

ENGINEERED CELLS AND USES THEREOF

BACKGROUND

[0001] Effector cell activities often involve binding of a ligand to a receptor bound on a membrane of the effector cell. Such interaction between the ligand and the membrane-bound receptor, often via its extracellular binding domain, may result in a conformational and/or chemical modification to the receptor itself, which in turn can yield an array of intracellular signaling that cumulates in effector cell activation. Attempts to harness this interaction for the development of immune cell therapies against cancer cells have shown promising efficacy against hematologic malignancies. However, there are a number of drawbacks including off-target toxicity and undesired cytokine release syndrome in treated subjects. This and other side effects can further exuberate into inflammatory responses, organ failure, and in extreme cases, death.

SUMMARY

[0002] In view of the foregoing, there exists a considerable need for alternative compositions and methods to carry out immunotherapy. The compositions and methods of the present disclosure address this need, and provide additional advantages as well. The various aspects of the disclosure provide systems, compositions, and methods for inducing activity of immune cells.

[0003] In one example, the present disclosure provides a system for inducing activity of an immune 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 devoid of a signaling domain of CD3 zeta (ζ); and (b) a modified T cell receptor (TCR) complex comprising a second antigen binding domain that 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. In one aspect, the present disclosure provides a system for inducing activity of an immune 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 devoid of a signaling domain of CD3 zeta; and (b) a modified T cell receptor (TCR) complex comprising a second antigen binding domain that 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.

[0004] In some examples, 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.

[0005] In some examples, two or more antigen binding domains are linked to, optionally in tandem, (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), (iii) a CD3 zeta chain, and wherein binding of the two or more antigen binding domains to their respective epitopes activates an immune cell activity of an immune cell expressing the system.

[0006] In some examples, said immune cell activity is selected from the group consisting of: clonal expansion of the immune cell; cytokine release by the immune cell; cytotoxicity of the immune cell; proliferation of the immune cell; differentiation, dedifferentiation or transdifferentiation of the immune cell; movement and/or trafficking of the immune cell; exhaustion and/or reactivation of the immune cell; and release of other intercellular molecules, metabolites, chemical compounds, or combinations thereof by the immune cell.

[0007] In some examples, the first epitope and the second epitope are the same. In some examples, the first epitope and the second epitope are different.

[0008] In some examples, the first antigen binding domain and the second antigen binding domain comprise the same amino acid sequence. In some examples, the first antigen binding domain and the second antigen binding domain comprise different amino acid sequence.

[0009] In some examples, the second antigen binding domain comprises a heterologous sequence exhibiting binding to the second epitope.

[0010] In some examples, the modified TCR comprises a third antigen binding domain linked to: (i) said second antigen binding domain, (ii) at least one TCR chain selected from the alpha chain, the beta chain, the gamma chain and the delta chain of a T cell receptor, (iii) the epsilon chain, the delta chain, and/or the gamma chain of cluster of differentiation 3 (CD3), or (iv) the CD3 zeta chain.

[0011] In some examples, said intracellular signaling domain of said CAR is devoid of an immunoreceptor tyrosine-based activation motif (ITAM).

[0012] In some examples, said CAR further comprises a co-stimulatory domain. In some examples, said 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, or a Toll ligand receptor.

[0013] In some examples, said co-stimulatory domain comprises a signaling domain of a molecule selected from: 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 α 4/CD49d, Integrin α 4 β 1, Integrin α 4 β 7/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.

[0014] In some examples, said first antigen binding domain and/or said second 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.

[0015] In some examples, said first antigen binding domain and/or said second antigen binding domain comprises a receptor. In some examples, said first antigen binding domain and/or said second antigen binding domain comprises a ligand for a receptor. In some examples, said first epitope and said second epitope are present on different antigens. In some examples, said first epitope and said second epitope are present on a common antigen. In some examples, said first epitope and/or said second epitope are present on one or more cell surface antigens. In some examples, said one or more cell surface antigens are tumor associated antigens, tyrosine kinase receptors, serine kinase receptors, and G-protein coupled receptors. In some examples, said first epitope and/or said second epitope is present on a universal antigen. In some examples, said first epitope and/or said second epitope is present on a neoantigen. In some examples, said first epitope and/or said second epitope is a neoepitope.

[0016] In some examples, said first epitope and/or said second epitope is present on a tumor-associated antigen. In some examples, 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, 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-11R α , IL-13R α 2, 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, TGF α RII, TGF β RII, 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.

[0017] In some examples, said first epitope and/or said second epitope is present on an immune checkpoint receptor or immune checkpoint receptor ligand. In some examples, said immune checkpoint receptor or immune checkpoint receptor ligand is PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, TIGIT, LAG3, BLTA, CD47 or CD40.

[0018] In some examples, said first epitope and/or said second epitope is present on a cytokine or a cytokine receptor. In some examples, said cytokine or cytokine receptor is CCR2b, CXCR2 (CXCL1 receptor), CCR4 (CCL17 receptor), Gro- α , IL-2, IL-7, IL-15, IL-21, IL-12, Heparanase, CD137L, LEM, Bcl-2, CCL17, CCL19 or CCL2.

[0019] In some examples, said first epitope and/or said second epitope is present on an antigen presented by a major histocompatibility complex (MHC). In some examples, the MHC is HLA class 1. In some examples, the MHC is HLA class 2.

[0020] In another aspect, the present disclosure provides an isolated host cell expressing the above system of the present disclosure. In some examples, the host cell is an immune cell. In some examples, the immune cell is a lymphocyte. In some examples, the lymphocyte is a T cell. In some examples, the T cell is a CD8 $^{+}$ T cell. In some examples, the T cell is a CD4 $^{+}$ T cell. In some examples, the lymphocyte is $\gamma\delta$ T cell. In some examples, the $\gamma\delta$ T cell is V γ 9 δ 2 T cell. In some examples, the $\gamma\delta$ T cell is V δ 1 T cell. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR, V γ 10/V δ 2 TCR, and/or V γ 2/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 10/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 2/V δ 2 TCR. In some examples, the lymphocyte is a natural killer (NK) cell, a KHYG such as KHYG-1 cell or a derivative thereof. In some examples, the host cell exhibits specific binding to two antigens simultaneously present in a target cell.

[0021] In another aspect, the present disclosure provides an antigen-specific immune cell comprising above system of the present disclosure. In some examples, the antigen binding domain linked to the CAR primarily mediates interaction between the immune cell and a target cell, and the antigen binding domain linked to the TCR complex primarily mediates an immune cell activity when the interaction between the immune cell and the target cell takes place.

[0022] In some examples, said immune cell activity is selected from the group consisting of: clonal expansion of the immune cell; cytokine release by the immune cell; cytotoxicity of the immune cell; proliferation of the immune cell; differentiation, dedifferentiation or transdifferentiation of the immune cell; movement and/or trafficking of the immune cell; exhaustion and/or reactivation of the immune cell; and release of other intercellular molecules, metabolites, chemical compounds, or combinations thereof by the immune cell. In some examples, said immune cell is a lymphocyte. In some examples, said lymphocyte is a T cell. In some examples, said T cell is a CD4+ T cell or a CD8+ T cell. In some examples, the lymphocyte is $\gamma\delta$ T cell. In some examples, the $\gamma\delta$ T cell is V γ 9 δ 2 T cell. In some examples, the $\gamma\delta$ T cell is V δ 1 T cell. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR, V γ 10/V δ 2 TCR, and/or V γ 2/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 10/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 2/V δ 2 TCR.

[0023] In some examples, the modified TCR complex comprises two or more antigen binding domains comprising heterologous sequences that are linked to, optionally in tandem, (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), (iii) a CD3 zeta chain. In some examples, said lymphocyte is a natural killer (NK) cell, a KHYG cell such as KHYG-1 cell or a derivative thereof.

[0024] In another example, the present disclosure provides a population of immune cells, individual immune cells expressing above system of the present disclosure. In some examples, said population of immune cells comprises at most about 10^{11} cells. In some examples, said immune cells comprise lymphocytes. In some examples, the lymphocytes are T cells. In some examples, the T cells are CD4+ T cells. In some examples, the T cells are CD8+ T cells. In some examples, the lymphocyte is $\gamma\delta$ T cell. In some examples, the $\gamma\delta$ T cell is V γ 9 δ 2 T cell. In some examples, the $\gamma\delta$ T cell is V δ 1 T cell. In some examples, the lymphocytes are natural killer (NK) cells, a KHYG cell such as KHYG-1 cell or a derivative thereof.

[0025] In another aspect, the present disclosure provides a method of inducing activity of an immune cell, comprising: (a) expressing above system of the present disclosure 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. In some examples, 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 cytotoxicity of the immune cell.

[0026] In some examples, two or more antigen binding domains comprise heterologous sequences that are linked to, optionally in tandem, (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), (iii) a CD3 zeta chain.

[0027] In some examples, the target cell is a cancer cell. In some examples, the target cell is a hematopoietic cell. In some examples, the target cell is a solid tumor cell. In some examples, the target cell is a cell identified in one or more of heart, blood vessels, salivary gland, esophagus, stomach, liver, gallbladder, pancreas, intestine, colon, rectum, anus, endocrine gland, adrenal gland, kidney, ureter, bladder, lymph node, tonsils, adenoid, thymus, spleen, skin, muscle, brain, spinal cord, nerve, ovary, fallopian tube, uterus, vagina, mammary gland, testes, prostate, penis, pharynx, larynx, trachea, bronchi, lung, diaphragm, cartilage, ligaments, and tendon.

[0028] In some examples, said immune cell is a lymphocyte. In some examples, the lymphocyte is a T cell. In some examples, the T cell is a CD4+ T cell or CD8+ T cell. In some examples, the lymphocyte is $\gamma\delta$ T cell. In some examples, the $\gamma\delta$ T cell is V γ 9 δ 2 T cell. In some examples, the $\gamma\delta$ T cell is V δ 1 T cell. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR, V γ 10/V δ 2 TCR, and/or V γ 2/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 9 δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 10/V δ 2 TCR. In some examples, the lymphocyte is the $\gamma\delta$ T cell comprising V γ 2/V δ 2 TCR.

[0029] In some examples, binding of the two or more antigen binding domains to their respective epitopes activates cytotoxicity of an immune cell expressing the system and increases persistence of said cytotoxicity, as compared to binding of the first antigen binding domain to the first epitope alone, when said system is expressed in an immune cell in a subject. In some examples, the lymphocyte is a natural killer (NK) cell, a KHYG cell such as KHYG-1 cell or a derivative thereof.

[0030] In another aspect, the present disclosure provides a composition comprising one or more polynucleotides that encodes: (a) a chimeric antigen receptor (CAR) comprising a first antigen binding domain having binding specificity for a first epitope, a transmembrane domain, and an intracellular signaling domain that is devoid of signaling domain of CD3 zeta; 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.

[0031] In some examples, the second antigen binding domain comprises a heterologous sequence exhibiting binding to the second epitope. In some examples, the one or more polynucleotides comprise a promoter operably linked thereto.

[0032] In another aspect, the present disclosure provides a method of producing a modified immune cell, comprising genetically modifying the immune cell by expressing the above composition of the present disclosure in said immune cell, thereby producing said modified immune cell.

[0033] In another example, the present disclosure provides a method of treating a cancer of a subject, said subject comprising a target cell expressing one or more antigens, the method comprising: (a) administering to the subject an antigen-specific immune cell comprising above system of the present disclosure, wherein the expressed one or more antigens are recognized by the first and/or second antigen binding domain, and (b) contacting the target cell with the antigen-specific immune cell via the first and/or second antigen binding domains under conditions that induces an immune cell activity of the immune cell against the target cell, thereby inducing death of the target cell of the cancer.

[0034] In some examples, the method further comprising genetically modifying an immune cell to yield said antigen-specific immune cell. In some examples, 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.

[0034a] In one aspect, the present disclosure provides a pharmaceutical composition comprising the host cell disclosed herein or the immune cell disclosed.

[0034b] In another aspect, the present disclosure provides use of an effective amount of immune cell comprising a system disclosed herein, the isolated host cell disclosed herein, the antigen-specific immune cell disclosed herein, the composition disclosed herein, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a cancer in an individual, optionally, 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.

INCORPORATION BY REFERENCE

[0035] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by

CLAIMS

WHAT IS CLAIMED IS:

1. A system for inducing activity of an immune 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 devoid of a signaling domain of CD3 zeta; and
 - (b) a modified T cell receptor (TCR) complex comprising a second antigen binding domain that 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.
2. The system of claim 1, 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.
3. The system of claim 1, wherein two or more antigen binding domains are linked to, optionally in tandem, (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), (iii) a CD3 zeta chain, and wherein binding of the two or more antigen binding domains to their respective epitopes activates an immune cell activity of an immune cell expressing the system.
4. The system of any one of claims 1 to 3, wherein
 - (i) the first epitope and the second epitope are the same;
 - (ii) the first epitope and the second epitope are different;
 - (iii) said first epitope and said second epitope are present on different antigens;
 - (iv) said first epitope and said second epitope are present on a common antigen;
 - (v) said first epitope and/or said second epitope is present on a universal antigen;
 - (vi) said first epitope and/or said second epitope is present on a neoantigen; or
 - (vii) said first epitope and/or said second epitope is a neoepitope.
5. The system of any one of claims 1 to 4, wherein
 - (i) the first antigen binding domain and the second antigen binding domain comprise the same amino acid sequence;

- (ii) the first antigen binding domain and the second antigen binding domain comprise different amino acid sequences;
- (iii) the second antigen binding domain comprises a heterologous sequence exhibiting binding to the second epitope; or
- (iv) said first antigen binding domain and/or said second antigen binding domain comprises a receptor or a ligand for a receptor.

6. The system of any one of claims 1 to 5, wherein said modified TCR comprises a third antigen binding domain linked to:

- (i) said second antigen binding domain,
- (ii) at least one TCR chain selected from the alpha chain, the beta chain, the gamma chain, and the delta chain of a T cell receptor,
- (iii) the epsilon chain, the delta chain, and/or the gamma chain of cluster of differentiation 3 (CD3), or
- (iv) the CD3 zeta chain.

7. The system of any one of claims 1 to 6, wherein said intracellular signaling domain of said CAR is devoid of an immunoreceptor tyrosine-based activation motif (ITAM).

8. The system of any one of claims 1 to 7, wherein said CAR further comprises a co-stimulatory domain, optionally, said 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, or a Toll ligand receptor.

9. The system of any one of claims 1 to 8, wherein said first antigen binding domain and/or said second 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 said first epitope and/or said second epitope are present on one or more cell surface antigens, optionally, wherein said one or more cell surface antigens are tumor associated antigens, tyrosine kinase receptors, serine kinase receptors, and G-protein coupled receptors.

11. The system of any one of claims 1 to 10, wherein

- (i) said first epitope and/or said second epitope is present on a tumor-associated antigen, optionally, 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, 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-11R α , IL-13R α 2, 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, TGF α RII, TGF β RII, 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;

(ii) said first epitope and/or said second epitope is present on an immune checkpoint receptor or immune checkpoint receptor ligand,

optionally, wherein said 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;

(iii) said first epitope and/or said second epitope is present on a cytokine or a cytokine receptor,

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

(iv) said first epitope and/or said second epitope is present on an antigen presented by a major histocompatibility complex (MHC),

optionally, the MHC is HLA class 1 or HLA class 2.

12. An isolated host cell expressing the system of any one of claims 1 to 11.

13. The host cell of claim 12, wherein the host cell is an immune cell, optionally, wherein the immune cell is a lymphocyte.

14. The host cell of claim 13, wherein the lymphocyte is a T cell or a natural killer (NK) cell, optionally, wherein the T cell is a CD8⁺ T cell, a CD4⁺ T cell, a $\gamma\delta$ T cell or a $\alpha\beta$ T cell.

15. An antigen-specific immune cell comprising a system of any one of claims 1 to 11.
16. A method of inducing activity of an immune cell, comprising:
- (a) expressing a system of any one of claims 1 to 11 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.
17. A composition comprising one or more polynucleotides that encodes:
- (a) a chimeric antigen receptor (CAR) comprising a first antigen binding domain having binding specificity for a first epitope, a transmembrane domain, and an intracellular signaling domain that is devoid of signaling domain of CD3 zeta; 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.
18. A method of producing a modified immune cell, comprising:
genetically modifying the immune cell by expressing the composition of claim 17 in said immune cell, thereby producing said modified immune cell.
19. A pharmaceutical composition comprising the host cell of any one of claims 12 to 14 or the immune cell of claim 15.
20. Use of an effective amount of immune cell comprising a system of any one of claims 1 to 11, the isolated host cell of any one of claims 12 to 14, the antigen-specific immune cell of claim 15, the composition of claim 17, or the pharmaceutical composition of claim 19 in the manufacture of a medicament for treating a cancer in an individual, optionally, 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.