence of SEQ ID NO: 12062-12173, 16157-16186 and the CDR3 amino acid sequence of SEQ ID NO: 12175-12280, 16188- 16217 listed in Table 4, and wherein the polynucleotide encoding the vL domain is at least 80% identical to the nucleotide sequence of SEQ ID NO 155-227, 8000-8029, 11300-11302, 12642-12671 provided that the vL domain comprises the CDR1 amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, CDR2 amino acid sequence of SEQ ID NO: 12068-12173, 16157-16186 and CDR3 amino acid sequence of SEQ ID NO:12175-12280,16188-16217; and b) wherein the complementary vH fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO: 12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310 as shown in Table 4, wherein the polynucleotide encoding the vH domain is at least 80% identical to the nucleotide sequence of SEQ ID NO: 229-301, 8031-8060, 11304-11306, 12673-12702 provided that the vH domain comprises the CDR1 amino acid sequence of SEQ ID NO:12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310. In another aspect, the present disclosure refers to a synthetic immune receptor-CD3z (zSIR) polypeptide dimer comprising two polypeptide chains, wherein each chain comprises one or more non-natural TCR antigen binding domains operably linked via linkers to a CD3z chain or a functional portion thereof, wherein the non-natural TCR antigen binding domain(s) are selected from the group consisting of: a) an antibody; b) an antibody fragment selected from a Fv, a Fab, or an (Fab')₂; c) a single chain variable fragment (scFv) or a fragment thereof; d) a single domain antibody (SDAB) or a fragment thereof; e) a camelid VHH domain or a fragment thereof; f) a monomeric variable region of an antibody; g) a non-immunoglobulin antigen binding scaffold or a fragment thereof; h) a receptor or a fragment thereof; i) a ligand or a fragment thereof; and wherein the linkers (1) are derived from antibodies; or (2) are longer than 100 amino acids in length; or (3) are between 5-20 amino acids in length; or (4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or (5) differ in length by no more than 20 amino acids; or comprise a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof. In another aspect, the present disclosure refers to a synthetic immune receptor-CD3z (zSIR) polypeptide dimer comprising two polypeptide chains where the first polypeptide chain comprises the vL fragment of an antibody operably linked to a first CD3z chain or a functional portion thereof and second polypeptide chain comprises the vH fragment of an antibody operably linked to a second CD3z chain or functional portion thereof, wherein when expressed in a cell, the vL and vH fragment can associate to bind to their cognate antigen, and wherein: (a) the vL and vH fragments are operably linked directly to one or both CD3z chains or functional portions thereof; and/or (b) the vL and vH fragments are operably linked to one or both CD3z chains or functional portions thereof via linker(s), where the linker(s) (1) are derived from antibodies; or (2) are longer than 100 amino acids in length; or (3) are between 5-20 amino acids in length; or (4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or (5) differ in length by no more than 20 amino acids; or comprises a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof. In another aspect, the present disclosure refers to a zSIR polypeptide dimer as disclosed herein, wherein the CD3z chain or a functional portion thereof comprises a polypeptide with at least 75% sequence identity to a polypeptide having a sequence selected from SEQ ID NO: 4064, 4065, 4070-4072, and 4075-4078.

In another aspect, the present disclosure refers to a zSIR polypeptide as disclosed herein, comprising the vL and vH fragments whose SEQ ID NOs and target antigens are listed in Table 3 and whose complementarity determining region 1 (CDR1), 2 (CDR2) and 3 (CDR3) SEQ ID NOs are listed in Table 4, wherein a) the vL fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, the CDR2 amino acid sequence of SEQ ID NO: 12062-12173, 16157-16186 and the CDR3 amino acid sequence of SEQ ID NO: 12175-12280, 16188- 16217 listed in Table 4, and wherein the polypeptide encoding the vL domain is at least 80% identical to the amino acid sequence of SEQ ID NO 4118 to 4190, 9631 to 9660 and 11460 to 11462, 14386 to 14415 provided that the vL domain comprises the CDR1 amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, CDR2 amino acid sequence of SEQ ID NO: 12068-12173, 16157-16186 and CDR3 amino acid sequence of SEQ ID NO:12175-12280,16188-16217; and b) wherein the complementary vH fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO: 12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310 as shown in Table 4, wherein the polynucleotide encoding the vH domain is at least 80% identical to the amino acid sequence of SEQ ID NO: 4192 to 4264, 9662 to 9691, 11464 to 11466 and 14417 to 14446 provided that the vH domain comprises the CDR1 amino acid sequence of SEQ ID NO:12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310. In another aspect, the present disclosure refers to at least one vector comprising the recombinant polynucleotide as disclosed herein, wherein the vector is selected from the group consisting of a DNA vector, an RNA vector, a plasmid, a lentivirus vector, adenoviral vector, a retrovirus vector, and a sleeping beauty transposon vector. In another aspect, the present disclosure refers to a recombinant cell comprising i) at least one polypeptide or heterodimer as disclosed herein; ii) at least one recombinant polynucleotide as disclosed herein; and/or iii) at least one vector as disclosed herein, wherein the cell is an autologous [cell](#) or an allogeneic cell, [and wherein the cell is](#) selected from the group of a T cell, an NKT cell, a NK cell, a hematopoietic stem cell, an embryonic stem cell or an induced pluripotent stem cell. In another aspect, the present disclosure refers to a composition comprising at least one polynucleotide, a polypeptide or polypeptide heterodimer, a vector or a cell as disclosed herein, and a pharmaceutically acceptable excipient. [In another aspect, the present disclosure refers to the use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of zSIR polynucleotides as disclosed herein or zSIR polypeptide heterodimers as disclosed herein in the manufacture of a medicament for treating a subject having a disease associated with expression of a disease associated antigen, wherein the zSIR binds to one or more disease associated antigens selected from a group consisting of: CD5, CD19; CD123; CD22; CD30; CD171; CS-1 \(also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24\); BAFF-R, C-type lectin-like molecule-1 \(CLL-1 or CLECL1\); CD33; MPL; 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 \(GalNAc \$\alpha\$ -Ser/Thr\)\); 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 \(IL-13Ra2 or CD213A2\); 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](#); [Receptor tyrosine-protein kinase ERBB2 \(Her2/neu\)](#); [Mucin 1, cell surface associated \(MUC1\)](#); [epidermal growth factor receptor \(EGFR\)](#); [neural cell adhesion molecule \(NCAM\)](#); [Protease](#); [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 \(EphA2\)](#); [Fucosyl GM1](#); [sialyl Lewis adhesion molecule \(sLe\)](#); [ganglioside GM3 \(aNeu5Ac\(2-3\)bDCIalp\(1-4\)bDGlcp\(1-1\)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 \(XAGEL\)](#); [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](#); [surviving](#); [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 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, MPL, GPA33, BST1/CD157, low conductance chloride channel, Integrin B7, Muc17, C16ORF54, VISTA, Muc5Ac, FCRH5, CLDN6, MMP16, UPK1B, BMPR1B, Ly6E, WISP1 and SLC34A2. In yet another aspect, the present disclosure refers to a use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of zSIR polynucleotides of claim 1 or 2 or zSIR ~~polypeptides or~~ polypeptide heterodimers of claim 7 or 8 for ~~use alone or in combination therapy with an agent that increases the efficacy and or safety of the immune effector cell~~ in the manufacture of a medicament for use in combination therapy for treating a subject having a disease associated with expression of a disease associated antigen, ~~wherein or in the zSIR binds to one or more~~ prevention of disease in a subject having an increased risk of a disease associated with expression of a disease associated antigens, ~~wherein 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(l-4)bDGlcpl(l-l)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

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, 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, MPL, GPA33, BST1/CD157, low conductance chloride channel, Integrin B7, Muc17, C16ORF54, VISTA, Muc5Ac, FCRH5, CLDN6, MMP16, UPK1B, BMPR1B, Ly6E, WISP1 and SLC34A2, ~~wherein said medicament is to be administered in combination with an agent that increases the efficacy and or safety of the immune effector cell; and the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of: (i) a protein phosphatase inhibitor; (ii) a kinase inhibitor; (iii) a cytokine; (iv) an inhibitor of an immune inhibitory molecule; or (v) an agent that decreases the level or activity of a TREG cell; vi) an agent that increase the proliferation and/or persistence of zSIR-modified cells; vii) a chemokine; viii) an agent that increases the expression of ZIR; ix) an agent that allows regulation of the expression or activity of zSIR; x) an agent that allows control over the survival and/or persistence of CAR-modified cells, xi) an agent that controls the side effects of zSIR-modified cells, xii) a Brd4 inhibitor xiii) an agent that delivers a therapeutic or prophylactic agent to the site of the disease, xiv) an agent that increases the expression of the target antigen against which zSIR is directed; xv) an adenosine A2a receptor antagonist; xvi) an agent that depletes monocytes and/or macrophages; xvii) Etoposide; xviii) dasatinib.~~ In yet another aspect, the present disclosure refers to an immune effector cell comprising a zSIR polynucleotide of claim 1 or 2 either alone or in combination with an agent that increases the efficacy and or safety of the immune cell for use in disease therapy, wherein the zSIR comprises one or more of antigen binding domains that bind to ~~the one or more~~ disease-associated antigens ~~associated with the disease, and 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-I)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 (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; 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

What is claimed is:

1. At least one recombinant polynucleotide encoding a synthetic immune receptor-CD3z (zSIR) comprising two polypeptide chains ~~where, wherein~~ each chain comprises one or more non-natural TCR antigen binding domains operably linked via linkers to a CD3z chain or fragmenta functional portion thereof, wherein the ~~CD3z chain or fragment thereof comprises the partial or entire transmembrane, cytosolic and optionally the extracellular domain of CD3z or a variant thereof.~~
- ~~2. The at least one recombinant polynucleotide of claim 1, wherein the CD3z chain or fragment thereof comprises a polypeptide with at least 75% sequence identity to a polypeptide having the sequence of SEQ ID NO: 4064, 4065 or 4066.~~
- ~~3. The at least one recombinant polynucleotide of claim 1, wherein one or both chains of the zSIR comprise one or more co-stimulatory domains.~~
- ~~4. The at least one recombinant polynucleotide of claim 3, wherein the co-stimulatory domain comprises the cytosolic domain of 4-1BB and/or CD28 or variants thereof.~~
- ~~5. The at least one recombinant polynucleotide of claim 1, further comprising a coding sequence for a linker between the one or more non-natural TCR antigen binding domain and the CD3z chain or variant thereof.~~
- ~~6. The at least one recombinant polynucleotide of claim 5, wherein the linker is derived from immunoglobulin.~~
- ~~7. The at least one recombinant polynucleotide of claim 6, wherein the linker comprises an IgCL or IgG1-CH1 sequence or fragment thereof.~~
- ~~8. The at least one recombinant polynucleotide of claim 5, wherein the linker comprises a polypeptide with at least 85% homology to a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037.~~
9. ~~A at least one recombinant polynucleotide of claim 1, where the one or more~~ non-natural TCR antigen binding domain(s) are selected from the group consisting of:
 - a) an antibody;

- b) an antibody fragment selected from ~~(e.g.~~ a Fv, a Fab, or an (Fab')₂);
- ~~c) a heavy chain variable region of an antibody (vH domain) or a fragment thereof;~~
- ~~d) a light chain variable region of an antibody (vL domain) or a fragment thereof;~~
- ~~e) a single chain variable fragment (scFv) or a fragment thereof;~~
- ~~f) a single domain antibody (SDAB) or a fragment thereof;~~
- ~~g) a camelid VHH domain or a fragment thereof;~~
- ~~h) a monomeric variable region of an antibody;~~
- ~~i) a non-immunoglobulin antigen binding scaffold or a fragment thereof;~~
- ~~j) a receptor or a fragment thereof;~~
- ~~k) a ligand or a fragment thereof;~~ and

wherein the linkers

- (1) are derived from antibodies; or
- (2) are longer than 100 amino acids in length; or
- (3) are between 5-20 amino acids in length; or
- (4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or
- (5) differ in length by no more than 20 amino acids; or
- comprises a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof.

~~10.2.~~ At least one recombinant polynucleotide encoding a synthetic immune receptor-CD3z (zSIR) polypeptide or polypeptide dimer comprising two polypeptide chains encoded by the at least one recombinant polynucleotide of claim 1-9, wherein the first polypeptide chain comprises the vL fragment of an antibody operably linked to a first CD3z chain or a functional portion thereof and second polypeptide chain comprises the vH fragment of an antibody wherein each chain comprises one or more non-natural TCR antigen binding domains operably linked to a second partial or entire transmembrane, cytosolic and optional extracellular domain of a CD3z chain or a variant functional portion thereof, wherein when expressed in a cell, the vL and vH fragment can associate to bind to their cognate antigen in an MHC-dependent and/or MHC-independent manner, and wherein:-

(a) the vL and vH fragments are operably linked directly to one or both CD3z chains or functional portions thereof; and/or

(b) the vL and vH fragments are operably linked to one or both CD3z chains or functional portions thereof via linker(s), where the linker(s)

(1) are derived from antibodies; or

(2) are longer than 100 amino acids in length; or

(3) are between 5-20 amino acids in length; or

(4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or

(5) differ in length by no more than 20 amino acids; or

comprise a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof.

3. The recombinant polynucleotide of claims 1 or 2, wherein the encoded CD3z chain or functional portion thereof comprises the transmembrane domain and/or cytoplasmic domain and optionally the extracellular domain of a CD3z protein.

4. The recombinant polynucleotide of claim 1 or 2, wherein encoded one or both CD3z chains comprise one or more co-stimulatory domains, wherein optionally the co-stimulatory domain comprises the cytosolic domain of 4-1BB and/or CD28 or variants thereof, wherein the costimulatory module comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 4067 and 4068.

5. The recombinant polynucleotide of claims 1, 2, or 4 wherein the encoded CD3z chain or functional portion thereof comprises a polypeptide with at least 75% sequence identity to a polypeptide having the sequence of SEQ ID NO: 4064-4065, 4070-4072 and 4075-4078 or equivalent residues from a non-human species.

6. A recombinant polynucleotide of claim 2, comprising a polynucleotide encoding the vL and vH fragments whose SEQ ID NOs and target antigens are listed in Table 3 and whose complementarity determining region 1 (CDR1), 2 (CDR2) and 3 (CDR3) SEQ ID NOs are listed in Table 4, wherein

a) the vL fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, the CDR2 amino acid

sequence of SEQ ID NO: 12062-12173, 16157-16186 and the CDR3 amino acid sequence of SEQ ID NO: 12175-12280, 16188- 16217 listed in Table 4, and wherein the polynucleotide encoding the vL domain is at least 80% identical to the nucleotide sequence of SEQ ID NO 155-227, 8000-8029, 11300-11302, 12642-12671 provided that the vL domain comprises the CDR1 amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, CDR2 amino acid sequence of SEQ ID NO: 12068-12173, 16157-16186 and CDR3 amino acid sequence of SEQ ID NO:12175-12280,16188-16217; and

b) wherein the complementary vH fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO: 12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310 as shown in Table 4, wherein the polynucleotide encoding the vH domain is at least 80% identical to the nucleotide sequence of SEQ ID NO: 229-301, 8031-8060, 11304-11306, 12673-12702 provided that the vH domain comprises the CDR1 amino acid sequence of SEQ ID NO:12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310.

7. A synthetic immune receptor-CD3z (zSIR) polypeptide dimer comprising two polypeptide chains, wherein each chain comprises one or more non-natural TCR antigen binding domains operably linked via linkers to a CD3z chain or a functional portion thereof, wherein the non-natural TCR antigen binding domain(s) are selected from the group consisting of:

- a) an antibody;
- b) an antibody fragment selected from a Fv, a Fab, or an (Fab')₂;
- c) a single chain variable fragment (scFv) or a fragment thereof;
- d) a single domain antibody (SDAB) or a fragment thereof;
- e) a camelid VHH domain or a fragment thereof;
- f) a monomeric variable region of an antibody;
- g) a non-immunoglobulin antigen binding scaffold or a fragment thereof;
- h) a receptor or a fragment thereof;
- i) a ligand or a fragment thereof; and

wherein the linkers

(1) are derived from antibodies; or
(2) are longer than 100 amino acids in length; or
(3) are between 5-20 amino acids in length; or
(4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or
(5) differ in length by no more than 20 amino acids; or
comprise a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof.

8. A synthetic immune receptor-CD3z (zSIR) polypeptide dimer comprising two polypeptide chains where the first polypeptide chain comprises the vL fragment of an antibody operably linked to a first CD3z chain or a functional portion thereof and second polypeptide chain comprises the vH fragment of an antibody operably linked to a second CD3z chain or functional portion thereof, wherein when expressed in a cell, the vL and vH fragment can associate to bind to their cognate antigen, and wherein:
(a) the vL and vH fragments are operably linked directly to one or both CD3z chains or functional portions thereof; and/or

(b) the vL and vH fragments are operably linked to one or both CD3z chains or functional portions thereof via linker(s), where the linker(s)

(1) are derived from antibodies; or
(2) are longer than 100 amino acids in length; or
(3) are between 5-20 amino acids in length; or
(4) are between 1-500 amino acids in length and the two linkers differ in length by no more than 20 amino acids; or
(5) differ in length by no more than 20 amino acids; or
comprises a polypeptide having the sequence of any one of SEQ ID NOs: 4007-4037 or with at least 85% homology thereof.

9. The zSIR polypeptide dimer of claims 7 or 8, wherein the CD3z chain or a functional portion thereof comprises the transmembrane domain and/or cytoplasmic domain and optionally the extracellular domain of a CD3z protein.

10. A zSIR polypeptide or polypeptide dimer of claims 7 or 8, wherein the CD3z chain or a functional portion thereof comprises a polypeptide with at least

75% sequence identity to a polypeptide having a sequence ~~of~~ selected from SEQ ID NO: 4064, 4065 ~~or 4066, 4070-4072, and 4075-4078.~~

~~12.11.~~ The zSIR polypeptide ~~or polypeptide~~ heterodimer of claim ~~107 or 8,~~ wherein said ~~vL and vH domains~~ ~~one or the more~~ non-natural TCR antigen binding domain(s) bind to one or more ~~of~~ disease-associated antigens 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; 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 (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; 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); Fucosyl GM1; 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; prostatein; surviving; 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 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-IGL1, 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, MPL, GPA33, BST1/CD157, low conductance chloride channel, Integrin B7, Muc17, C16ORF54, VISTA, Muc5Ac, FCRH5, CLDN6, MMP16, UPK1B, BMPR1B, Ly6E, WISP1 and SLC34A2.

12. A zSIR polypeptide of claims 7 or 8, comprising the vL and vH fragments whose SEQ ID NOs and target antigens are listed in Table 3 and whose complementarity determining region 1 (CDR1), 2 (CDR2) and 3 (CDR3) SEQ ID NOs are listed in Table 4, wherein

a) the vL fragment contains the complementarity determining region 1 (CDR1) amino acid sequence of SEQ ID NO.:11961-12066, 16126-16155, the CDR2 amino acid sequence of SEQ ID NO: 12062-12173, 16157-16186 and the CDR3 amino acid sequence of SEQ ID NO: 12175-12280, 16188- 16217 listed in Table 4, and wherein the polypeptide encoding the vL domain is at least 80% identical to the amino acid sequence of SEQ ID NO 4118 to 4190, 9631 to 9660 and 11460 to 11462, 14386 to 14415 provided that the vL domain comprises the CDR1 amino acid sequence of SEQ

[ID NO.:11961-12066, 16126-16155, CDR2 amino acid sequence of SEQ ID NO: 12068-12173, 16157-16186 and CDR3 amino acid sequence of SEQ ID NO:12175-12280,16188-16217; and](#)

[b\) wherein the complementary vH fragment contains the complementarity determining region 1 \(CDR1\) amino acid sequence of SEQ ID NO: 12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310 as shown in Table 4, wherein the polynucleotide encoding the vH domain is at least 80% identical to the amino acid sequence of SEQ ID NO: 4192 to 4264, 9662 to 9691, 11464 to 11466 and 14417 to 14446 provided that the vH domain comprises the CDR1 amino acid sequence of SEQ ID NO:12282-12387, 16219-16248, CDR2 amino acid sequence of SEQ ID NO: 12389-12494, 16250-16279 and CDR3 amino acid sequence of SEQ ID NO:12497-12602, 6281-16310.](#)

13. The zSIR polypeptide or polypeptide heterodimer of claims ~~40-7~~ or ~~44~~[8](#), wherein said one or more non-natural TCR antigen binding domain(s) comprise:

(i) a heavy chain variable region (vH) comprising a sequence as set forth in any of SEQ ID Nos: SEQ ID NO 4192 to 4264, 9662 to 9691, 11464 to 11466 and 14417 to 14446 wherein up to 9 amino acid residues but no more than 10 amino acids are replaced by any other amino acid residues or sequences with 80-100% identity to amino acid sequences of SEQ ID NO 4192 to 4264, 9662 to 9691, 11464 to 11466, and 14417 to 14446 or sequences with 85-100% identity to the complementarity determining regions (CDR's) of any one of SEQ ID NO 4192 to 4264, 9662 to 9691, 11464 to 11466, and 14417 to 14446, [whose SEQ ID NOs are provided in Table 4,](#) and which [vH region](#) encodes a polypeptide that [associates with the complementary vL chain listed in Table 3 and](#) binds to its [cognate](#) antigen; and/or

(ii) a light chain variable region (vL) comprising a sequence as set forth in any one of SEQ ID NO SEQ ID NO 4118 to 4190, 9631 to 9660 and 11460 to 11462, 14386 to 14415 targeting that antigen as listed in **Table 3** wherein up to 9 amino acid residues but no more than 10 amino acids are replaced by any other amino acid residues, or sequences with 80-100% identity to amino acid sequences as set forth in any one of SEQ ID NO 4118 to 4190, 9631 to 9660, or 11460 to 11462 and 14386 to 14415, or sequences with 85-100% identity to the complementarity determining regions (CDR's) of any one of SEQ ID NO SEQ ID NO 4118 to 4190, 9631 to 9660, or 11460 to 11462

and 14386 to 14415, whose SEQ ID NOs are provided in Table 4, and which vL region encodes a polypeptide that associates with the complementary vH chain listed in Table 3 and binds to its cognate antigen;~~or~~

(iii) a single chain variable fragment (scFv) comprising a sequence as set forth in any one SEQ ID NO: SEQ ID NO 4266 to 4338, 9693 to 9722, 11468 to 11470, and 14448-14477 wherein up to 9 amino acid residues but no more than 10 amino acids are replaced by any other amino acid residues or sequences with 80-100% identity to amino acid sequences of SEQ ID NO 4266 to 4338, 9693 to 9722, 11468 to 11470, and 14448-14477 or sequences with 85-100% identity to the complementarity determining regions (CDR's) of SEQ ID NO 4266 to 4338, 9693 to 9722, 11468 to 11470 and 14448-14477 and which encodes a polypeptide that binds to its antigen.

14. At least one vector comprising the recombinant polynucleotide of claims 1 or 2, wherein the vector is selected from the group consisting of a DNA vector, an RNA vector, a plasmid, a lentivirus vector, adenoviral vector, a retrovirus vector, and a sleeping beauty transposon vector.

15. A recombinant cell comprising

- i) at least one polypeptide or heterodimer of claims 7 or 8~~10~~;
- ii) at least one recombinant polynucleotide of claims 1 or 2; and/or
- iii) at least one vector of claim 14,

wherein the cell is an autologous cell or an allogeneic cell, and where the cell is selected from the group of a T cell, an NKT cell, a NK cell, a hematopoietic stem cell, an embryonic stem cell or an induced pluripotent stem cell.

16. A composition comprising at least one polynucleotide of claims 1 or 2, a polypeptide or polypeptide heterodimer of claims 107 or 8, a vector of claim 14 or the cell of claim 15, and a pharmaceutically acceptable excipient.

17. Use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of zSIR polynucleotides of claim 1 or 2 or zSIR polypeptide heterodimers of claim 7 or 8 in the manufacture of a medicament for treating a subject having a disease associated with expression of a disease associated antigen, wherein the zSIR binds to one or more disease associated

antigens 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; 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 (GalNAcα-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 (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; 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); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanomaassociated 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; prostatein;](#)
[surviving; 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 \(CYPIB 1 \); 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 \(OY-TESI\); 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](#), [GPCR5D](#), [claudin18.2 \(CLD18A2 OR CLDN18A.2\)](#), [P-glycoprotein](#), [STEAP1](#), [LIV1](#), [NECTIN-4](#), [CRIPTO](#), [MPL](#), [GPA33](#), [BST1/CD157](#), [low conductance chloride channel](#), [Integrin B7](#), [Muc17](#), [C16ORF54](#), [VISTA](#), [Muc5Ac](#), [FCRH5](#), [CLDN6](#), [MMP16](#), [UPK1B](#), [BMPRI1B](#), [Ly6E](#), [WISP1](#) and [SLC34A2](#).

~~17-18.~~ Use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of zSIR polynucleotides [of claim 1 or 2](#) or zSIR ~~polypeptides or~~ polypeptide heterodimers [of claim 7 or 8](#) for ~~use alone or in combination therapy with an agent that increases the efficacy and or safety of the immune effector cell~~ in the manufacture of a medicament for [use in combination therapy for](#) treating a subject having a disease associated with expression of a disease associated antigen, ~~wherein or in the zSIR binds to one or more prevention of disease in a subject having an increased risk of a disease associated with expression of a disease associated antigens, wherein 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlcp(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 (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; 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); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(l-4)bDGlcpl(l-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanomaassociated 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; prostatein; surviving; 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-TESI); 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 (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, ALK TCRgamma-delta, NKG2D, CD32 (FCGR2A), CSPG4-HMW-MAA, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, VEGFR2/KDR, Lewis 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, MPL, GPA33, BST1/CD157, low conductance chloride channel, Integrin B7, Muc17, C16ORF54, VISTA, Muc5Ac, FCRH5, CLDN6, MMP16, UPK1B, BMPR1B, Ly6E, WISP1 and SLC34A2; ~~and the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of: (i) a protein phosphatase inhibitor; (ii) a kinase inhibitor; (iii) a cytokine; (iv) an inhibitor of an immune inhibitory molecule; or (v) an agent that decreases the level or activity of a TREG cell; vi) an agent that increase the proliferation and/or persistence of zSIR modified cells; vii) a chemokine; viii) an agent that increases the expression of ZIR; ix) an agent that allows regulation of the expression or activity of zSIR; x) an agent that allows control over the survival and/or persistence of CAR modified cells; xi) an agent that controls the side effects of zSIR modified cells; xii) a Brd4 inhibitor xiii) an agent that delivers a therapeutic or prophylactic agent to the site of the disease, xiv) an agent that increases the expression of the target antigen against which zSIR is directed; xv) an adenosine A2a receptor antagonist; xvi) an agent that depletes monocytes and/or macrophages; xvii) Etoposide; xviii) dasatinib, wherein said medicament is to be administered in combination with an agent that increases the efficacy and or safety of the immune effector cell.~~

~~18-19.~~ An immune effector cell comprising a zSIR polynucleotide of claim 1 or 2 either alone or in combination with an agent that increases the efficacy and or safety of the immune cell for use in disease therapy, wherein the zSIR comprises one or more of antigen binding domains that bind to the one or more disease-associated antigens ~~associated with the disease, and 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); BAFF-R, C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; MPL; 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 (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; 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); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3 (aNeu5Ac(2-3)bDCIalp(l-4)bDGlcpl(l-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanomaassociated 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; surviving; 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 (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-TESI); 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 (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, 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, MPL, GPA33, BST1/CD157, low conductance chloride channel, Integrin B7, Muc17, C16ORF54, VISTA, Muc5Ac, FCRH5, CLDN6, MMP16, UPK1B, BMPR1B, Ly6E, WISP1 and SLC34A2; and the agent that increases the efficacy and or safety of the immune cell is chosen from one or more of:

(i) a protein phosphatase inhibitor; (ii) a kinase inhibitor; (iii) a cytokine; (iv) an inhibitor of an immune inhibitory molecule; or (v) an agent that decreases the level or activity of a TREG cell; vi) an agent that increase the proliferation and/or persistence of zSIR-modified cells; vii) a chemokine; viii) an agent that increases the expression of ZIR; ix) an agent that allows regulation of the expression or activity of zSIR; x) an agent that allows control over the survival and/or persistence of CAR-modified cells, xi) an agent that controls the side effects of zSIR-modified cells, xii) a Brd4 inhibitor xiii) an agent that delivers a therapeutic or prophylactic agent to the site of the disease, xiv) an agent that increases the expression of the target antigen against which zSIR is directed; xv) an adenosine A2a receptor antagonist; xvi) an agent that depletes monocytes and/or macrophages; xvii) Etoposide; xviii) dasatinib.

~~19-20.~~ 19-20. The use of claim 17 or 18, or the immune effector cell comprising a zSIR for use of claim ~~18~~19, wherein the disease is 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, pre-leukemia, 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.

~~20-21.~~ 21. A kit comprising at least one polynucleotide of claims 1 or 2, a SIR polypeptide molecule of claims 4 or 8, a vector of claim 14 or the cell of claim 15 and/or a composition of claim 16.