CLAIMS

WHAT IS CLAIMED IS:

1. A system for inducing activity of an immune cell and/or a target cell, comprising:

(a) a chimeric antigen receptor (CAR) comprising a first antigen binding domain which exhibits specific binding to a first epitope, a transmembrane domain, and an intracellular signaling domain; and

(b) a modified T cell receptor (TCR) complex comprising a second antigen binding domain which exhibits specific binding to a second epitope, wherein said second antigen binding domain is linked to:

(i) at least one TCR chain selected from an alpha chain, a beta chain, a gamma chain and a delta chain of a T cell receptor,

(ii) an epsilon chain, a delta chain, and/or a gamma chain of cluster of differentiation 3 (CD3), or

(iii)a CD3 zeta chain,

wherein binding of the first antigen binding domain to the first epitope, and/or binding of the second antigen binding domain to the second epitope activates an immune cell activity of an immune cell expressing the system.

2. The system of claim 1, wherein said TCR comprises one or more additional antigen binding domains linked to (i) at least one TCR chain selected from an alpha chain, a beta chain, a gamma chain and a delta chain of a T cell receptor, (ii) an epsilon chain, a delta chain, and/or a gamma chain of cluster of differentiation 3 (CD3), and/or (iii) a CD3 zeta chain, and wherein binding of said one or more additional antigen binding domains to their respective epitopes activates an immune cell activity of an immune cell expressing the system.

3. The system of claim 2, wherein said second antigen binding domain and said one or more additional antigen binding domains are linked in tandem.

4. The system of claims 2 or 3, wherein said one or more additional antigen binding domains exhibit specific binding to one or more additional epitopes that are same as or different from the first or second epitope.

5. The system of any one of claims 1 to 4, wherein said CAR comprises one or more additional antigen binding domains.

6. The system of claim 5, wherein said one or more additional antigen binding domains in said CAR exhibit specific binding to one or more additional epitopes that are same as or different from the first or second epitope.

7. The system of claim 1, wherein said intracellular signaling domain of said CAR comprises an immunoreceptor tyrosine-based activation motif (ITAM), an immunoreceptor tyrosine-based inhibition motif (ITIM), or an signaling domain of an Fcγ receptor (FcγR), an Fcε receptor (FcεR), an Fcα receptor (FcαR), neonatal Fc receptor (FcRn), CD3, CD3 ζ, CD3 γ, CD3 δ, CD3 ε, CD4, CD5, CD8, CD21, CD22, CD28, CD32, CD40L (CD154), CD45, CD66d, CD79a, CD79b, CD80, CD86, CD278 (also known as ICOS), CD247 ζ, CD247 η, DAP10, DAP12, FYN, LAT, Lck, MAPK, MHC complex, NFAT, NF-κB, PLC-γ, iC3b, C3dg, C3d, or Zap70.

8. The system of any one of claims 1 to 7, wherein said CAR further comprises a co-stimulatory domain, optionally wherein the co-stimulatory domain comprises a signaling domain of a MHC class I molecule, a TNF receptor protein, an immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, a Toll ligand receptor, or a molecule selected from the group consisting of 2B4/CD244/SLAMF4, 4-1BB/TNFSF9/CD137, B7-1/CD80, B7-2/CD86, B7-H1/PD-L1, B7-H2, B7-H3, B7-H4, B7-H6, B7-H7, BAFF-R/TNFRSF13C, BAFF/BLyS/TNFSF13B, BLAME/SLAMF8, BTLA/CD272, CD100 (SEMA4D), CD103, CD11a, CD11b, CD11c, CD11d, CD150, CD160 (BY55), CD18, CD19, CD2, CD200, CD229/SLAMF3, CD27 Ligand/TNFSF7, CD27/TNFRSF7, CD28, CD29, CD2F-10/SLAMF9, CD30 Ligand/TNFSF8, CD30/TNFRSF8, CD300a/LMIR1, CD4, CD40 Ligand/TNFSF5, CD40/TNFRSF5, CD48/SLAMF2, CD49a, CD49D, CD49f, CD53, CD58/LFA-3, CD69, CD7, CD8 α, CD8 β, CD82/Kai-1, CD84/SLAMF5, CD90/Thy1, CD96, CDS, CEACAM1, CRACC/SLAMF7, CRTAM, CTLA-4, DAP12, Dectin-1/CLEC7A, DNAM1 (CD226), DPPIV/CD26, DR3/TNFRSF25, EphB6, GADS, Gi24/VISTA/B7-H5, GITR Ligand/TNFSF18, GITR/TNFRSF18, HLA Class I, HLA-DR, HVEM/TNFRSF14, IA4, ICAM-1, ICOS/CD278, Ikaros, IL2R β, IL2R γ, IL7R α, Integrin α4/CD49d, Integrin α4β1, Integrin α4β7/LPAM-1, IPO-3, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB1, ITGB2, ITGB7, KIRDS2, LAG-3, LAT, LIGHT/TNFSF14, LTBR, Ly108, Ly9 (CD229), lymphocyte function associated antigen-1 (LFA-1), Lymphotoxin-α/TNF-β, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), NTB-A/SLAMF6, OX40 Ligand/TNFSF4, OX40/TNFRSF4, PAG/Cbp, PD-1, PDCD6, PD-L2/B7-DC, PSGL1, RELT/TNFRSF19L, SELPLG (CD162), SLAM (SLAMF1), SLAM/CD150, SLAMF4 (CD244), SLAMF6 (NTB-A), SLAMF7, SLP-76, TACI/TNFRSF13B, TCL1A, TCL1B, TIM-1/KIM-1/HAVCR, TIM-4, TL1A/TNFSF15, TNF RII/TNFRSF1B, TNF-α, TRANCE/RANKL, TSLP, TSLP R, VLA1, and VLA-6.

9. The system of any one of claims 1 to 8, wherein said antigen binding domain comprises a Fab, a Fab', a $F(ab')_2$, an Fv, a single-chain Fv (scFv), minibody, a diabody, a single-domain antibody, a light chain variable domain (VL), or a variable domain (V_HH) of camelid antibody.

10. The system of any one of claims 1 to 9, wherein at least one epitope is present on an tumor associated antigen, a tyrosine kinase receptor, a serine kinase receptor, a G-protein coupled receptor, an immune checkpoint receptor or immune checkpoint receptor ligand, a cytokine, a cytokine receptor, or an antigen presented by a major histocompatibility complex (MHC).

11. The system of claim 10, wherein the tumor-associated antigen is selected from the group consisting of: 707-AP, a biotinylated molecule, a-Actinin-4, abl-bcr alb-b3 (b2a2), abl-bcr alb-b4 (b3a2), adipophilin, AFP, AIM-2, Annexin II, ART-4, BAGE, BCMA, b-Catenin, bcr-abl, bcr-abl p190 (e1a2), bcr-abl p210 (b2a2), bcr-abl p210 (b3a2), BING-4, CA-125, CAG-3, CAIX, CAMEL, Caspase-8, CD171, CD19, CD20, CD22, CD4, CD23, CD24, CD30, CD33, CD38, CD44v7/8, CD70, CD123, CD133, CDC27, CDK-4, CEA, CLCA2, CLL-1, CTAG1B, Cyp-B, DAM-10, DAM-6, DEK-CAN, DLL3, EGFR, EGFRvIII, EGP-2, EGP-40, ELF2, Ep-CAM, EphA2, EphA3, erb-B2, erb-B3, erb-B4, ES-ESO-1a, ETV6/AML, FAP, FBP, fetal acetylcholine receptor, FGF-5, FN, FR-α, G250, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7B, GAGE-8, GD2, GD3, GnT-V, Gp100, gp75, GPC3, GPC-2, Her-2, HLA-A*0201-R170I, HMW-MAA, HSP70-2 M, HST-2 (FGF6), HST-2/neu, hTERT, iCE, IL-11Rα, IL-13Rα2, KDR, KIAA0205, K-RAS, L1-cell adhesion molecule, LAGE-1, LDLR/FUT, Lewis Y, L1-CAM, MAGE-1, MAGE-10, MAGE-12, MAGE-2, MAGE-3, MAGE-4, MAGE-6, MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A6, MAGE-B1, MAGE-B2, Malic enzyme, Mammaglobin-A, MART-1/Melan-A, MART-2, MC1R, M-CSF, mesothelin, MUC1, MUC16, MUC2, MUM-1, MUM-2, MUM-3, Myosin, NA88-A, Neo-PAP, NKG2D, NPM/ALK, N-RAS, NY-ESO-1, OA1, OGT, oncofetal antigen (h5T4), OS-9, P polypeptide, P15, P53, PRAME, PSA, PSCA, PSMA, PTPRK, RAGE, ROR1, RU1, RU2, SART-1, SART-2, SART-3, SOX10, SSX-2, Survivin, Survivin-2B, SYT/SSX, TAG-72, TEL/AML1, TGFαRII, TGFβRII, TP1, TRAG-3, TRG, TRP-1, TRP-2, TRP-2/INT2, TRP-2-6b, Tyrosinase, VEGF-R2, WT1, α-folate receptor, and κ-light chain,

wherein the immune checkpoint receptor or immune checkpoint receptor ligand is PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG3, TIGIT, BLTA, CD47 or CD40,

wherein the cytokine or cytokine receptor is CCR2b, CXCR2 (CXCL1 receptor), CCR4 (CCL17 receptor), Gro-a, IL-2, IL-7, IL-15, IL-21, IL-12, Heparanase, CD137L, LEM, Bcl-2, CCL17, CCL19 or CCL2,

wherein the MHC is HLA class 1 or HLA class 2.

12. The system of any one of claims 1 to 11, wherein said first antigen binding domain, said second antigen binding domain, said one or more additional antigen binding domains in said TCR and/or said one or more additional antigen binding domains in said CAR each comprises the formula: A-X-B-Y-C-Z-D,

A comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 47-56 ;

B comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 57-66 ;

C comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 67-76 ;

D comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 77-86 ;

X comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 87-96 ;

Y comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 97-106 ; and

Z comprises an amino acid sequence having at least 80% or at least 90% identity to any one selected from the group consisting of SEQ ID NOs : 107-116.

13. The system of any one of claims 1 to 12, wherein said first antigen binding domain, said second antigen binding domain, said one or more additional antigen binding domains in said TCR and/or said one or more additional antigen binding domains in said CAR each comprises the amino acid sequence of any one of SEQ ID NOs: 3 to 23, and 38 to 46.

14. An isolated host cell expressing the system of any one of claims 1 to 13.

15. The host cell of claim 14, wherein the host cell is an immune cell selected from the group consisting of a T cell, a natural killer (NK) cell, an effector T cell, a memory T cell, a cytotoxic T cell, a NKT cell, a T helper cell, and a KHYG-1 cell, preferably wherein the immune cell is a α/β T cell and/or γ/δ T cell.

16. A population of immune cells, individual immune cells expressing the system of any one of claims 1 to 13, wherein said population of immune cells is characterized in that: upon exposing said population of immune cells to a target cell population in a subject, the population

of immune cells induces death of at least 5% of the target cells within about 2 days, optionally wherein population of immune cells comprises at most about 10^{11} cells.

17. A composition comprising an effective amount of the host cell of claim 14 or 15, the population of immune cells of claim 16, or one or more polynucleotides that encodes the system of any one of claims 1 to 13.

18. A method of inducing activity of an immune cell and/or a target cell, comprising:

(a) expressing the system of any one of claims 1 to 13 in an immune cell; and

(b) contacting a target cell with the immune cell under conditions that induce said activity of the immune cell and/or the target cell.

19. Use of an effective amount of the host cell of claim 14 or 15, or the population of immune cells of claim 16 in the manufacture of a medicament for treating a cancer of a subject in need thereof.

20. The use of claim 19, wherein said cancer is selected from bladder cancer, bone cancer, brain cancer, breast cancer, cervical cancer, colon cancer, esophageal cancer, gastric cancer, glioma, head and neck cancer, kidney cancer, leukemia, acute myeloid leukemia (AML), multiple myeloma, liver cancer, lung cancer, lymphoma, melanoma, mesothelioma, medulloblastoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, testicular cancer, tracheal cancer, and vulvar cancer.