

NO:3049 and which may comprise an optional accessory module; (vi) an amino acid sequence that is at least 98% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and (vii) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), and (v) and (vi); (b) an optional linker; and (c) one or more non-natural TCR antigen binding domain(s) linked to (a) selected from the group consisting of: (1) an antibody; (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂); (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof; (4) a light chain variable region of an antibody (vL domain) or a fragment thereof; (5) a single chain variable fragment (scFv) or a fragment thereof; (6) a single domain antibody (SDAB) or a fragment thereof; (7) a camelid VHH domain or a fragment thereof; (8) a monomeric variable region of an antibody; (9) a non-immunoglobulin antigen binding scaffold such as a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof; (10) a receptor or a fragment thereof; (11) a ligand or a fragment thereof; (12) a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and (13) an autoantigen or a fragment thereof, wherein the mutations of (a)(i) – (a)(iii) and the dimer of (a)(vii) provide a diverse binding affinity to a target antigen of the antigen binding domain and that is at least 5% greater than the binding affinity of a cTCR having the same binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted and MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen. In one example, comprising TCR constant chains of (a)(vii) the non-natural TCR binding domains is selected from the group consisting of: variable regions of a heavy and light chains of an antibody or fragments thereof specific for a predefined target antigen, such that, when expressed, one of said heavy and light chains of the antibody or fragments thereof is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said heavy and light chains of the antibody or fragments thereof is attached to the other of said two chains of said T-cell constant regions; two single chain variable fragments (scFv) specific for one or more predefined target antigens, such that, when expressed, one of said scFv is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said scFv is attached to the other of said two chains of said T-cell constant regions; two antibody fragment specific for one or more predefined target antigens, such that, when

chains of said T-cell constant regions; and two vH or fragment thereof, such that, when expressed, one of said vH or fragments thereof is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said vH or fragments thereof is attached to the other of said two chains of said T-cell constant regions. In yet another or further example of any of the foregoing, the TCR constant chains of (a)(iv) has a non-natural TCR binding domains selected from the group consisting of the variable region of the heavy chain (vH) of an antibody or a fragment thereof specific for a predefined target antigen; the variable region of the light chain (vL) of an antibody or a fragment thereof specific for a predefined target antigen; a single chain variable fragment (scFv) or a fragment thereof specific for a predefined target antigens; an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen; a single domain antibody (SDAB) fragments specific for a predefined target antigen; a camelid vHH domain specific for a predefined target antigen; a non-immunoglobulin antigen binding scaffolds specific for a predefined target antigen; a receptors specific or a fragment thereof for a predefined target antigen; a ligands or a fragment thereof specific for a predefined target antigens; a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand specific for one or more predefined target antigens; and an autoantigen or a fragment thereof. In yet another example, a polynucleotide encoding for (i), (ii), (iii), (iv), (v), or (vi), the non-natural TCR binding domains is selected from the group consisting of a variable region of the heavy chain (vH) of an antibody specific for the predefined target antigen; a variable region of the light chain (vL) of an antibody specific for the predefined target antigen; a single chain variable fragment (scFv) specific for a predefined target antigens; an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen; a single domain antibody (SDAB) fragments specific for a predefined target antigen; a camelid vHH domains specific for a predefined target antigen; a non-immunoglobulin antigen binding scaffolds specific for a predefined target antigen; a receptors specific for a predefined target antigen or fragments thereof; a ligands specific for a predefined target antigens or fragments thereof; a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand specific for one or more predefined target antigens; and an autoantigen or a fragment thereof. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain is a codon-optimized sequences. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (a) encodes a TCR constant chain(s) comprising mutations that enhance the expression and/or pairing of TCR constant chains and reduce their pairing with the endogenous T cell receptor chains. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (a)

comprises a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 730 to 743 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 730 to 743, and which is capable of dimerizing with a TCR β 1 or TCR β 2 chain. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (b) or (c) comprises a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 744 to 765 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 744 to 765 and which is capable of dimerizing with a TCR α chain. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (v) comprises a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 769 to 770 or a sequence with at least 70% identity to an nucleic acid sequences of SEQ ID NO: 769 to 770 and which is capable of pairing with a TCR δ chain. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (vi) comprises a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 771 to 772 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 771 to 772 and which is capable of dimerizing with a TCR γ chain. In another or further example of any of the foregoing, the polynucleotide encoding the TCR constant chain of (iv) comprises a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 766 to 768 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 766 to 768 and which is capable of dimerizing with a TCR β 1 or TCR β 2 chain. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) bind to one or more of disease-associated antigens are selected from a group consisting of: CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor

(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 Endproducts (RAGE-1); renal ubiquitous 1 (RUI); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1), MPL, , Biotin, c-MYC epitope Tag, CD34, LAMP1 TROP2, GFRalpha4, CDH17, CDH6, NYBR1, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, gpNMB, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL1, ALK TCR gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), KSHV-K8.1 protein, KSHV-gH protein, auto antibody to desmoglein 3 (Dsg3), autoantibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2)), P-glycoprotein, STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, BST1/CD157, low conductance chloride channel, and antigen recognized by TNT antibody. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises an antibody, an antibody fragment, an scFv, a Fv, a Fab, a (Fab')₂, a single domain antibody (SDAB), a vH or vL domain, a camelid vHH domain, a non-immunoglobulin antigen binding scaffolds such as DARPINs, affibodies, affilins, adnectins, affitins, obodies, repebodies, fynomers, alphabodies, avimers, atrimers, centyrins, pronectins, anticalins, kunitz domains, Armadillo repeat proteins, a receptor or a ligand. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) is selected from the group consisting of: (i) a heavy chain variable region (vH) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 226 to 400 or 10203

to 10321 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (ii) a light chain variable region (vL) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 16 to 191 or 10085 to 10202 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (iii) a single chain variable fragment (scFv) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 488 to 657, 10346 to 10400 or 18098 to 18160 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (iv) a camelid VHH domain encoded by a polynucleotide having a sequence of any one of SEQ ID NO 421 to 445 or 10322 to 10337 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (v) a non-immunoglobulin scaffold encoded by a polynucleotide having a sequence of any one of SEQ ID NO 439 to 443 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (vi) a receptor encoded by a polynucleotide having a sequence of any one of SEQ ID NO 456 to 468 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its cognate; and (vii) a ligand encoded by a polynucleotide having a sequence of any one of SEQ ID NO 476 to 486 or 10402 to 10404 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its cognate. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprise one or more of light chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:13999 to 14879 or 14880 and/or one or more of heavy chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:14881 to 15761 or 15762. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 having up to 10 conservative amino acid substitutions and/or a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises one or more of camelid vHH complementary determining regions for a selected antigen as set forth in any of SEQ ID Nos:2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises a non-immunoglobulin antigen binding domains having a sequence as set forth in any of SEQ ID NOS: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises an scFv domains comprising one or more light chain

complementary determining region of a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 and one or more heavy chain complementary determining regions of a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises an scFv fragment having a sequence selected from the group consisting of SEQ ID NO:2770 to 2939, 12303 to 12357 or 18162 to 18224 each having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises one or more receptors comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises one or more ligands comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprising an extracellular domain of CD16A, NKG2D, CD4, PD1, desmoglein 3 (Dsg3), or CD4-DC-SIGN. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprising an extracellular domain of one or more of hTPO, mTPO, CGH α chain, CGH β chain, FH β chain, LH β chain, TSH β chain, APRIL or combination thereof. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises any single chain variable fragment (scFv) comprising a sequence of any of SEQ ID Nos:2770 to 2939, 12303 to 12357 or 18162 to 18224 and having up to 10 conservative amino acid substitutions, and a) any camelid vHH as set forth in any of SEQ ID Nos:2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, or b) any non-immunoglobulin antigen binding domains having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions; or c) any extracellular domain of a receptor comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions; or d) any extracellular domain of a ligand comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises a camelid vHH as set forth in any of SEQ ID Nos:2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, and a) any single chain variable fragment (scFv) comprising a sequence of any of SEQ ID Nos:2770 to 2939, 12303 to 12357 or 18162 to 18224 and having up to 10 conservative amino acid substitutions, or b) any non-immunoglobulin

antigen binding domains having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions; or c) any extracellular domain of a receptor comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions; or d) any extracellular domain of a ligand comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) is optionally connected to each of the TCR constant region chain by a linker region, wherein said linker region nucleic acid encodes an amino acid sequence selected from the group consisting of SEQ ID NO:2981 to 2992 and any combination thereof, or a sequence with at least 98% identity thereto; or said linker is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:701 to 714, or sequences with at least 98% identity thereto. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) has a binding affinity to its target antigen of at least 5-fold less than the antibody from which it is obtained. In another or further example of any of the foregoing, the polynucleotide encoding the SIR further comprises a leader sequence or signal peptide that is present at the N-terminal of each chain and comprises a sequence selected from the group consisting of SEQ ID NO:1-9 and 10. In another or further example of any of the foregoing, the at least one polynucleotide encodes two SIRs. In another or further example of any of the foregoing, the polynucleotide encodes two SIRs that are linked by nucleotide sequences encoding a cleavable linker. In another or further example of any of the foregoing, the cleavable linker is a self-cleaving cleavable linker. In another or further example of any of the foregoing, the cleavable linker is any one or more of a 2A linker, a 2A-like linker or functional equivalent thereof. In another or further example of any of the foregoing, the cleavable linker is any one or more of T2A linker, P2A, F2A, E2A linker or functional equivalent thereof. In another or further example of any of the foregoing, the cleavable linker comprises a sequence of any one or more of SEQ ID Nos:780 to 785. In another or further example of any of the foregoing, the polynucleotide sequences encoding the cleavable linker is optionally preceded by a nucleotide sequence encoding a furine cleavage site or furine like cleavage site or functional equivalent thereof. In another or further example of any of the foregoing, the furine cleavage site preceding the cleavable linker comprises a sequence of any one or more of SEQ ID Nos:788 to 790. In another or further example of any of the foregoing, the polynucleotide sequences encoding the cleavable linker is preceded by a nucleotide sequence encoding a flexible linker. In another or further example of any of the foregoing, the flexible linker preceding the cleavable linker encodes for one or more of Ser-Gly

linker, Ser-Gly-Ser-Gly linker or functional equivalent thereof. In another or further example of any of the foregoing, the flexible linker preceding the cleavable linker comprises a sequence of SEQ ID Nos: 786 or 787. In another or further example of any of the foregoing, the polynucleotide sequences encoding the furine cleavage site is followed by polynucleotide encoding the flexible linker which is followed by polynucleotide encoding the cleavable linker so that the order is Furine cleavage site-Flexible linker-cleavable linker. In another or further example of any of the foregoing, the polynucleotide encoding the cleavable linker are present before a sequence encoding a leader sequence (signal peptide) encoding a second SIR. In another or further example of any of the foregoing, the SIRs can be designed to have a diverse binding affinity for a selected antigen. In another or further example of any of the foregoing, the SIRs comprise an accessory module. In another or further example of any of the foregoing, the accessory module comprises a CD3z domain. In a further example of any of the foregoing, the TCR constant chain is selected from the group consisting of (viii) an amino acid sequence that is at least 98% identical to SEQ ID NO:12401 or 12402 or 12403 or 12408 or 12409; (ix) an amino acid sequence that is at least 98% identical to SEQ ID NO:12421 or 12422 or 12423 or 12427 or 12428; and (x) a dimer combination of two TCR constant chains of (viii) and (ix). In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) bind to CD19. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2318-2324, 12060-12068, 12108, 12127, or 12156 or any complement determining region (CDR) contained in any of the foregoing polypeptide; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO: 2517-2523, 12178-12186, 1227, 12246 or 12275 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:12288; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2770-2774, 12325, 12308, 18162-18170 or 12354. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3135-3235, 3250-3346, 3396, 3401-3403, 3406, 3429-3432, 3435-3439, 3540, 3855-3859, 12431-12489, 12491-12493, 12495-12530, 12534, 13195-13203, 13250, 13267, 13289, 13429-13437, 13483, 13501 and 13523. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CD20. In another or further example of any of the foregoing the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of a polypeptide comprising a sequence that is

at least 98% identical to any one of SEQ ID NO:2325-2326, 12069-12077 or 12078 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO: 2524-2525, 12187-12195 or 12196 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:12289 or 12290; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2787-2788, 18177-18186 or 18187. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3263, 3348, 3456-3457, 3876-3877, 12464-12465, 12477-12482, 12492, 12534, 13204-13213, 13438-13446 and 13447. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CD22. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2327-2329, 12122-12126 or 12132 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO: 2526-2528, 12241-12245, or 12251 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2789-2791, 12320-12330, or 18188. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3332, 3433, 3458-3460, 3878-3880, 12483, 12485, 12488-12490, 13241-13245, 13268, 13475-13479 and 13502. In another example, said one or more non-natural TCR antigen binding domain(s) bind to BCMA. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2310-2313, 12046-12048, 12118-12119, 12139-12145 or 12146 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO: 2509-2512, 12164-12166, 12237-12238, 12258-12264 or 12265 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:12279-12281, 12283-12285, 12287, 12291-12292, 12293 or 12294; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2780-2783, 12237-12344, 18174-18175 or 18176. In another or further example of any of the foregoing, the recombinant

polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3445-3449, 3866-3869, 12463, 12533, 12535-12536, 13181-13183, 13261-13262, 13277-13284, 13415-13417, 13495-13496, 13511-13517 and 13518. In another example, said one or more non-natural TCR antigen binding domain(s) bind to MPL. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2414-2421, 12120, 12128 or 12129 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO: 2611-2618, 12239, 12247 or 12248 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2871-2878, 12326-12327 and 12318. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3347, 3373, 3427-3428, 3495, 3556-3562, 3979-3985, 4025, 12454, 12456, 12458, 12462, 12532, 13259, 13265-13266, 13493, 13499 and 13500. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CS1. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2355-2358, 12090-12094 or 12095 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2553-2555, 12209-12213, or 12214 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2817-2819, 18211-18215 or 18216. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3376, 3487-3489, 3907-3909, 12455, 12457, 12459, 12461, 12476, 13226-13231, 13460-13464 and 13465. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CD33. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2336-2337, 12079-12084 or 12085 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2535-2536, 12197-12202 or 12203 or any complement determining region (CDR) contained

in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2795-2796, 18189-18193 or 18194. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3464-3465, 3884-3885, 12460, 12473, 12479, 13214-13220, 13448-13453 and 13454. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CD123. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2315, 2472, 12049-12058 or 12059 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2514, 2670, 12167-12176 or 12177 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2716 or 2717; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2801, 2929, 18196-18205 or 18206. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3266-3267, 3366-3368, 3375, 3378, 3405, 3409, 3434, 3470, 3492-3497, 3617, 3890, 3912-3913, 4041, 12480, 13184-13194, 13418-13427 and 13428. In yet another example, said one or more non-natural TCR antigen binding domain(s) bind to folate receptor 1. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to 2373 or any complement determining region (CDR) contained therein; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2570 or any complement determining region (CDR) contained in therein; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2833. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3511 and 3928. In yet another example, said one or more non-natural TCR antigen binding domain(s) bind to mesothelin. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2413, 12154 or 12155 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2609-2610, 12273 or 12274 or any complement determining region (CDR

contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2713-2714 or 2725; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2870, 2899, 12352 or 12353. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3414, 3419, 3554, 3585, 3976, 4008, 13287-13288, 13521 and 13522. In yet another example, said one or more non-natural TCR antigen binding domain(s) bind to IL13Ra2. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: -a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2399 or 2400 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2595 or 2596 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2858 or 2859. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3541-3542, 3963 and 3964. In another example, said one or more non-natural TCR antigen binding domain(s) bind to CD138. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2316 or any complement determining region (CDR) contained therein; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2515 or any complement determining region (CDR) contained therein; and a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2802. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3268, 3374, 3404, 3471 and 3891. In yet another example, said one or more non-natural TCR antigen binding domain(s) bind to TCRgd. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2449 or any complement determining region (CDR) contained therein; a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2646 or any complement determining region (CDR) contained therein; and a polypeptide comprising a sequence that is at least 98% identical to SEQ ID NO:2907. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting

of SEQ ID Nos:3594 and 4017. In still another example, said one or more non-natural TCR antigen binding domain(s) bind to TCRB1. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2445 or 2446 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2642 or 2643 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2903 or 2904. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3590-3591, 4013 and 4014. In another example, said one or more non-natural TCR antigen binding domain(s) bind to TCRB2. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) are selected from the group consisting of: a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2447 or 2448 or any complement determining region (CDR) contained in any of the foregoing polypeptides; a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2644 or 2645 or any complement determining region (CDR) contained in any of the foregoing polypeptides; and a polypeptide comprising a sequence that is at least 98% identical to any one of SEQ ID NO:2905 or 2906. In another or further example of any of the foregoing, the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3353-3364, 3592-3593, 4015 and 4016.

[0010a] In one aspect, the present disclosure refers to at least one recombinant polynucleotide encoding at least one synthetic immune receptor (SIR), the at least one SIR comprising:

- (a) a T-cell receptor (TCR) constant chain having an amino acid sequence selected from the group consisting of:
 - (i) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 and has one or more mutations at positions 48, 61, 91, 92, 93, and/or 94 and which may comprise an optional accessory module;
 - (ii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 and has one or more mutations at positions 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
 - (iii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3025 and has one or more mutations at position 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;

- (iv) an amino acid sequence that is at least 95% identical to SEQ ID NO:3046, 3047 or 3048 and which may comprise an optional accessory module;
- (v) an amino acid sequence that is at least 95% identical to SEQ ID NO:3049 and which may comprise an optional accessory module;
- (vi) an amino acid sequence that is at least 95% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and
- (vii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 or 3011 and which may comprise an optional accessory module; and
- (viii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 or 3025 or 3026 and which may comprise an optional accessory module; and
- (ix) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), (v) and (vi), and (vii) and (viii);
- (b) an optional linker; and
- (c) one or more non-natural TCR antigen binding domain(s) linked to (a), wherein the binding domain retains the antigen-binding specificity of the molecule from which it is derived, selected from the group consisting of:

- (1) an antibody;
- (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂);
- (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof;
- (4) a light chain variable region of an antibody (vL domain) or a fragment thereof;
- (5) a single chain variable fragment (scFv) or a fragment thereof;
- (6) a single domain antibody (SDAB) or a fragment thereof;
- (7) a camelid VHH domain or a fragment thereof;
- (8) a monomeric variable region of an antibody;
- (9) a non-immunoglobulin antigen binding scaffold selected from a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof;
- (10) a receptor or a fragment thereof;
- (11) a ligand or a fragment thereof;
- (12) a bispecific-antibody, -antibody fragment, -scFV, -VHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and
- (13) an autoantigen or a fragment thereof,

wherein the mutations of (a)(i) – (a)(iii) and the dimer of (a)(ix) provide a diverse binding affinity to a target antigen of the antigen binding domain and that is at least 5% greater than the binding affinity of a wild-type TCR (cTCR) having the same binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted and MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen.

[0011] The disclosure also provide a recombinant expression system comprising any of the recombinant polynucleotide described herein an above which is/are co-expressed with a therapeutic control, wherein the therapeutic control is selected from the group consisting of a truncated epidermal growth factor receptor (tEGFR), truncated epidermal growth factor receptor viii (tEGFRviii), truncated CD30 (tCD30), truncated BCMA (tBCMA), truncated CD19 (tCD19), CD34, thymidine kinase, cytosine deaminase, nitroreductase, xanthine-guanine phosphoribosyl transferase, human caspase 8, human caspase 9, inducible caspase 9 (icaspase9), purine nucleoside phosphorylase, linamarase/linamarin/glucose oxidase, deoxyribonucleoside kinase, horseradish peroxidase (HRP)/indole-3-acetic (IAA), Gamma-glutamylcysteine synthetase, CD20/alphaCD20, CD34/thymidine kinase chimera, dox-dependent caspase-2, mutant thymidine kinase (HSV-TKSR39), AP1903/Fas system, a chimeric cytokine receptor (CCR), a selection marker, and combinations thereof. In one example, the tEGFR and tEGFRviii bind any one or more of an EGFR-specific siRNA, a small molecule, an anti-EGFR

antibody or a fragment thereof, or a combination thereof. In another example, the tCD30 binds any one or more of a CD30-specific siRNA, a small molecule, an anti-CD30 antibody or a fragment thereof, or a combination thereof. In still another example, the tCD19 binds any one or more of a CD19-specific siRNA, a small molecule, an anti-CD19 antibody or a fragment thereof, or a combination thereof. In another example, the CD34 binds any one or more of a CD34-specific siRNA, a small molecule, an anti-CD34 antibody or a fragment thereof, or a combination thereof. In yet another example, the selection marker comprises any one or more of dihydroxyfolate receptor (DHFR), mutant DHFR, methylated-DNA-protein-cysteine methyltransferase, inosine monophosphate dehydrogenase II (IMDHP2), puromycin acetyltransferase (PAC), blasticidin-resistance gene, mutant calcineurin α/β (Can/b), CNa12, CNb30 or combinations thereof. In another example, the CCR comprises any one or more of (i) IL-7 cytokine-linker- IL 7Ra, (ii) IL-7 cytokine-linker-extracellular domain of IL-7Ra-transmembrane domain of IL-7Ra-cytoplasmic domain of IL2R β , (iii) IL-7 cytokine linker-IL2R β , and (iv) combinations thereof. In another or further example of any of the foregoing, the recombinant expression system comprises a recombinant polynucleotide of the disclosure which is co-expressed with an accessory module, wherein the accessory module is selected from the group consisting of 41BBL, CD40L, K13, MC159, cFLIP-L/MRIT α , cFLIP-p22, HTLV1 Tax, HTLV2 Tax, HTLV2 Tax-RS mutant, FKBPx2-K13, FKBPx2-HTLV2-Tax, FKBPx2-HTLV2-Tax-RS, IL6R-304-vHH-Alb8-vHH, IL12f, PD1-4H1 scFV, PD1-5C4 scFV, PD1-4H1-Alb8-vHH, PD1-5C4-Alb8-vHH, CTLA4-Ipilimumab-scFv, CTLA4-Ipilimumab-Alb8-vHH, IL6-19A-scFV, IL6-19A-scFV-Alb8-vHH, sHVEM, sHVEM-Alb8-vHH, hTERT, Fx06, CD3z, CD3z-GGGS-41BB, CD3-BBz, CD3-CD28z, CD3-CD28-Lck fusion protein, shRNA targeting Brd4, chimeric antigen receptor (CAR), hTERT, heparinase, a CAR, an inhibitory CAR and any combination thereof. In another or further example of any of the foregoing, the recombinant polynucleotide encoding the SIR and one or more therapeutic control and/or one or more accessory module are linked by nucleotide sequences encoding a cleavable linker. In a further example, the cleavable linker is a self-cleaving cleavable linker. In another or further example of any of the foregoing, the polynucleotide sequences encoding the cleavable linker is preceded by nucleotide sequence encoding a furine cleavage site or furine like cleavage site or functional equivalent thereof. In another or further example of any of the foregoing, the polynucleotide sequences encoding the cleavable linker is optionally preceded by nucleotide sequence encoding a flexible linker.

[0011a] In another aspect, the present disclosure refers to a recombinant polynucleotide as described herein which is co-expressed with an accessory module, wherein the accessory module is selected from the group consisting of 41BBL, CD40L, K13, MC159, cFLIP-L/MRIT α , cFLIP-p22, HTLV1 Tax, HTLV2 Tax, HTLV2 Tax-RS mutant, FKBPx2-K13, FKBPx2-HTLV2-Tax, FKBPx2-HTLV2-Tax-RS, IL6R-304-vHH-Alb8-vHH, IL12f, PD1-4H1 scFV, PD1-5C4 scFV, PD1-4H1-Alb8-vHH, PD1-5C4-Alb8-vHH, CTLA4-Ipilimumab-scFv, CTLA4-Ipilimumab-Alb8-vHH, IL6-19A-scFV, IL6-19A-scFV-Alb8-vHH, sHVEM, sHVEM-Alb8-vHH, hTERT, Fx06, CD3z, CD3z-GGGS-41BB, CD3-BBz, CD3-CD28z, CD3-CD28-Lck fusion protein, shRNA targeting Brd4, chimeric antigen receptor (CAR), hTERT, heparinase, a CAR, an inhibitory CAR and combination thereof.

[0012] The disclosure also provides at least one vector comprising the recombinant polynucleotide of as described herein and above, 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, a baculovirus vector, a sleeping beauty transposon vector, and a piggybac transposon vector. In one example, the vector backbone has a sequence selected from the group consisting of SEQ ID NO: 870 to 875 and 876. In another example, the vector comprises a promoter chosen from an EF-1 promoter, a CMV IE gene promoter, an EF-1a promoter, an ubiquitin C promoter, a MSCV LTR promoter, or a phosphoglycerate kinase (PGK) promoter. In a further example, the EF-1 promoter comprises a sequence of SEQ ID NO: 877 or a sequence with or a sequence with 80-99% identity thereto. In another or further example of any of the foregoing, the vector is an *in vitro* transcribed vector, or the vector further comprises a poly(A) tail or a 3'UTR.

[0012a] In another aspect, the present disclosure refers to at least one vector comprising the recombinant polynucleotide as described 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, a baculovirus vector, a sleeping beauty transposon vector, and a piggybac transposon vector.

[0013] The disclosure provide at least one polypeptide encoded by the at least one recombinant polynucleotide of the disclosure.

[0014] The disclosure also provides a recombinant cell that expresses the at least one recombinant polynucleotide as described herein and above.

[0015] The disclosure also provides an isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer comprising: (a) a T-cell receptor (TCR) constant chain having an amino acid sequence selected from the group consisting of: (i) an amino acid sequence that is at least 98% identical to SEQ ID NO:3010 and has one or more mutations at positions 48, 61, 91, 92, 93, and/or 94 and which may comprise an optional accessory module; (ii) an amino acid sequence that is at least 98% identical to SEQ ID NO:3024 and has one or more mutations at positions 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module; (iii) an amino acid sequence that is at least 98% identical to SEQ ID NO:3025 and has one or more mutations at position 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module; (iv) an amino acid sequence that is at least 98% identical to SEQ ID NO:3046, 3047 or 3048 and which may comprise an optional accessory module; (v) an amino acid sequence that is at least 98% identical to SEQ ID NO:3049 and which may comprise an optional accessory module; (vi) an amino acid sequence that is at least 98% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and (vii) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), or (v) and (vi); (b) an optional linker; and (c) one or more non-natural TCR antigen binding domain(s) linked to (a) selected from the group consisting of: (1) an antibody; (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂); (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof; (4) a light chain variable region of an antibody (vL domain) or a fragment thereof; (5) a single chain variable fragment (scFv) or a fragment thereof; (6) a single domain antibody (SDAB) or a fragment thereof; (7) a camelid VHH domain or a fragment thereof; (8) a monomeric variable region of an antibody; (9)

a non-immunoglobulin antigen binding scaffold such as a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof; (10) a receptor or a fragment thereof; (11) a ligand or a fragment thereof; (12) a bispecific-antibody, -antibody fragment, -scFv, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and (13) an autoantigen or a fragment thereof, wherein the mutations of (a)(i) – (a)(iii) provide a diverse binding affinity to a target antigen of the antigen binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted or MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen. In another or further example of any of the foregoing, the TCR constant chains of (a)(vii) has a non-natural TCR binding domains selected from the group consisting of: variable regions of a heavy and light chains of an antibody or fragments thereof specific for a predefined target antigen, such that, when expressed, one of said heavy and light chains of the antibody or fragments thereof is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said heavy and light chains of the antibody or fragments thereof is attached to the other of said two chains of said T-cell constant regions; two single chain variable fragments (scFv) specific for one or more predefined target antigens, such that, when expressed, one of said scFv is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said scFv is attached to the other of said two chains of said T-cell constant regions; two antibody fragment specific for one or more predefined target antigens, such that, when expressed, one of said antibody fragments is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said antibody fragments is attached to the other of said two chains of said T-cell constant regions; two single domain antibody (SDAB) fragments specific for one or more predefined target antigens, such that, when expressed, one of said SDAB fragments is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of SDAB fragments is attached to the other of said two chains of said T-cell constant regions; two camelid vHH domains specific for one or more predefined target antigens, such that, when expressed, one of said vHH domains is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of vHH domains is attached to the other of said two chains of said T-cell constant regions; two non-immunoglobulin antigen binding scaffolds specific for one or more predefined target antigens, such that, when expressed, one of said non-immunoglobulin antigen binding scaffolds

is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said non-immunoglobulin antigen binding scaffolds domains is attached to the other of said two chains of said T-cell constant regions; two receptors or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said receptors or a fragment thereof is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said receptors or a fragment thereof is attached to the other of said two chains of said T-cell constant regions; two ligands or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said ligands or a fragment thereof is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said ligands or a fragment thereof is attached to the other of said two chains of said T-cell constant regions; two structurally distinct antigen binding fragments specific for one or more predefined target antigens, such that, when expressed, one of said antigen binding fragments is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions; two binding fragments one or both of which are bispecific or multispecific such that, when expressed, one of said antigen binding fragments is attached to one of said two chains of (a)(vii) of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions; two autoantigens or fragment thereof, such that, when expressed, one of said autoantigens or fragments thereof is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said autoantigens or fragments thereof is attached to the other of said two chains of said T-cell constant regions; and two vL or fragment thereof, such that, when expressed, one of said vL or fragments thereof is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said vL or fragments thereof is attached to the other of said two chains of said T-cell constant regions; two vH or fragment thereof, such that, when expressed, one of said vH or fragments thereof is attached to one of (a)(vii) of said two chains of said T-cell constant region and the other of said vH or fragments thereof is attached to the other of said two chains of said T-cell constant regions. In another or further example of any of the foregoing, the TCR constant chains of (a)(iv) has a non-natural TCR binding domains selected from the group consisting of: the variable region of the heavy chain (vH) of an antibody or a fragment thereof specific for a predefined target antigen; the variable region of the light chain (vL) of an antibody or a fragment thereof specific for a predefined target antigen; a single chain variable fragment (scFv) or a fragment thereof specific for a predefined target antigens; an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen; a single domain antibody (SDAB) fragments specific for a predefined target antigen; a camelid vHH domain specific for a predefined target antigen; a

non-immunoglobulin antigen binding scaffolds specific for a predefined target antigen; a receptors specific or a fragment thereof for a predefined target antigen; a ligands or a fragment thereof specific for a predefined target antigens; a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand specific for one or more predefined target antigens; and an autoantigen or a fragment thereof. In another or further example of any of the foregoing, a TCR constant domain of (i), (ii), (iii), (iv), (v), or (vi) comprises a non-natural TCR binding domains selected from the group consisting of: a variable region of the heavy chain (vH) of an antibody specific for the predefined target antigen; a variable region of the light chain (vL) of an antibody specific for the predefined target antigen; a single chain variable fragment (scFv) specific for a predefined target antigens; an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen; a single domain antibody (SDAB) fragments specific for a predefined target antigen; a camelid vHH domains specific for a predefined target antigen; a non-immunoglobulin antigen binding scaffolds specific for a predefined target antigen; a receptors specific for a predefined target antigen or fragments thereof; a ligands specific for a predefined target antigens or fragments thereof; a bispecific-antibody, -antibody fragment, -scFV, -vHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand specific for one or more predefined target antigens; and an autoantigen or a fragment thereof. In another or further example of any of the foregoing, the TCR constant chain(s) comprise mutations that enhance the expression and/or pairing of TCR constant chains and reduce their pairing with the endogenous T cell receptor chains. In another or further example of any of the foregoing, the constant region of TCR is a TCR receptor α chain (C α) comprising an amino acid sequence having at having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3010 to 3023 or a sequence that is at least 98% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3010 to 3023. In another or further example of any of the foregoing, the constant region of TCR is a TCR receptor β chain (C β) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3024 to 3044 or a sequence that is at least 98% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3024 to 3044. In another or further example of any of the foregoing, the constant region of TCR is a TCR receptor γ chain (C γ) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3049 to 3050 or a sequence that is at least 98% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3049 to 3050. In another or further example of any of the foregoing, the constant region of TCR is a TCR

receptor δ chain (C δ) comprising an amino acid sequence 1-40 amino acid substitutions or mutations to an amino acid sequence selected from the group consisting of SEQ ID NO:3051 to 3052 or a sequence that is at least 98% identical to a sequence selected from the group consisting of SEQ ID NO:3051 to 3052. In another or further example of any of the foregoing, the constant region of TCR is a preTCR receptor α chain (preC α) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to an amino acid sequence selected from the group consisting of SEQ ID NO:3046 to 3048 or a sequence that is at least 98% identical to a sequence selected from the group consisting of SEQ ID NO: 3046 to 3048. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) bind to one or more of disease-associated antigens are selected from a group consisting of: CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; 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)bDGlc(1-4)bDGlc(1-1)Cer); transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta;

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 TCR gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), KSHV-K8.1 protein, KSHV-gH protein, auto antibody to desmoglein 3 (Dsg3), autoantibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2)), P-glycoprotein, STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, BST1/CD157, low conductance chloride channel, and antigen recognized by TNT antibody. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises an antibody, an antibody fragment, an scFv, a Fv, a Fab, a (Fab')₂, a single domain antibody (SDAB), a vH or vL domain, a camelid vHH domain, a non-immunoglobulin antigen binding scaffolds such as DARPINs, affibodies, affilins, adnectins, affitins, obodies, reprobodies, fynomers, alphabodies, avimers, atrimers, centyrins, pronectins, anticalins, kunitz domains, Armadillo repeat proteins, a receptor or a ligand. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) is selected from the group consisting of: (i) a heavy chain variable region (vH) comprising a sequence as set forth in any of SEQ ID Nos:2506 to 2680 or 12160 to 12278 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (ii) a light chain variable region (vL) comprising a sequence as set forth in any one of SEQ ID NO 2307 to 2482 or 12042 to 12159 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (iii) a single chain variable fragment (scFv) comprising a sequence as set forth in any one SEQ ID NO: 2770 to 2939, 12303 to 12357, or 18162 to 18224 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (iv) a camelid VHH domain comprising a sequence as set forth in any one of SEQ ID NO: 2701 to 2725 or 12279 to 12294 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (v) a non-immunoglobulin scaffold encoded by a polynucleotide of any one of SEQ ID NO 439 to 443 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its antigen; (vi) a receptor comprising a

sequence as set forth in any one of SEQ ID NO 2736 to 2748 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its cognate; and (vii) a ligand comprising a sequence as set forth in any one of SEQ ID NO 2758 to 2768 or 12359 to 12361 or sequences with at least 98% identity thereto and which encodes a polypeptide the binds to its cognate. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprise one or more of light chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:13999 to 14879 or 14880 and/or one or more of heavy chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:14881 to 15761 or 15762. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 having up to 10 conservative amino acid substitutions and/or a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises one or more of camelid vHH complementary determining regions for a selected antigen as set forth in any of SEQ ID Nos:2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises a non-immunoglobulin antigen binding domains having a sequence as set forth in any of SEQ ID NOS: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises an scFv domains comprising one or more light chain complementary determining region of a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 and one or more heavy chain complementary determining regions of a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises an scFv fragment having a sequence selected from the group consisting of SEQ ID NO:2770 to 2939, 12303 to 12357 or 18162 to 18224 each having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises one or more receptors comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprises one or more ligands comprising a sequence of

any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, the one or more non-natural TCR antigen binding domain(s) comprising an extracellular domain of CD16A, NKG2D, CD4, PD1, desmoglein 3 (Dsg3), or CD4-DC-SIGN. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprising an extracellular domain of extracellular domain of one or more of hTPO, mTPO, CGH α chain, CGH β chain, FH β chain, LH β chain, TSH β chain, APRIL or combination thereof. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises any single chain variable fragment (scFv) comprising a sequence of any of SEQ ID Nos: 2770 to 2939, 12303 to 12357 or 18162 to 18224 and having up to 10 conservative amino acid substitutions, and a) any camelid vHH as set forth in any of SEQ ID Nos: 2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, or b) any non-immunoglobulin antigen binding domains having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions; or c) any extracellular domain of a receptor comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions; or d) any extracellular domain of a ligand comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) comprises a camelid vHH as set forth in any of SEQ ID Nos: 2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, and a) any single chain variable fragment (scFv) comprising a sequence of any of SEQ ID Nos: 2770 to 2939, 12303 to 12357 or 18162 to 18224 and having up to 10 conservative amino acid substitutions, or b) any non-immunoglobulin antigen binding domains having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions; or c) any extracellular domain of a receptor comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions; or d) any extracellular domain of a ligand comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions. In another or further example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) is optionally connected to each of the TCR constant region chain by a linker region, wherein said linker region nucleic acid encodes an amino acid sequence selected from the group consisting of SEQ ID NO: 2981 to 2992 and any combination thereof, or a sequence with at least 98% identity thereto; or said linker is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 701 to 714, or sequences with at least 98% identity thereto. In another or further

example of any of the foregoing, said one or more non-natural TCR antigen binding domain(s) has a binding affinity to its target antigen of at least 5-fold less than the antibody from which it is obtained. In another or further example of any of the foregoing, the polynucleotide encoding the SIR further comprises a leader sequence or signal peptide that is present at the N-terminal of each chain and comprises a sequence selected from the group consisting of SEQ ID NO:1-9 and 10. In another or further example of any of the foregoing, the SIR comprises a SIR heterodimer. In another or further example of any of the foregoing, the polypeptide comprises two SIRs that are linked by a cleavable linker. In a further example, the cleavable linker is a self-cleaving cleavable linker. In a further example, the cleavable linker is any one or more of a 2A linker, a 2A-like linker or functional equivalent thereof. In still a further example, the cleavable linker is any one or more of T2A linker, P2A, F2A, E2A linker or functional equivalent thereof. In still a further example, the cleavable linker comprises a sequence of any one or more of SEQ ID Nos:780 to 785. In a further example, the cleavable linker is optionally preceded by a furine cleavage site or furine like cleavage site or functional equivalent thereof. In yet a further example, the furine cleavage site preceding the cleavable linker comprises a sequence of any one or more of SEQ ID Nos:788 to 790. In any of the foregoing example, the cleavable linker is preceded by a flexible linker. In a further example, the flexible linker preceding the cleavable linker encodes for one or more of Ser-Gly linker, Ser-Gly-Ser-Gly linker or functional equivalent thereof. In yet a further example, the flexible linker preceding the cleavable linker comprises a sequence of SEQ ID Nos: 786 or 787. In yet a further example, the furine cleavage site is followed by the flexible linker which is followed by the cleavable linker so that the order is Furine cleavage site-Flexible linker-cleavable linker. In another or further example of any of the foregoing, the SIRs is designed to have a desired binding affinity for a selected antigen.

[0015a] In another aspect, the present disclosure refers to an isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer comprising:

- (a) a T-cell receptor (TCR) constant chain having an amino acid sequence selected from the group consisting of:
 - (i) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 and has one or more mutations at positions 48, 61, 91, 92, 93, and/or 94 and which may comprise an optional accessory module;
 - (ii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 and has one or more mutations at positions 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;

- (iii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3025 and has one or more mutations at position 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
- (iv) an amino acid sequence that is at least 95% identical to SEQ ID NO:3046, 3047 or 3048 and which may comprise an optional accessory module;
- (v) an amino acid sequence that is at least 95% identical to SEQ ID NO:3049 and which may comprise an optional accessory module;
- (vi) an amino acid sequence that is at least 95% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and
- (vii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 or 3011 and which may comprise an optional accessory module; and
- (viii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 or 3025 or 3026 and which may comprise an optional accessory module; and
- (ix) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), and (v) and (vi); and (vii) and (viii);
- (b) an optional linker; and
- (c) one or more non-natural TCR antigen binding domain(s) linked to (a), wherein the binding domain retains the antigen-binding specificity of the molecule from which it is derived, selected from the group consisting of:
 - (1) an antibody;
 - (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂);
 - (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof;
 - (4) a light chain variable region of an antibody (vL domain) or a fragment thereof;
 - (5) a single chain variable fragment (scFv) or a fragment thereof;
 - (6) a single domain antibody (SDAB) or a fragment thereof;
 - (7) a camelid VHH domain or a fragment thereof;
 - (8) a monomeric variable region of an antibody;
 - (9) a non-immunoglobulin antigen binding scaffold selected from a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof;
 - (10) a receptor or a fragment thereof;

(11) a ligand or a fragment thereof;

(12) a bispecific-antibody, -antibody fragment, -scFV, -VHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and

(13) an autoantigen or a fragment thereof,

wherein the mutations of (a)(i) – (a)(iii) provide a diverse binding affinity to a target antigen of the antigen binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted or MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen.

[0016] The disclosure also provide an immune effector cell or stem cell comprising at least one polypeptide or heterodimer as described herein and above.

[0017] The disclosure also provides an immune effector cell or stem cell comprising at least one recombinant polynucleotide as described herein and above.

[0018] The disclosure also provide an immune effector cell or stem cell comprising at least one vector of the disclosure as described herein and above.

[0018a] In another aspect, the present disclosure refers to an immune effector cell or a stem cell comprising

i) at least one isolated SIR polypeptide or polypeptide heterodimer as described herein;

ii) at least one recombinant polynucleotide as described herein;

iii) at least one vector as described herein,

wherein the immune cell optionally further comprises at least one chimeric antigen receptor (CAR) polypeptide,

wherein the CAR polypeptide comprises an intracellular signaling domain comprising a costimulatory signaling domain, but does not comprise a primary signaling domain or comprises an intracellular signaling domain comprising a primary signaling domain, but does not comprise a costimulatory signaling domain.

[0019] In another or further example of any of the foregoing, the immune cell or stem cell of any comprises a plurality of SIR polypeptides. In another or further example of any of the foregoing, at least one SIR polypeptide of the plurality of SIR polypeptides targets a different antigen than at least one other SIR polypeptide. In another or further example of

any of the foregoing, at least one SIR polypeptide of the plurality of SIR polypeptides target the same antigen. In another or further example of any of the foregoing, at least one SIR polypeptide of the plurality of SIR polypeptides comprises a different binding affinity for the antigen than at least one other SIR polypeptide. In another or further example of any of the foregoing, the immune cell further comprises at least one chimeric antigen receptor (CAR) polypeptide. In another or further example of any of the foregoing, the antigen binding domain of the SIR polypeptide targets a different antigen than the antigen binding domain of the CAR polypeptide. In another or further example of any of the foregoing, the CAR polypeptide comprises an intracellular signaling domain comprising a costimulatory signaling domain, but does not comprise a primary signaling domain or comprises an intracellular signaling domain comprising a primary signaling domain, but does not comprise a costimulatory signaling domain. In another or further example of any of the foregoing, the CAR polypeptide comprises a costimulatory signaling domain comprising a functional signaling domain of a protein selected from the group consisting of 4-1BB, CD28, CD27 or OX-40, or the CAR molecule comprises a primary signaling domain comprising a functional signaling domain of CD3 zeta. In another or further example of any of the foregoing, the CAR polypeptide is an inhibitory CAR polypeptide, wherein the inhibitory CAR polypeptide comprises an antigen binding domain, a transmembrane domain, and an intracellular domain of an inhibitory molecule, wherein the inhibitory molecule is selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, TGFR beta, CEACAM-1, CEACAM-3, and CEACAM-5. In another or further example of any of the foregoing, the CAR polypeptide further comprises an intracellular signaling domain comprising a primary signaling domain and/or an intracellular signaling domain, wherein the intracellular signaling domain comprises a primary signaling domain comprising the functional domain of CD3 zeta and a costimulatory signaling domain comprising the functional domain of 4-1BB or CD28 or both. In another or further example of any of the foregoing, the CAR polypeptide comprises the amino acid sequence of SEQ ID NO: 3077 to SEQ ID NO: 3083. In another or further example of any of the foregoing, the immune effector cell is a human T cell, a human NK cell or a stem cell that can give rise to an immune effector cell, optionally, wherein the T cell is diacylglycerol kinase (DGK) and/or Ikaros deficient and/or Brd4 deficient.

[0020] The disclosure provides a method of making a SIR-expressing immune effector cell, comprising introducing at least one vector of the disclosure or at least one recombinant polynucleotide of the disclosure into an immune effector cell or a hematopoietic stem cell or progenitor cell that can give rise to an immune effector cell, under conditions such that the SIR polypeptide is expressed. In another or further example of any of the foregoing, the method

further comprises a) providing a population of immune effector cells; and b) removing T regulatory cells from the population, thereby providing a population of T regulatory-depleted cells; wherein steps a) and b) are performed prior to introducing the vector or recombinant polynucleotide encoding the SIR to the population. In another or further example of any of the foregoing, the T regulatory cells are removed from the cell population using an anti-CD25 antibody, or an anti-GITR antibody. In another or further example of any of the foregoing, the method further comprises: a) providing a population of immune effector cells; and b) enriching P-glycoprotein (P-gp or Pgp; MDR1, ABCB1, CD243)-positive cells from the population, thereby providing a population of P-glycoprotein (P-gp or Pgp; MDR1, ABCB1, CD243)-enriched cells; wherein steps a) and b) are performed prior to or after introducing the vector or recombinant polynucleotide encoding the SIR. In another or further example of any of the foregoing, the P-glycoprotein positive cells are enriched using any one or more of the methods selected from the group consisting of: i) immunoselection using one or a cocktail of P-glycoprotein specific antibodies, ii) staining with one or more of fluorescent dyes that are substrates of P-glycoprotein, tetramethylrhodamine methyl ester (TMRM), Adriamycin and actinomycin-D) under conditions at which P-glycoprotein is active as a pump and enriching for cells that stain less with the dye, iii) selection of cells that are resistant to phototoxic compounds that are substrates of P-glycoprotein, such as any one or more of TH9402, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid ethyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid octyl ester hydrochloride, 2-(4,5-dibromo-6-amino-3-imino-3H-xanthen-9-yl)-benzoic acid n-butyl ester hydrochloride, 2-(6-ethyl amino-3-ethyl imino-3H-xanthen-9-yl)-benzoic acid n-butyl ester hydrochloride, or derivatives thereof or combinations thereof, and iv) selection of cells that are resistant to cytotoxic compounds that are substrates of P-glycoprotein, such as vincristine, vinblastine, taxol, paclitaxel, mitoxantrone, etoposide, adriamycin, daunorubicin and actinomycin-D.

[0021] The disclosure provides a method of generating a population of RNA-engineered cells comprising introducing *in vitro* transcribed RNA or RNAs or synthetic RNA or RNAs into a cell or population of cells, where the RNA or RNAs comprises a recombinant polynucleotide or polynucleotides as described herein an above.

[0022] The disclosure provides a method of providing anti-disease immunity in a subject comprising administering to the subject an effective amount of the immune effector cell or a stem cell that can give rise to an immune effector cell of the disclosure, wherein the cell is an autologous T cell or an allogeneic T cell, or an autologous NK cell or an allogeneic NK cell or an autologous or an allogeneic hematopoietic stem cell that can give rise to an immune effector

cell. In one example, the allogeneic T cell or allogeneic NK cell lacks expression or has low expression of a functional TCR or a functional HLA.

[0022a] In another aspect, the present disclosure refers to use of an effective amount of the immune effector cell or stem cell that can give rise to an immune effector cell or stem cell as described herein in the manufacture of a medicament for providing anti-disease immunity in a subject, wherein the cell is an autologous T cell or an allogeneic T cell, or an autologous NKT cell or an allogeneic NKT cell or an autologous or an allogeneic hematopoietic stem cell or an autologous or an allogeneic induced pluripotent stem cells (iPSC) that can give rise to an immune effector cell or stem cell.

[0023] The disclosure also provides a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of synthetic immune receptor (SIR) molecules for use in combination with an agent that increases the efficacy of the immune effector cell in the treatment of a subject having a disease associated with expression of a disease associated antigen or in the prevention of disease in a subject having an increased risk of a disease associated with expression of a disease associated antigen, wherein: (i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more antigen binding domains that bind to the disease-associated antigen 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); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3 (aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp(1-4)bDGlc(1-1)Cer); TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; 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

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 TCR gamma-delta, NKG2D, CD32 (FCGR2A), CSPG4-HMW-MAA, Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, VEGFR2/KDR, Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Chorionic Gonadotropin Hormone receptor (CGHR), CCR4, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), KSHV-K8.1 protein, KSHV-gH protein, auto-antibody to desmoglein 3 (Dsg3), autoantibody to desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2)), P-glycoprotein, STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, BST1/CD157, low conductance chloride channel, and antigen recognized by TNT antibody, (ii) the agent that increases the efficacy of the immune cell is chosen from one or more of: a protein phosphatase inhibitor; a kinase inhibitor (*e.g.*, a PI3K/AKT inhibitor or an mTOR inhibitor); a cytokine; an inhibitor of an immune inhibitory molecule; an agent that decreases the level or activity of a TREG cell; an agent that increase the proliferation and/or persistence of SIR-modified cells; a chemokine; an agent that increases the expression of SIR; an agent that allows regulation of the expression or activity of SIR; an agent that allows control over the survival and/or persistence of SIR-modified cells; an agent that controls the side effects of SIR-modified cells; a Brd4 inhibitor; an agent that delivers a therapeutic (*e.g.* sHVEM) or prophylactic agent to the site of the disease; an agent that increases the expression of the target antigen against which SIR is directed; and an adenosine A2a receptor antagonist.

[0023a] In another aspect, the present disclosure refers to use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of synthetic immune receptor (SIR) polynucleotides or SIR polypeptides or polypeptide heterodimers in the manufacture of a medicament for the treatment of a subject having a disease associated with expression of a disease associated antigen that causes cancer or is associated with a viral or microbial pathogen, or in the prevention of disease in a subject having an increased risk of a disease associated with expression of a disease associated antigen that causes cancer or is associated with a viral or microbial pathogen, wherein the medicament is to be administered alone or in combination with an agent that increases the efficacy and or safety of the immune effector cell, wherein:

(i) the SIR polypeptide or polypeptide heterodimers comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more antigen binding domains

that bind to the disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CA1X); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, SleA (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157, and, (ii) the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of:

- a protein phosphatase inhibitor;
- a kinase inhibitor (*e.g.*, a PI3K/AKT inhibitor or an mTOR inhibitor or a LCK inhibitor or a BTK inhibitor);
- a cytokine;
- an inhibitor of an immune inhibitory molecule;
- an agent that decreases the level or activity of a T_{REG} cell;
- an agent that increase the proliferation and/or persistence of SIR-modified cells;
- a chemokine;
- an agent that increases the expression of SIR;
- an agent that allows regulation of the expression or activity of SIR;
- an agent that allows control over the survival and/or persistence of SIR-modified cells;
- an agent that controls the side effects of SIR-modified cells;
- a Brd4 inhibitor;
- an agent that delivers a therapeutic (*e.g.* sHVEM) or prophylactic agent to the site of the disease;
- an agent that increases the expression of the target antigen against which SIR is directed; and
- an adenosine A2a receptor antagonist.

[0024] The disclosure provides a method of treating or preventing a disease associated with expression of a disease-associated antigen in a subject, comprising administering to the subject an effective amount of an immune effector cell comprising a synthetic immune receptor (SIR) molecule, in combination with an agent that increases the efficacy of the immune cell, wherein: (i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more of antigen binding domains that bind to the disease-associated antigen 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); C-type lectin-like molecule-1 (CLL-

Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2)), P-glycoprotein, STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, BST1/CD157, low conductance chloride channel, and antigen recognized by TNT antibody, (ii) the agent that increases the efficacy of the immune cell is chosen from one or more of: a protein phosphatase inhibitor; a kinase inhibitor; a cytokine; an inhibitor of an immune inhibitory molecule; an agent that decreases the level or activity of a TREG cell; an agent that increase the proliferation and/or persistence of SIR-modified cells; a chemokine; an agent that increases the expression of SIR; an agent that allows regulation of the expression or activity of SIR; an agent that allows control over the survival and/or persistence of SIR-modified cells; an agent that controls the side effects of SIR-modified cells; a Brd4 inhibitor; an agent that delivers a therapeutic (*e.g.* sHVEM) or prophylactic agent to the site of the disease; an agent that increases the expression of the target antigen against which SIR is directed; and an adenosine A2a receptor antagonist, thereby treating the subject or preventing a disease in the subject.

[0024a] In another aspect, the present disclosure refers to use of an effective amount of an immune effector cell comprising a synthetic immune receptor (SIR) molecule in the manufacture of a medicament for use in combinatorial therapy for treating or preventing a disease associated with expression of a disease-associated antigen that causes cancer or is associated with a viral or microbial pathogen in a subject, wherein the immune effector cell comprising a synthetic immune receptor molecule is to be administered simultaneously or sequentially, in combination with an agent that increases the efficacy and/or safety of the immune cell, wherein:

(i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more of antigen binding domains that bind to the disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CA1X); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157

(ii) the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of:

- a protein phosphatase inhibitor;
- a kinase inhibitor (*e.g.*, a PI3K/AKT inhibitor or an mTOR inhibitor or a LCK inhibitor or a BTK inhibitor);
- a cytokine;

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, TCR gamma-delta, NKG2D, CD32 (FCGR2A), Tim1-/HVCR1, CSF2RA (GM-CSFR-alpha), TGFbetaR2, , Lews Ag, TCR-beta1 chain, TCR-beta2 chain, TCR-gamma chain, TCR-delta chain, FITC, Leutenizing hormone receptor (LHR), Follicle stimulating hormone receptor (FSHR), Chorionic Gonadotropin Hormone receptor (CGHR), CCR4, SLAMF6, SLAMF4, HIV1 envelope glycoprotein, HTLV1-Tax, CMV pp65, EBV-EBNA3c, KSHV K8.1, KSHV-gH, influenza A hemagglutinin (HA), GAD, PDL1, Guanylyl cyclase C (GCC), auto antibody to desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), HLA, HLA-A, HLA-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2)), P-glycoprotein, STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, BST1/CD157, low conductance chloride channel, and antigen recognized by TNT antibody; and (ii) the antigen binding domain of the SIR molecule has a binding affinity at least 5-fold less than an antibody from which the antigen binding domain is derived.

[0025a] In another aspect, the present disclosure refers to use of an effective amount of an immune effector cell comprising a synthetic immune receptor (SIR) molecule in the manufacture of a medicament for treating or preventing a disease associated with expression of a disease-associated antigen that causes cancer or is associated with a viral or microbial pathogen in a subject, wherein:

(i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more of antigen binding domains that bind to disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or

CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CAIX); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157; and

(ii) the antigen binding domain of the SIR molecule has a binding affinity at least 5-fold less than an antibody from which the antigen binding domain is derived.

[0026] In another or further example of any of the foregoing methods or uses, the disease associated with expression of the disease associated antigen is selected from the group consisting of a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the disease-associated antigen. In another or further example of any of the foregoing methods or uses, the cancer is a hematologic cancer chosen from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma,

primary effusion lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, or pre-leukemia. In another or further example of any of the foregoing methods or uses, the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, Merkel cell cancer, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, and metastatic lesions of said cancers. In another or further example of any of the foregoing methods or uses, the disease is associated with infection by a virus including but not limited to HIV1, HIV2, HTLV1, Epstein Barr virus (EBV), cytomegalovirus (CMV), adenovirus, adeno-associated virus, BK virus, Human Herpesvirus 6, Human Herpesvirus 8 influenza virus, parainfluenza virus, avian flu virus, MERS and SARS coronaviruses, Crimean Congo Hemorrhagic fever virus, rhino virus, enterovirus, Dengue virus, West Nile virus, Ebola virus, Marburg virus, Lassa fever virus, zika virus, RSV, measles virus, mumps virus, rhino virus, varicella virus, herpes simplex virus 1 and 2, varicella zoster virus, HIV-1, HTLV1, Hepatitis virus, enterovirus, hepatitis B virus, Hepatitis C virus, Nipah and Rift valley fever viruses, Japanese encephalitis virus, Merkel cell polyomavirus, or is associated with infection with mycobacterium tuberculosis, atypical mycobacteria species, Pneumocystis jirovecii, toxoplasmosis, rickettsia, nocardia, aspergillus, mucor, or candida. In another or further example of any of the foregoing methods or uses, the disease is an immune or degenerative disease including but not limited to diabetes mellitus, multiple sclerosis, rheumatoid arthritis, pemphigus vulgaris, ankylosing spondylitis, Hoshimoto's thyroiditis, SLE, sarcoidosis, scleroderma, mixed connective tissue disease, graft versus host disease or

Alzheimer's disease. In another or further example of any of the foregoing methods or uses, (i) the protein phosphatase inhibitor is a SHP-1 inhibitor and/or an SHP-2 inhibitor; (ii) the kinase inhibitor is chosen from one or more of a CDK4 inhibitor, a CDK4/6 inhibitor, a mTOR inhibitor, a MNK inhibitor, or a dual P13K/mTOR inhibitor; (iii) the agent that inhibits the immune inhibitory molecule comprises an antibody or antibody fragment, an inhibitory nucleic acid, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN) that inhibits the expression of the inhibitory molecule; (iv) the agent that decreases the level or activity of the T REG cells is chosen from cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof; and/or (v) the Brd4 inhibitor is chosen from JQ1, MS417, OTX015, LY 303511 and Brd4 inhibitor as described in US 20140256706 A1 or their derivatives. In another or further example of any of the foregoing methods or uses, the immune inhibitory molecule is selected from the group consisting of PD1, PD-L1, CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, TGFR beta, CEACAM-1, CEACAM-3, and CEACAM-5. In another or further example of any of the foregoing methods or uses, the agent that inhibits the inhibitory molecule comprises a first polypeptide comprising an inhibitory molecule or a fragment thereof and a second polypeptide that provides a positive signal to the cell, and wherein the first and second polypeptides are expressed on the SIR-containing immune cells, wherein (i) the first polypeptide comprises PD1, PD-L1, CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, TGFR beta, CEACAM-1, CEACAM-3, and CEACAM-5 or a fragment thereof; and/or (ii) the second polypeptide comprises an intracellular signaling domain comprising a primary signaling domain and/or a costimulatory signaling domain. In another or further example of any of the foregoing methods or uses, the primary signaling domain comprises a functional domain of CD3 zeta; and/or the costimulatory signaling domain comprises a functional domain of a protein selected from 41BB, CD27 and CD28. In another or further example of any of the foregoing methods or uses, the cytokine is chosen from IL- 15 or IL-21, or both. In another or further example of any of the foregoing methods or uses, the immune effector cell comprising the SIR molecule or molecules and the agent that increases the efficacy of the immune effector cell are administered substantially simultaneously or sequentially. In another or further example of any of the foregoing methods or uses, the immune cell comprising the SIR molecule is administered in combination with a molecule that targets GITR and/or modulates GITR function. In another or further example of any of the foregoing methods or uses, the molecule targeting GITR and/or modulating GITR function is administered prior to the SIR-expressing cell or population of cells, or prior to apheresis. In another or further example of any of the foregoing methods or uses, the subject is a human.

[0027] The disclosure also provides a composition comprising at least one polynucleotide of the disclosure, a SIR polypeptide molecule of the disclosure, a vector of the disclosure or the cell of the disclosure and a pharmaceutically acceptable excipient.

[0027a] In another aspect, the present disclosure refers to a composition comprising at least one recombinant polynucleotide as described herein, an isolated SIR polypeptide or polypeptide heterodimer as described herein, a vector as described herein or the cell as described herein and a pharmaceutically acceptable excipient.

[0028] The disclosure also provides a kit comprising at least one polynucleotide of the disclosure, a SIR polypeptide molecule of the disclosure, a vector of the disclosure or the cell of the disclosure and/or a composition of the disclosure.

[0028a] In another aspect, the present disclosure refers to a kit comprising at least one recombinant polynucleotide as described herein, an isolated SIR polypeptide as described herein, a vector as described herein or the cell as described herein and/or a composition as described herein.

[0029] The disclosure also provides a recombinant polynucleotide encoding a synthetic immune receptor comprising a sequence selected from the group consisting of SEQ ID NO: 900 to 2264, SEQ ID NO: 4531 to 6013, SEQ ID NO: 7519 to 8160, SEQ ID NO: 8803 to 9230, SEQ ID NO: 9659 to 9856, SEQ ID NO: 10474 to 12041, SEQ ID NO: 15786 to 16011, SEQ ID NO: 16240 to 16465, SEQ ID NO: 16694 to 16926, SEQ ID NO: 17162 to SEQ ID NO: 17394, SEQ ID NO: 17864 to 17979, SEQ ID NO: 18321 to 18322, SEQ ID NO: 18242 to 18259, SEQ ID NO: 18280 to 18588, SEQ ID NO: 18899, SEQ ID NO: 18915 to 18916 or a sequence with at least 75% identity to a nucleotide sequence encoding a synthetic immune receptor set forth in any one of SEQ ID NO: 900 to 2264, SEQ ID NO: 4531 to 6013, SEQ ID NO: 7519 to 8160, SEQ ID NO: 8803 to 9230, SEQ ID NO: 9659 to 9856, SEQ ID NO: 10474 to 12041, SEQ ID NO: 15786 to 16011, SEQ ID NO: 16240 to 16465, SEQ ID NO: 16694 to 16926, SEQ ID NO: 17162 to SEQ ID NO: 17394, SEQ ID NO: 17864 to 17979, SEQ ID NO: 18321 to 18322, SEQ ID NO: 18242 to 18259, SEQ ID NO: 18280 to 18588, SEQ ID NO: 18899 and SEQ ID NO: 18915 to 18916.

[0030] The disclosure also provides an amino acid sequence encoding a synthetic immune receptor polypeptide selected from the group consisting of SEQ ID NO: 3135 to 4498, SEQ ID NO: 6044 to 7518, SEQ ID NO: 8161 to 8802, SEQ ID NO: 9231 to 9658, SEQ ID NO: 9873 to 10070, SEQ ID NO: 12431 to 13998, SEQ ID NO: 16013 to 16238, SEQ ID NO: 16467 to 16692, SEQ ID NO: 16928 to 17160, SEQ ID NO: 17396 to 17628, SEQ ID NO: 17981 to 18096, SEQ ID NO: 18239 to 18240, SEQ ID NO: 18261 to 18278, SEQ ID NO: 18590 to 18898, SEQ ID NO: 18900 and SEQ ID NO: 18919 to 18920 or a sequence with at least 75% identity to an amino acid sequence encoding the synthetic immune receptor polypeptide set forth in any one of SEQ ID NO: 3135 to 4498, SEQ ID NO: 6044 to 7518, SEQ ID NO: 8161 to 8802, SEQ ID NO: 9231 to 9658, SEQ ID NO: 9873 to 10070, SEQ ID NO: 12431 to 13998, SEQ ID NO: 16013 to 16238, SEQ ID NO: 16467 to 16692, SEQ ID NO: 16928 to 17160, SEQ ID NO: 17396 to 17628, SEQ ID NO: 17981 to 18096, SEQ ID NO: 18239 to 18240, SEQ ID NO: 18261 to 18278, SEQ ID NO: 18590 to 18898, SEQ ID NO: 18900 and SEQ ID NO: 18919 to 18920.

[0031] The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **Figure 1** shows a Schematic description of an antibody, a TCR, a double chain chimeric receptor and different generations of CAR.

[0033] **Figure 2** shows an exemplary vector construct of the disclosure.

[0034] **Figure 3A-Q** show depictions of various formats that SIRs of the disclosure can have upon expression. In these depictions each TCR of the pair of TCRs is linked to a vH or vL binding domain. In other embodiments each TCR can be bound to a vHH domain rather than a vH or vL.

[0035] **Figure 4A-Q** show depictions of various formats that SIRs of the disclosure can have upon expression. In these depictions one TCR of the pair of TCRs is linked to a vH or vL and the vH or vL is then linked to the opposite vH or vL. Although in (A) the vL is shown linked to the TCRb chain, it will be recognized that the orientation in all the depictions of (A)-(Q) could be swapped such that in (A) the vL is linked to the TCRa *etc.*

[0036] **Figure 5A-Q** show depictions of various formats that SIRs of the disclosure can have upon expression. In these constructs, SIRs are based on a single domain antibody (vHH), which bind to only one of the two TCR constant chains and the other chain is left empty. An exemplary such construct is CD8SP-V5-[hTCRb-KACIAH]-F-P2A-CD8SP-Her3-17B05So-vHH-Myc-[hTCRa-CSDVP]-F-F2A-PAC [SEQ ID NO:1715]. Similar constructs can be made that are based on other non-immunoglobulin binding domains instead of a vHH domain. For example, such non-immunoglobulin binding domains may be based on affibodies, DARPINs, autoantigens (*e.g.* Dsg3), ligands (*e.g.* MPL or TRAIL) or receptors (*e.g.*, CD16).

[0037] **Figure 6A-Q** show depictions of various formats that SIRs of the disclosure can have upon expression. In these constructs, SIRs contain two different types of antigen binding domains that are structurally different. In one example, one antigen binding domain comprises of a single domain antibody (vHH), while the other antigen binding domain comprises of an scFV fragment in a vL-Linker-vH orientation or a vH-Linker-vL orientation. In another example, one antigen binding domain comprises of a single domain antibody (vHH), while the other antigen binding domain comprises of a receptor (*e.g.* CD16). In another example, one antigen binding domain comprises of a single domain antibody (vHH), while the other antigen binding domain comprises of an affibody. The advantage of using two different types of antigen binding domains is that they are less likely to interfere with each other. The first antigen binding domain (*e.g.* vHH) can be directed to one antigen and the second antigen binding domain (*e.g.*,

WHAT IS CLAIMED IS:

1. At least one recombinant polynucleotide encoding at least one synthetic immune receptor (SIR), the at least one SIR comprising:

(a) a T-cell receptor (TCR) constant chain having an amino acid sequence selected from the group consisting of:

- (i) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 and has one or more mutations at positions 48, 61, 91, 92, 93, and/or 94 and which may comprise an optional accessory module;
- (ii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 and has one or more mutations at positions 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
- (iii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3025 and has one or more mutations at position 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
- (iv) an amino acid sequence that is at least 95% identical to SEQ ID NO:3046, 3047 or 3048 and which may comprise an optional accessory module;
- (v) an amino acid sequence that is at least 95% identical to SEQ ID NO:3049 and which may comprise an optional accessory module;
- (vi) an amino acid sequence that is at least 95% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and
- (vii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 or 3011 and which may comprise an optional accessory module; and
- (viii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 or 3025 or 3026 and which may comprise an optional accessory module; and
- (ix) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), (v) and (vi), and (vii) and (viii);

(b) an optional linker; and

(c) one or more non-natural TCR antigen binding domain(s) linked to (a), wherein the binding domain retains the antigen-binding specificity of the molecule from which it is derived, selected from the group consisting of:

- (1) an antibody;
- (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂);
- (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof;

- (4) a light chain variable region of an antibody (vL domain) or a fragment thereof;
- (5) a single chain variable fragment (scFv) or a fragment thereof;
- (6) a single domain antibody (SDAB) or a fragment thereof;
- (7) a camelid VHH domain or a fragment thereof;
- (8) a monomeric variable region of an antibody;
- (9) a non-immunoglobulin antigen binding scaffold selected from a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof;
- (10) a receptor or a fragment thereof;
- (11) a ligand or a fragment thereof;
- (12) a bispecific-antibody, -antibody fragment, -scFV, -VHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and
- (13) an autoantigen or a fragment thereof,

wherein the mutations of (a)(i) – (a)(iii) and the dimer of (a)(ix) provide a diverse binding affinity to a target antigen of the antigen binding domain and that is at least 5% greater than the binding affinity of a wild-type TCR (cTCR) having the same binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted and MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen.

2. The recombinant polynucleotide of claim 1, comprising TCR constant chains of (a)(ix) wherein the non-natural TCR antigen binding domains are selected from the group consisting of:

- variable regions of a heavy and light chains of an antibody or fragments thereof specific for a predefined target antigen, such that, when expressed, one of said heavy and light chains of the antibody or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said heavy and light chains of the antibody or fragments thereof is attached to the other of said two chains of said T-cell constant regions;
- two single chain variable fragments (scFv) specific for one or more predefined target antigens, such that, when expressed, one of said scFv is attached to one of said two chains of

(a)(ix) of said T-cell constant region and the other of said scFv is attached to the other of said two chains of said T-cell constant regions;

- two antibody fragments specific for one or more predefined target antigens, such that, when expressed, one of said antibody fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said antibody fragments is attached to the other of said two chains of said T-cell constant regions;

- two single domain antibody (SDAB) fragments specific for one or more predefined target antigens, such that, when expressed, one of said SDAB fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of SDAB fragments is attached to the other of said two chains of said T-cell constant regions;

- two camelid VHH domains specific for one or more predefined target antigens, such that, when expressed, one of said VHH domains is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of VHH domains is attached to the other of said two chains of said T-cell constant regions;

- two non-immunoglobulin antigen binding scaffolds specific for one or more predefined target antigens, such that, when expressed, one of said non-immunoglobulin antigen binding scaffolds is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said non-immunoglobulin antigen binding scaffolds domains is attached to the other of said two chains of said T-cell constant regions;

- two receptors or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said receptors or a fragment thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said receptors or a fragment thereof is attached to the other of said two chains of said T-cell constant regions;

- two ligands or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said ligands or a fragment thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said ligands or a fragment thereof is attached to the other of said two chains of said T-cell constant regions.

- two structurally distinct antigen binding fragments specific for one or more predefined target antigens, such that, when expressed, one of said antigen binding fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions;

- two binding fragments one or both of which are bispecific or multispecific such that, when expressed, one of said antigen binding fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions;

- two autoantigens or fragment thereof, such that, when expressed, one of said autoantigens or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said autoantigens or fragments thereof is attached to the other of said two chains of said T-cell constant regions; and

-two vL or fragment thereof, such that, when expressed, one of said vL or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said vL or fragments thereof is attached to the other of said two chains of said T-cell constant regions; and

-two vH or fragment thereof, such that, when expressed, one of said vH or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said vH or fragments thereof is attached to the other of said two chains of said T-cell constant regions.

3. The recombinant polynucleotide of claim 1, wherein the polynucleotide encoding the TCR constant chain of (a) encodes a TCR constant chain(s) comprising mutations that enhance the expression and/or pairing of TCR constant chains and reduce their pairing with the endogenous T cell receptor chains; and is optionally codon-optimized and/or comprises

- (i) a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 730 to 743 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 730 to 743, and which is capable of dimerizing with a TCR β 1 or TCR β 2 chain, or
- (ii) a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 744 to 765 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 744 to 765 and which is capable of dimerizing with a TCR α chain, or
- (iii) a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 769 to 770 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 769 to 770 and which is capable of pairing with a TCR δ chain, or
- (iv) a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 771 to 772 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 771 to 772 and which is capable of dimerizing with a TCR γ chain, or
- (v) a nucleic acid sequence of 1-40 modifications of a nucleic acid sequence of SEQ ID NO: 766 to 768 or a sequence with at least 70% identity to a nucleic acid sequences of SEQ ID NO: 766 to 768 and which is capable of dimerizing with a TCR β 1 or TCR β 2 chain.

4. The recombinant polynucleotide of claim 1, wherein said one or more non-natural TCR antigen binding domain(s) bind to one or more of disease-associated antigens selected from a

group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CAIX); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157.

5. The recombinant polynucleotide of claim 4, wherein said one or more non-natural TCR antigen binding domain(s) is selected from the group consisting of:

(i) a heavy chain variable region (vH) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 226 to 400 or 10203 to 10321 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its antigen;

(ii) a light chain variable region (vL) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 16 to 191 or 10085 to 10202 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its antigen;

(iii) a single chain variable fragment (scFv) encoded by a polynucleotide having a sequence of any one of SEQ ID NO 488 to 657, 10346 to 10400 or 18098 to 18160 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its antigen;

(iv) a camelid VHH domain encoded by a polynucleotide having a sequence of any one of SEQ ID NO 421 to 445 or 10322 to 10337 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its antigen;

(v) a non-immunoglobulin antigen binding scaffold encoded by a polynucleotide having a sequence of any one of SEQ ID NO 439 to 443 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its antigen;

(vi) a receptor encoded by a polynucleotide having a sequence of any one of SEQ ID NO 456 to 468 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its cognate;

(vii) a ligand encoded by a polynucleotide having a sequence of any one of SEQ ID NO 476 to 486 or 10402 to 10404 or sequences with at least 85% identity thereto and which encodes a polypeptide that binds to its cognate;

(viii) a light chain variable region (vL) that

comprise one or more of light chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos: 13999 to 14879 or 14880 and/or one or more of

heavy chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos: 14881 to 15761 or 15762.

6. The recombinant polynucleotide of claim 1, wherein said one or more non-natural TCR antigen binding domain(s) encodes

i) a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos: 2307 to 2482 or 12042 to 12159 having up to 10 conservative amino acid substitutions and/or a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos: 2506 to 2680 or 12160 to 12278 having up to 10 conservative amino acid substitutions, and/or

ii) one or more of camelid VHH complementary determining regions for a selected antigen as set forth in any of SEQ ID Nos: 2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, and/or

iii) a non-immunoglobulin antigen binding scaffold having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions, and/or

iv) a scFv domain comprising one or more light chain complementary determining region of a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos: 2307 to 2482 or 12042 to 12159 and one or more heavy chain complementary determining regions of a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos: 2506 to 2680 or 12160 to 12278, and/or

v) a scFv fragment having a sequence selected from the group consisting of SEQ ID NO: 2770 to 2939, 12303 to 12357 or 18162 to 18224 each having up to 10 conservative amino acid substitutions, and/or

vi) one or more receptors comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions, and/or

vii) one or more ligands comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions, and/or

viii) an extracellular domain of CD16A, NKG2D, CD4, PD1, desmoglein 3 (Dsg3), or CD4-DC-SIGN, and/or

ix) an extracellular domain of one or more of hTPO, mTPO, CGH α chain, CGH β chain, FH β chain, LH β chain, TSH β chain, APRIL or combination thereof.

7. The recombinant polynucleotide of claim 4, wherein said one or more non-natural TCR antigen binding domain(s) bind to CD19 and encode a polypeptide sequence consisting of:

-a polypeptide comprising a sequence that is at least 95% identical to any one of SEQ ID NO:2318-2324, 12060-12068, 12108, 12127, or 12156 or any complement determining region (CDR) contained in any of the foregoing polypeptide;

-a polypeptide comprising a sequence that is at least 95% identical to any one of SEQ ID NO: 2517-2523, 12178-12186, 1227, 12246 or 12275 or any complement determining region (CDR) contained in any of the foregoing polypeptides;

-a polypeptide comprising a sequence that is at least 95% identical to SEQ ID NO: 12288; and

-a polypeptide comprising a sequence that is at least 95% identical to any one of SEQ ID NO: 2770-2774, 12325, 12308, 18162-18170 or 12354.

8. The recombinant polynucleotide of claim 7, wherein the recombinant polynucleotide encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID Nos:3135-3235, 3250-3346, 3396, 3401-3403, 3406, 3429-3432, 3435-3439, 3540, 3855-3859, 12431-12489, 12491-12493, 12495-12530, 12534, 13195-13203, 13249, 13267, 13289, 13429-13437, 13483, 13501 and 13523.

9. A recombinant polynucleotide of claim 1 which is co-expressed with an accessory module, wherein the accessory module is selected from the group consisting of 41BBL, CD40L, K13, MC159, cFLIP-L/MRIT α , cFLIP-p22, HTLV1 Tax, HTLV2 Tax, HTLV2 Tax-RS mutant, FKBPx2-K13, FKBPx2-HTLV2-Tax, FKBPx2-HTLV2-Tax-RS, IL6R-304-vHH-Alb8-vHH, IL12f, PD1-4H1 scFV, PD1-5C4 scFV, PD1-4H1-Alb8-vHH, PD1-5C4-Alb8-vHH, CTLA4-Ipilimumab-scFv, CTLA4-Ipilimumab-Alb8-vHH, IL6-19A-scFV, IL6-19A-scFV-Alb8-vHH, sHVEM, sHVEM-Alb8-vHH, hTERT, Fx06, CD3z, CD3z-GGGS-41BB, CD3-BBz, CD3-CD28z, CD3-CD28-Lck fusion protein, shRNA targeting Brd4, chimeric antigen receptor (CAR), hTERT, heparinase, a CAR, an inhibitory CAR and combination thereof.

10. 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, a baculovirus vector, a sleeping beauty transposon vector, and a piggybac transposon vector.

11. An isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer comprising:

- (a) a T-cell receptor (TCR) constant chain having an amino acid sequence selected from the group consisting of:
- (i) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 and has one or more mutations at positions 48, 61, 91, 92, 93, and/or 94 and which may comprise an optional accessory module;
 - (ii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 and has one or more mutations at positions 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
 - (iii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3025 and has one or more mutations at position 18, 22, 57, 79, 133, 136 and/or 139 and which may comprise an optional accessory module;
 - (iv) an amino acid sequence that is at least 95% identical to SEQ ID NO:3046, 3047 or 3048 and which may comprise an optional accessory module;
 - (v) an amino acid sequence that is at least 95% identical to SEQ ID NO:3049 and which may comprise an optional accessory module;
 - (vi) an amino acid sequence that is at least 95% identical to SEQ ID NO:3051 or 3052 and which may comprise an optional accessory module; and
 - (vii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3010 or 3011 and which may comprise an optional accessory module; and
 - (viii) an amino acid sequence that is at least 95% identical to SEQ ID NO:3024 or 3025 or 3026 and which may comprise an optional accessory module; and
 - (ix) a dimer combination of two TCR constant chains selected from (i) and (ii), (i) and (iii), (iv) and (ii), (iv) and (iii), and (v) and (vi); and (vii) and (viii);
- (b) an optional linker; and
- (c) one or more non-natural TCR antigen binding domain(s) linked to (a), wherein the binding domain retains the antigen-binding specificity of the molecule from which it is derived, selected from the group consisting of:
- (1) an antibody;
 - (2) an antibody fragment (*e.g.* a Fv, a Fab, a (Fab')₂);
 - (3) a heavy chain variable region of an antibody (vH domain) or a fragment thereof;
 - (4) a light chain variable region of an antibody (vL domain) or a fragment thereof;

- (5) a single chain variable fragment (scFv) or a fragment thereof;
- (6) a single domain antibody (SDAB) or a fragment thereof;
- (7) a camelid VHH domain or a fragment thereof;
- (8) a monomeric variable region of an antibody;
- (9) a non-immunoglobulin antigen binding scaffold selected from a DARPIN, an affibody, an affilin, an adnectin, an affitin, an obodies, a repebody, a fynomer, an alphabody, an avimer, an atrimer, a centyrin, a pronectin, an anticalin, a kunitz domain, an Armadillo repeat protein or a fragment thereof;
- (10) a receptor or a fragment thereof;
- (11) a ligand or a fragment thereof;
- (12) a bispecific-antibody, -antibody fragment, -scFv, -VHH, -SDAB, -non-immunoglobulin antigen binding scaffold, -receptor or -ligand; and
- (13) an autoantigen or a fragment thereof,

wherein the mutations of (a)(i) – (a)(iii) provide a diverse binding affinity to a target antigen of the antigen binding domain and which synthetic immune receptor, upon expression in a lymphocyte, expresses both said antigen binding domain and said T cell receptor constant chain in one or more continuous chains on the surface of the lymphocytes such that lymphocytes are triggered to activate, proliferate, secrete cytokines and/or modulate (induce or suppress) killing of the target cells and have MHC-restricted or MHC-non-restricted antibody-type specificity when said expressed antigen binding domain binds to its antigen.

12. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, comprising TCR constant chains of (a)(ix) wherein the non-natural TCR antigen binding domains are selected from the group consisting of:

- variable regions of a heavy and light chains of an antibody or fragments thereof specific for a predefined target antigen, such that, when expressed, one of said heavy and light chains of the antibody or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said heavy and light chains of the antibody or fragments thereof is attached to the other of said two chains of said T-cell constant regions;

- two single chain variable fragments (scFv) specific for one or more predefined target antigens, such that, when expressed, one of said scFv is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said scFv is attached to the other of said two chains of said T-cell constant regions;

- two antibody fragments specific for one or more predefined target antigens, such that, when expressed, one of said antibody fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said antibody fragments is attached to the other of said two chains of said T-cell constant regions;

- two single domain antibody (SDAB) fragments specific for one or more predefined target antigens, such that, when expressed, one of said SDAB fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of SDAB fragments is attached to the other of said two chains of said T-cell constant regions;

- two camelid VHH domains specific for one or more predefined target antigens, such that, when expressed, one of said VHH domains is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of VHH domains is attached to the other of said two chains of said T-cell constant regions;

- two non-immunoglobulin antigen binding scaffolds specific for one or more predefined target antigens, such that, when expressed, one of said non-immunoglobulin antigen binding scaffolds is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said non-immunoglobulin antigen binding scaffolds domains is attached to the other of said two chains of said T-cell constant regions;

- two receptors or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said receptors or a fragment thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said receptors or a fragment thereof is attached to the other of said two chains of said T-cell constant regions;

- two ligands or a fragment thereof specific for one or more predefined target antigens, such that, when expressed, one of said ligands or a fragment thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said ligands or a fragment thereof is attached to the other of said two chains of said T-cell constant regions.

- two structurally distinct antigen binding fragments specific for one or more predefined target antigens, such that, when expressed, one of said antigen binding fragments is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions;

- two binding fragments one or both of which are bispecific or multispecific such that, when expressed, one of said antigen binding fragments is attached to one of said

two chains of (a)(ix) of said T-cell constant region and the other of said antigen binding fragments is attached to the other of said two chains of said T-cell constant regions;

- two autoantigens or fragment thereof, such that, when expressed, one of said autoantigens or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said autoantigens or fragments thereof is attached to the other of said two chains of said T-cell constant regions; and

-two vL or fragment thereof, such that, when expressed, one of said vL or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said vL or fragments thereof is attached to the other of said two chains of said T-cell constant regions; and

-two vH or fragment thereof, such that, when expressed, one of said vH or fragments thereof is attached to one of said two chains of (a)(ix) of said T-cell constant region and the other of said vH or fragments thereof is attached to the other of said two chains of said T-cell constant regions.

13. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, comprising:

a TCR constant domain of (i), (ii), (iii), (iv), (v), (vi), (vii) or (viii) wherein the non-natural TCR binding domains is selected from the group consisting of:

- a variable region of the heavy chain (vH) of an antibody specific for the predefined target antigen;
- a variable region of the light chain (vL) of an antibody specific for the predefined target antigen;
- a single chain variable fragment (scFv) specific for a predefined target antigen;
- an antibody fragment (*e.g.*, Fv, a Fab, a (Fab')₂) specific for a predefined target antigen;
- a single domain antibody (SDAB) fragment specific for a predefined target antigen;
- a camelid VHH domain specific for a predefined target antigen;
- a non-immunoglobulin antigen binding scaffold specific for a predefined target antigen;
- a receptor specific for a predefined target antigen or fragments thereof;
- a ligand specific for a predefined target antigens or fragments thereof;

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

14. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, wherein the TCR constant chain(s) comprise mutations that enhance the expression and/or pairing of TCR constant chains and reduce their pairing with the endogenous T cell receptor chains and wherein the constant region of TCR is

- i) a TCR receptor α chain ($C\alpha$) comprising an amino acid sequence having at having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3010 to 3023 or a sequence that is at least 95% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3010 to 3023, or
- ii) a TCR receptor β chain ($C\beta$) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3024 to 3044 or a sequence that is at least 95% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3024 to 3044, or
- iii) a TCR receptor γ chain ($C\gamma$) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to a sequence selected from the group consisting of SEQ ID NO: 3049 to 3050 or a sequence that is at least 95% identical to an amino acid sequences selected from the group consisting of SEQ ID NO: 3049 to 3050, or
- iv) a TCR receptor δ chain ($C\delta$) comprising an amino acid sequence 1-40 amino acid substitutions or mutations to an amino acid sequence selected from the group consisting of SEQ ID NO:3051 to 3052 or a sequence that is at least 95% identical to a sequence selected from the group consisting of SEQ ID NO:3051 to 3052, or
- v) a preTCR receptor α chain (preC α) comprising an amino acid sequence having 1-40 amino acid substitutions or mutations to an amino acid sequence selected from the group consisting of SEQ ID NO:3046 to 3048 or a sequence that is at least 95% identical to a sequence selected from the group consisting of SEQ ID NO: 3046 to 3048.

15. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, wherein said one or more non-natural TCR antigen binding domain(s) bind to one or more of disease-associated antigens selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal

growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CAIX); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157.

16. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11 and 15, wherein said one or more non-natural TCR antigen binding domain(s) is selected from the group consisting of:

(i) a heavy chain variable region (vH) comprising a sequence as set forth in any of SEQ ID Nos:2506 to 2680 or 12160 to 12278 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its antigen;

(ii) a light chain variable region (vL) comprising a sequence as set forth in any one of SEQ ID NO 2307 to 2482 or 12042 to 12159 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its;

(iii) a single chain variable fragment (scFv) comprising a sequence as set forth in any one of SEQ ID NO: 2770 to 2939, 12303 to 12357, or 18162 to 18224 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its antigen;

(iv) a camelid VHH domain comprising a sequence as set forth in any one of SEQ ID NO: 2701 to 2725 or 12279 to 12294 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its antigen;

(v) a non-immunoglobulin antigen binding scaffold encoded by a polynucleotide of any one of SEQ ID NO 439 to 443 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its antigen;

(vi) a receptor comprising a sequence as set forth in any one of SEQ ID NO 2736 to 2748 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its cognate;

(vii) a ligand comprising a sequence as set forth in any one of SEQ ID NO 2758 to 2768 or 12359 to 12361 or sequences with at least 95% identity thereto and which encodes a polypeptide that binds to its cognate; and

(viii) a light chain variable region (vL) comprising one or more of light chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:13999 to 14879 or 14880 and/or one or more of heavy chain complementary determining region for a selected target antigen as set forth in any of SEQ ID Nos:14881 to 15761 or 15762.

17. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, wherein said one or more non-natural TCR antigen binding domain(s) comprises

- i) a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 having up to 10 conservative amino acid substitutions and/or a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278 having up to 10 conservative amino acid substitutions, and/or
- ii) one or more of camelid VHH complementary determining regions for a selected antigen as set forth in any of SEQ ID Nos:2701 to 2725 or 12279 to 12294 having up to 10 conservative amino acid substitutions, and/or
- iii) a non-immunoglobulin antigen binding scaffold having a sequence as set forth in any of SEQ ID NOs: 2728-2732 or 12296 to 12301 and having up to 10 conservative amino acid substitutions, and/or
- iv) a scFv domain comprising one or more light chain complementary determining region of a variable light (vL) domain comprising a sequence of any one of SEQ ID Nos:2307 to 2482 or 12042 to 12159 and one or more heavy chain complementary determining regions of a variable heavy (vH) domain comprising a sequence of any one of SEQ ID Nos:2506 to 2680 or 12160 to 12278, and/or
- v) a scFv fragment having a sequence selected from the group consisting of SEQ ID NO:2770 to 2939, 12303 to 12357 or 18162 to 18224 each having up to 10 conservative amino acid substitutions, and/or
- vi) one or more receptors comprising of amino acid sequences of any of SEQ ID Nos: 2736 to 2748 having up to 10 conservative amino acid substitutions, and/or
- vii) one or more ligands comprising a sequence of any of SEQ ID NOs: 2758-2768 or 12359 to 12361 having up to 10 conservative amino acid substitutions, and/or
- viii) an extracellular domain of CD16A, NKG2D, CD4, PD1, desmoglein 3 (Dsg3), or CD4-DC-SIGN, and/or
- ix) an extracellular domain of one or more of hTPO, mTPO, CGH α chain, CGH β chain, FH β chain, LH β chain, TSH β chain, APRIL or combination thereof.

18. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claim 11, wherein said one or more non-natural TCR antigen binding domain(s) bind to CD19 and comprise:

- a polypeptide sequence that is at least 95% identical to any one of SEQ ID NO:2318-2324, 12060-12068, 12108, 12127, or 12156 or any complement determining region (CDR) contained in any of the foregoing polypeptide;

-a polypeptide sequence that is at least 95% identical to any one of SEQ ID NO: 2517-2523, 12178-12186, 1227, 12246 or 12275 or any complement determining region (CDR) contained in any of the foregoing polypeptides;

-a polypeptide sequence that is at least 95% identical to SEQ ID NO: 12288; and

-a polypeptide sequence that is at least 95% identical to any one of SEQ ID NO: 2770-2774, 12325, 12308, 18162-18170 or 12354.

19. The isolated synthetic immune receptor (SIR) polypeptide or polypeptide heterodimer of claims 11 and 18, wherein polypeptide comprises a sequence selected from the group consisting of SEQ ID Nos: 3135-3235, 3250-3346, 3396, 3401-3403, 3406, 3429-3432, 3435-3439, 3540, 3855-3859, 12431-12489, 12491-12493, 12495-12530, 12534, 13195-13203, 13249, 13267, 13289, 13429-13437, 13483, 13501 and 13523.

20. An immune effector cell or a stem cell comprising

i) at least one isolated SIR polypeptide or polypeptide heterodimer of claims 11 and 18;

ii) at least one recombinant polynucleotide of claims 1 and 7;

iii) at least one vector of claim 10,

wherein the immune cell optionally further comprises at least one chimeric antigen receptor (CAR) polypeptide,

wherein the CAR polypeptide comprises an intracellular signaling domain comprising a costimulatory signaling domain, but does not comprise a primary signaling domain or comprises an intracellular signaling domain comprising a primary signaling domain, but does not comprise a costimulatory signaling domain.

21. A composition comprising at least one recombinant polynucleotide of claims 1 and 7, an isolated SIR polypeptide or polypeptide heterodimer of claims 11 and 18, a vector of claim 10 or the cell of claim 20 and a pharmaceutically acceptable excipient.

22. Use of a composition comprising an immune effector cell or a stem cell that can generate immune effector cells comprising one or more of synthetic immune receptor (SIR) polynucleotides or SIR polypeptides or polypeptide heterodimers in the manufacture of a medicament for the treatment of a subject having a disease associated with expression of a disease associated antigen that causes cancer or is associated with a viral or microbial pathogen, or for the prevention of disease in a subject having an increased risk of a disease associated with expression of a disease associated antigen that causes cancer or is associated with a viral or

microbial pathogen, wherein the medicament is to be administered alone or in combination with an agent that increases the efficacy and or safety of the immune effector cell, wherein:

(i) the SIR polypeptide or polypeptide heterodimers comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more antigen binding domains that bind to the disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CA1X); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein coupled receptor class C group 5, member D (GPC5D); chromosome X open reading frame 61 (CXORF61); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157, and, (ii) the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of:

- a protein phosphatase inhibitor;
- a kinase inhibitor (*e.g.*, a PI3K/AKT inhibitor or an mTOR inhibitor or a LCK inhibitor or a BTK inhibitor);
- a cytokine;
- an inhibitor of an immune inhibitory molecule;
- an agent that decreases the level or activity of a T_{REG} cell;
- an agent that increase the proliferation and/or persistence of SIR-modified cells;
- a chemokine;
- an agent that increases the expression of SIR;
- an agent that allows regulation of the expression or activity of SIR;
- an agent that allows control over the survival and/or persistence of SIR-modified cells;
- an agent that controls the side effects of SIR-modified cells;
- a Brd4 inhibitor;
- an agent that delivers a therapeutic (*e.g.* sHVEM) or prophylactic agent to the site of the disease;
- an agent that increases the expression of the target antigen against which SIR is directed; and
- an adenosine A2a receptor antagonist.

23. Use of an effective amount of the immune effector cell or stem cell that can give rise to an immune effector cell or stem cell of claim 20 in the manufacture of a medicament for

providing anti-disease immunity in a subject, wherein the cell is an autologous T cell or an allogeneic T cell, or an autologous NKT cell or an allogeneic NKT cell or an autologous or an allogeneic hematopoietic stem cell or an autologous or an allogeneic induced pluripotent stem cells (iPSC) that can give rise to an immune effector cell or stem cell.

24. Use of an effective amount of an immune effector cell comprising a synthetic immune receptor (SIR) molecule in the manufacture of a medicament for use in combinatorial therapy for treating or preventing a disease associated with expression of a disease-associated antigen that causes cancer or is associated with a viral or microbial pathogen in a subject, wherein the immune effector cell comprising a synthetic immune receptor molecule is to be administered simultaneously or sequentially in combination with an agent that increases the efficacy and/or safety of the immune cell, wherein:

(i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more of antigen binding domains that bind to the disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CAIX); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase

(ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MART1); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157

(ii) the agent that increases the efficacy and/or safety of the immune cell is chosen from one or more of:

- a protein phosphatase inhibitor;
- a kinase inhibitor (*e.g.*, a PI3K/AKT inhibitor or an mTOR inhibitor or a LCK inhibitor or a BTK inhibitor);
- a cytokine;
- an inhibitor of an immune inhibitory molecule;
- an agent that decreases the level or activity of a T_{REG} cell;
- an agent that increase the proliferation and/or persistence of SIR-modified cells;
- a chemokine;
- an agent that increases the expression of SIR;
- an agent that allows regulation of the expression or activity of SIR;
- an agent that allows control over the survival and/or persistence of SIR-modified cells;

- an agent that controls the side effects of SIR-modified cells;
 - a Brd4 inhibitor;
 - an agent that delivers a therapeutic (*e.g.* sHVEM) or prophylactic agent to the site of the disease;
 - an agent that increases the expression of the target antigen against which SIR is directed; and
 - an adenosine A2a receptor antagonist,
- thereby treating the subject or preventing a disease in the subject.

25. Use of an effective amount of an immune effector cell comprising a synthetic immune receptor (SIR) molecule in the manufacture of a medicament for treating or preventing a disease associated with expression of a disease-associated antigen that causes cancer or is associated with a viral or microbial pathogen in a subject, wherein:

(i) the SIR molecule comprises one or more of T-cell receptor constant chains joined via an optional linker to one or more of antigen binding domains that bind to disease-associated antigen associated with the disease, and said disease-associated antigen is selected from a group consisting of: CD19; CD20, CD5, CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECL1); CD33; epidermal growth factor receptor variant III (EGFRviii); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member B cell maturation (BCMA); Tn antigen ((Tn Ag) or (GalNAc α -Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; a glycosylated CD43 epitope expressed on acute leukemia or lymphoma but not on hematopoietic progenitors, a glycosylated CD43 epitope expressed on non-hematopoietic cancers, Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); Interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); Mesothelin (MSLN); Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); 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); carbonic anhydrase IX (CAIX); tyrosinase; Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma associated antigen (HMWMAA); 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); CD179a; anaplastic lymphoma kinase (ALK); mammary gland differentiation antigen (NY-BR-1); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ES0-1); Melanoma-associated antigen 1 (MAGE-A1); telomerase; melanoma antigen recognized by T cells 1 (MelanA or MARTI); Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); C-type lectin domain family 12 member A (CLEC12A); 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, CDH19, CD200R, Slea (CA19.9; Sialyl Lewis Antigen) Fucosyl-GM1, PTK7, CDH1-CD324, DLL3, CD276/B7H3, IL11Ra, IL13Ra2, CD179b-IGL11, ALK TCR-gamma-delta, NKG2D, CD32 (FCGR2A), Tn ag, 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, GD3, 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-A2, HLA-B, HLA-C, HLA-DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, HLA-G, IGE, CD99, Lym1, Lym2, RAS G12V, Tissue Factor 1 (TF1), AFP, GPRC5D, claudin18.2 (CLD18A2 OR CLDN18A.2), STEAP1, LIV1, NECTIN-4, CRIPTO, GPA33, and BST1/CD157; and

(ii) the antigen binding domain of the SIR molecule has a binding affinity at least 5-fold less than an antibody from which the antigen binding domain is derived.

26. The use of any one of claims 23-25, wherein the disease associated with expression of the disease associated antigen is selected from the group consisting of a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the disease-associated antigen.

27. The use of claim 26, wherein the cancer 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.

28. The use of claim 26, wherein the disease is associated with infection by a virus selected from the group consisting of HIV1, HIV2, HTLV1, Epstein Barr virus (EBV), cytomegalovirus (CMV), adenovirus, adeno-associated virus, BK virus, Human Herpesvirus 6, Human Herpesvirus 8 influenza virus, parainfluenza virus, avian flu virus, MERS and SARS coronaviruses, Crimean Congo Hemorrhagic fever virus, rhino virus, enterovirus, Dengue virus, West Nile virus, Ebola virus, Marburg virus, Lassa fever virus, zika virus, RSV, measles virus, mumps virus, rhino virus, varicella virus, herpes simplex virus 1 and 2, varicella zoster virus, HIV-1, HTLV1, Hepatitis virus, enterovirus, hepatitis B virus, Hepatitis C virus, Nipah and Rift valley fever viruses, Japanese encephalitis virus, Merkel cell polyomavirus, or is associated with infection with mycobacterium tuberculosis, atypical mycobacteria species, Pneumocystis jirovecii, toxoplasmosis, rickettsia, nocardia, aspergillus, mucor, and candida.

29. The use of claim 26, wherein the disease is an immune or degenerative disease selected from the group consisting of diabetes mellitus, multiple sclerosis, rheumatoid arthritis, pemphigus

vulgaris, ankylosing spondylitis, Hashimoto's thyroiditis, SLE, sarcoidosis, scleroderma, mixed connective tissue disease, graft versus host disease and Alzheimer's disease.

30. A kit comprising at least one recombinant polynucleotide of claim 1, an isolated SIR polypeptide of claim 11, a vector of claim 10 or the cell of claim 20 and/or a composition of claims 21-22.