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 wherein the first polypeptide chain comprises the vL fragment of an antibody operably linked to a first CD3z chain via a cL linker having the sequence of SEQ ID NO: 4027 and second polypeptide chain comprises the vH fragment of the antibody operably linked to a second CD3z chain via a CH1 linker having the sequence of any one of SEQ ID NOs: 402804937, wherein when expressed in a cell, the vL and vH fragments can associate to bind to their cognate antigen in an MHC-dependent or MHC-independent manner..

[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.

[0008b] 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 via a cL linker having the sequence of SEQ ID NO: 4027 and second polypeptide chain comprises the vH fragment of the antibody operably linked to a second CD3z chain having a CH1 linker having the sequence of any one of SEQ ID NOs: 4028-4037, wherein when expressed in a cell, the vL and vH fragments can associate to bind to their cognate antigen in an MHC-dependent or MHC-independent manner.

[0008c] In another aspect, the present disclosure refers to a zSIR polypeptide dimer as disclosed herein, wherein the CD3z chain comprises a polypeptide having a sequence selected from SEQ ID NO: 4064, 4065, 4070-4072, and 4075-4078.

[0008d] In another aspect, the present disclosure refers to a zSIR polypeptide dimer 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.

[0008e] 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.

[0008f] In another aspect, the present disclosure refers to a recombinant cell comprising i) at least one zSIR polypeptide dimer 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.

[0008g] In another aspect, the present disclosure refers to a composition comprising at least one polynucleotide as described herein, a zSIR polypeptide dimer as described herein, a vector as described herein or the cell as described herein, and a pharmaceutically acceptable excipient.

[0008h] 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 dimer 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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.

[0008i] 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 as described herein or zSIR polypeptide dimer as described herein 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 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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, wherein said medicament is to be administered in combination with an agent that increases the efficacy and/or safety of the immune effector cell.

[0008j] In yet another aspect, the present disclosure refers to an immune effector cell comprising a zSIR polynucleotide as described herein either alone or in combination with one or more agents that increase the efficacy and/or safety of the immune cell for use in disease therapy, wherein the zSIR comprises vL and vH fragments that bind 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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

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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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; and the one or more agents that increase the efficacy and/or safety of the immune cell are 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.

[0008k] In yet another aspect, the present disclosure refers to a kit comprising at least one polynucleotide as described herein, a zSIR polypeptide dimer as described herein, a vector as described herein or the cell as described herein, and/or a composition as described herein. In certain examples, the disclosure provides compositions comprising genetically engineered effector cells (such as NK cells and T cells) that include polynucleotides that encode chimeric antigen receptors, synthetic immune receptors (SIRs) and the like that can be used on adoptive cell therapy for treatment of cancer, infectious, autoimmune and degenerative diseases.

[0009] In certain examples, the disclosure provides a platform of synthetic immune receptors, designated zSIRs, containing two CD3z chains. The polynucleotide sequences of the CD3z chains that can be used in the construction of zSIR are provided in, for example, SEQ ID NO: 67 and 71. The corresponding amino acid sequenecs are provided in SEQ ID NO: 4066 and 4070, respectively. The disclosure provides that the vL fragment of an antibody can be joined to one of the two CD3z chains and the vH fragment can be joined to the other CD3z chain. When the two such chains (*e.g.* vL-CD3z and vH-CD3z) are co-expressed in the same cell, the vL and vH fragments can bind their cognate antigen and transmit a T cell signal. In particular, T cells expressing such zSIR when exposed to a cell line expressing the cognate target antigen can activate NFAT signaling, induce IL2 production, promote T cell proliferation, promote T cell activation and exert cytotoxicity. The

expression and activity of the zSIR can be further increased by incorporation of a linker between the vL/vH and the CD3z fragments. In particular, the IgCL (SEQ ID NO: 28 and 4027) and IgCH domains (SEQ ID NO: 29 and 4028) derived from antibodies serve as useful linkers between the vL/vH and CD3z fragments.

[0010] The disclosure futher provides several new antigen binding domains that can be used in the generation of conventional CARs (*e.g.*, 2nd generation CAR containing 41BB costimulatory domain) as well next generation CARs such as SIRs, zSIRs, Ab-TCR, Tri-TAC and TFPs, for applications in adoptive cellular therapy. In some examples, these antigen binding domains are derived from antibodies and target antigens expressed in both

What is claimed is:

1. 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 via a cL linker having the sequence of SEQ ID NO: 4027 and second polypeptide chain comprises the vH fragment of the antibody operably linked to a second CD3z chain via a CH1 linker having the sequence of any one of SEQ ID NOs: 4028-4037, wherein when expressed in a cell, the vL and vH fragments can associate to bind to their cognate antigen in an MHC-dependent or MHC-independent manner.

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

3. The recombinant polynucleotide of claim 1, 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, wherein the costimulatory module comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 4067 and 4068.

4. The recombinant polynucleotide of any one of claims 1 to 3, wherein the encoded CD3z chain or functional portion thereof comprises a polypeptide having the sequence of any one of SEQ ID NOs: 4064-4065, 4070-4072 and 4075-4078.

5. A recombinant polynucleotide of claim 1, 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.

6. 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 via a cL linker having the sequence of SEQ ID NO: 4027 and second polypeptide chain comprises the vH fragment of the antibody operably linked to a second CD3z chain via a CH1 linker having the sequence of any one of SEQ ID NOs: 4028-4037, wherein when expressed in a cell, the vL and vH fragments can associate to bind to their cognate antigen in an MHC-dependent or MHC-independent manner.

7. The zSIR polypeptide dimer of claim 6, wherein the CD3z chain comprises the transmembrane domain and/or cytoplasmic domain and optionally the extracellular domain of a CD3z protein, optionally wherein the encoded one or both CD3z chains comprise one or more co-stimulatory domains.

8. A zSIR polypeptide dimer of claim 6, wherein the CD3z chain comprises a polypeptide having a sequence selected from SEQ ID NO: 4064, 4065, 4070-4072, and 4075-4078.

9. The zSIR polypeptide dimer of claim 6, wherein said vL and vH fragments bind 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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.

10. A zSIR polypeptide dimer of claim 6, 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.

11. The zSIR polypeptide dimer of claim 6, wherein said vL and vH fragments comprise:

(i) a heavy chain variable region (vH) comprising a sequence as set forth in any of SEQ ID NOs: 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 NOs: 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 NOs: 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 NOs: 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 regon encodes a polypeptide that associates with the complementary vH chain listed in **Table 3** and binds to its cognate antigen.

12. At least one vector comprising the recombinant polynucleotide of claim 1, 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.

13. A recombinant cell comprising

    i) at least one zSIR polypeptide dimer of claim 6;

    ii) at least one recombinant polynucleotide of claim 1; and/or

    iii) at least one vector of claim 12,

    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.

14. A composition comprising at least one polynucleotide of claim 1, a zSIR polypeptide dimer of claim 6, a vector of claim 12 or the cell of claim 13, and a pharmaceutically acceptable excipient.

15. 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 zSIR polypeptide dimer of claim 6 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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.

16. 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 zSIR polypeptide dimer of claim 6 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 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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 glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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, wherein said medicament is to be administered in combination with an agent that increases the efficacy and/or safety of the immune effector cell.

17. An immune effector cell comprising a zSIR polynucleotide of claim 1 either alone or in combination with one or more agents that increase the efficacy and/or safety of the immune cell for use in disease therapy, wherein the zSIR comprises vL and vH

fragments that bind 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(l-4)bDGlcp(l-l)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-llRa); 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 (CAlX); 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)bDClalp(l-4)bDGlcp(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

glycoceramide (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 lA (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 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 Bl; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 lB 1 (CYPlB 1); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator oflmprinted Sites), Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TESl); 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 (RUl); 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 (LAIRl); 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 (IGLLl), 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; and the one or more agents that increase the efficacy and/or safety of the immune cell are 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.

18. The use of claim 15 or 16 or the immune effector cell comprising a zSIR for use of claim 17, 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.

19. A kit comprising at least one polynucleotide of claim 1, a zSIR polypeptide dimer of claim 6, a vector of claim 12 or the cell of claim 13 and/or a composition of claim 14.