

What is claimed is:

1. A recombinant T cell receptor (TCR) comprising an antigen binding chain that comprises an extracellular antigen-binding domain and a constant domain, wherein the recombinant TCR binds to an antigen in an HLA-independent manner, wherein the
5 constant domain comprises a native or modified TRAC peptide and/or a native or modified TRBC peptide.
2. The recombinant TCR of claim 1, wherein the recombinant TCR is expressed from an expression cassette placed in an endogenous *TRAC* locus and/or a *TRBC* locus of an immunoresponsive cell.
- 10 3. The recombinant TCR of claim 2, wherein the placement of the recombinant TCR expression cassette disrupts or abolishes the endogenous expression of a TCR comprising a native TCR α chain and/or a native TCR β chain in the immunoresponsive cell.
4. The recombinant TCR of claim 2, wherein the placement of the recombinant TCR expression cassette prevents or eliminates mispairing between the recombinant TCR and
15 a native TCR α chain and/or a native TCR β chain in the immunoresponsive cell.
5. The recombinant TCR of any one of claims 1-4, wherein the constant domain is capable of forming a homodimer or a heterodimer with another constant domain.
6. The recombinant TCR of any one of claims 1-5, wherein the antigen binding chain is capable of associating with a CD3 ζ polypeptide.
- 20 7. The recombinant TCR of claim 6, wherein the antigen binding chain, upon binding to an antigen, is capable of activating the CD3 ζ polypeptide associated to the antigen binding chain.
8. The recombinant TCR of claim 7, wherein activation of the CD3 ζ polypeptide is capable of activating an immunoresponsive cell.
- 25 9. The recombinant TCR of claim 6, wherein the CD3 ζ polypeptide is endogenous and integrated in the native CD3 complex.
10. The recombinant TCR of claim 6, wherein the CD3 ζ polypeptide is exogenous and optionally integrated with a co-stimulatory molecule selected from the group

consisting of a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide and any combination thereof.

11. The recombinant TCR of any one of claims 1-10, wherein the antigen binding chain further comprises a co-stimulatory region, wherein the recombinant TCR, upon
5 binding to an antigen, is capable of stimulating an immunoresponsive cell.
12. The recombinant TCR of claim 11, wherein the co-stimulatory region comprises a co-stimulatory molecule selected from the group consisting of a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide and any combination thereof.
- 10 13. The recombinant TCR of claim 12, wherein the co-stimulatory region comprises a CD28 polypeptide.
14. The recombinant TCR of any one of claims 1-13, wherein the recombinant TCR is capable of integrating with a CD3 complex and providing HLA-independent antigen recognition.
- 15 15. The recombinant TCR of claim 14, wherein the CD3 complex is endogenous.
16. The recombinant TCR of claim 15, wherein the recombinant TCR replaces an endogenous TCR in a CD3/TCR complex.
17. The recombinant TCR of any one of claims 1-16, wherein the extracellular antigen-binding domain is capable of dimerizing with another extracellular antigen-
20 binding domain.
18. The recombinant TCR of any one of claims 1-17, wherein the extracellular antigen-binding domain comprises a ligand for a cell-surface receptor, a receptor for a cell surface ligand, an antigen binding portion of an antibody or a fragment thereof or an antigen binding portion of a TCR.
- 25 19. The recombinant TCR of any one of claims 1-18, wherein the extracellular antigen-binding domain comprises one or two immunoglobulin variable region(s).
20. The recombinant TCR of claim 18, wherein the extracellular antigen-binding domain comprises a heavy chain variable region (V_H) of an antibody.

21. The recombinant TCR of claim 18, wherein the extracellular antigen-binding domain comprises a light chain variable region (V_L) of an antibody.
22. The recombinant TCR of claim 18, wherein the extracellular antigen-binding domain is capable of dimerizing with another extracellular antigen-binding domain.
- 5 23. The recombinant TCR of claim 20, wherein the extracellular antigen-binding domain comprises a V_H of an antibody, wherein the V_H is capable of dimerizing with another extracellular antigen-binding domain comprising a V_L of the antibody and form a fragment variable (F_v).
- 10 24. The recombinant TCR of claim 21, wherein the extracellular antigen-binding domain comprises a V_L of an antibody, wherein the V_L is capable of dimerizing with another extracellular antigen-binding domain comprising a V_H of the antibody and form a fragment variable (F_v).
25. The recombinant TCR of any one of claims 1-24, wherein the recombinant TCR binds to a tumor antigen.
- 15 26. The recombinant TCR of claim 25, wherein the tumor antigen is selected from the group consisting of CD19, MUC16, MUC1, CAIX, CEA, CD8, CD7, CD10, CD20, CD22, CD30, CLL1, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD133, CD138, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-a, GD2, GD3, HER-2, hTERT, IL-13R-a2, K-light chain, KDR, LeY, L1 cell
20 adhesion molecule, MAGE-A1, Mesothelin, ERBB2, MAGEA3, p53, MART1, GP100, Proteinase3 (PR1), Tyrosinase, Survivin, hTERT, EphA2, NKG2D ligands, NY-ES0-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, WT-1, BCMA, CD123, CD44V6, NKCS1, EGF1R, EGFR-VIII, and CD99, CD70, ADGRE2, CCR1, LILRB2, LILRB4, PRAME, and ERBB.
- 25 27. The recombinant TCR of claim 25 or 26, wherein the tumor antigen is CD19.
28. The recombinant TCR of any one of claims 1-27, wherein the recombinant TCR exhibits greater antigen sensitivity than a CAR targeting the same antigen.

29. The recombinant TCR of any one of claims 1-28, wherein the recombinant TCR is capable of inducing an immune response when binds to an antigen that has a low density on the surface of a tumor cell.
30. The recombinant TCR of any one of claims 1-28, wherein the antigen that has a
5 low density on the cell surface has a density of less than about 10,000 molecules per cell.
31. An immunoresponsive cell comprising a recombinant TCR of any one of claims 1-30.
32. The immunoresponsive cell of claim 31, wherein the expression cassette of at
10 least one antigen binding chain of the recombinant TCR is placed at an endogenous gene locus of the immunoresponsive cell.
33. The immunoresponsive cell of claim 32, wherein the expression cassettes of two antigen binding chains of the recombinant TCR are placed at an endogenous gene locus of the immunoresponsive cell, wherein the two antigen binding chains are capable of dimerization.
- 15 34. The immunoresponsive cell of any one of claims 31-33, wherein the endogenous gene locus is a *CD3 δ* locus, a *CD3 ϵ* locus, a *CD247* locus, a *B2M* locus, a *TRAC* locus, a *TRBC* locus, a *TRDC* locus and/or a *TRGC* locus.
35. The immunoresponsive cell of claim 34, wherein the endogenous gene locus is a *TRAC* locus and/or a *TRBC* locus.
- 20 36. The immunoresponsive cell of claim 35, wherein the placement of the expression cassette of the recombinant TCR disrupts or abolishes the endogenous expression of a TCR comprising a native TCR α chain and/or a native TCR β chain in the immunoresponsive cell, whereby preventing or eliminating mispairing between the recombinant TCR and a native TCR α chain and/or a native TCR β chain in the
25 immunoresponsive cell.
37. The immunoresponsive cell of any one of claims 32-36, wherein the endogenous gene locus comprises a modified transcription terminator region.

38. The immunoresponsive cell of claim 37, wherein the modified transcription terminator region comprises a genomic element selected from the group consisting of a TK transcription terminator, a GCSF transcription terminator, a TCRA transcription terminator, an HBB transcription terminator, a bovine growth hormone transcription terminator, an SV40 transcription terminator and a P2A element.
39. The immunoresponsive cell of any one of claims 32-38, wherein when one endogenous T cell receptor locus in a cell is modified to express the at least one antigen binding chain of the recombinant TCR, one or more other endogenous T cell receptor locus in the cell is modified to eliminate the expression of an endogenous TCR chain.
40. The immunoresponsive cell of claim 39, wherein the one or more other endogenous T cell receptor locus are further modified to express a gene of interest.
41. The immunoresponsive cell of claim 40, wherein the gene of interest is an anti-tumor cytokine, a co-stimulatory molecule ligand, a tracking gene or a suicide gene.
42. The immunoresponsive cell of any one of claims 31-41, wherein the cell is selected from the group consisting of a T cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a Natural Killer T (NKT) cell, a human embryonic stem cell, and a pluripotent stem cell from which lymphoid cells may be differentiated.
43. The immunoresponsive cell of any one of claims 31-42, wherein the immunoresponsive cell is autologous.
44. The immunoresponsive cell of any one of claims 31-43, further comprising at least one exogenous co-stimulatory ligand.
45. The immunoresponsive cell of claim 44, wherein the exogenous co-stimulatory ligand is selected from the group consisting of CD80, CD86, 41BBL, CD275, CD40L, OX40L and any combination thereof.
46. The immunoresponsive cell of claim 44 or 45, wherein the cell further comprises or consists of one exogenous co-stimulatory ligand.
47. The immunoresponsive cell of claim 46, wherein the one exogenous co-stimulatory ligand is CD80 or 4-1BBL.

48. The immunoresponsive cell of claim 44 or 45, wherein the cell further comprises or consists of two exogenous co-stimulatory ligands.
49. The immunoresponsive cell of claim 48, wherein the two exogenous co-stimulatory ligands are CD80 and 4-1BBL.
50. The immunoresponsive cell of any one of claims 31-49, further comprising at least one chimeric costimulatory receptor (CCR).
51. The immunoresponsive cell of claim 50, wherein the CCR comprises a co-stimulatory molecule selected from the group consisting of a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide and any combination thereof.
52. A pharmaceutical composition comprising an effective amount of an immunoresponsive cell of any one of claims 31-47 and a pharmaceutically acceptable excipient.
53. The pharmaceutical composition of claim 52, which is for treating a neoplasm.
54. A method of reducing tumor burden in a subject, the method comprising administering to the subject an effective amount of the immunoresponsive cells of any one of claims 31-51 or the pharmaceutical composition of claim 52 or 53.
55. A method of treating or preventing a neoplasm, the method comprising administering to the subject an effective amount of the immunoresponsive cells of any one of claims 31-51 or the pharmaceutical composition of claim 52 or 53.
56. The method of claim 55, wherein the neoplasm is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia, non-Hodgkin's lymphoma adenocarcinomas.
57. The method of claim 55 or 56, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the recombinant TCR binds to CD19.

58. The method of claim 55 or 56, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the recombinant TCR binds to BCMA, ADGRE2, CCR1, CD22, CD70 or combinations thereof.
- 5 59. The method of any one of claims 55-58, wherein the neoplasm is CD19⁺ ALL.
60. A method for producing an antigen-specific immunoresponsive cell, the method comprising introducing into an immunoresponsive cell a nucleic acid sequence encoding a recombinant TCR according to any one of claims 1-30.
61. The method of claim 60, wherein the nucleic acid sequence is comprised in a
10 vector.
62. The method of claim 60 or 61, wherein the expression cassette of at least one antigen binding chain of the recombinant TCR is placed at an endogenous gene locus of the immunoresponsive cell.
63. The method of claim 62, wherein the expression cassettes of two antigen binding
15 chains of the recombinant TCR are placed at an endogenous gene locus of the immunoresponsive cell, wherein the two antigen binding chains are capable of dimerization.
64. The method of claim 62 or 63, wherein the endogenous gene locus is a *CD3δ* locus, a *CD3ε* locus, a *CD247* locus, a *B2M* locus, a *TRAC* locus, a *TRBC* locus, a *TRDC*
20 locus and/or a *TRGC* locus.
65. The method of claim 64, wherein the endogenous gene locus is a *TRAC* locus and/or a *TRBC* locus.
66. The method of any one of claims 63-65, wherein the placement of the expression cassette of the recombinant TCR disrupts or abolishes the endogenous expression of a
25 TCR comprising a native TCR α chain and/or a native TCR β chain in the immunoresponsive cell, whereby preventing or or eliminating mispairing between the recombinant TCR and a native TCR α chain and/or a native TCR β chain in the immunoresponsive cell.

67. The method of any one of claims 62-66, wherein the endogenous gene locus comprises a modified transcription terminator region.
68. The method of claim 67, wherein the modified transcription terminator region comprises a genomic element selected from the group consisting of a TK transcription terminator, a GCSF transcription terminator, a TCRA transcription terminator, a HBB transcription terminator, a bovine growth hormone transcription terminator, an SV40 transcription terminator and a P2A element.
69. The method of any one of claims 62-68, wherein when one endogenous T cell receptor locus in a cell is modified to express the at least one antigen binding chain of the recombinant TCR, one or more other endogenous T cell receptor locus in the cell is modified to eliminate the expression of an endogenous TCR chain.
70. The method of claim 69, wherein the one or more other endogenous T cell receptor locus are further modified to express a gene of interest.
71. The method of claim 70, wherein the gene of interest is an anti-tumor cytokine, a co-stimulatory molecule ligand, a tracking gene or a suicide gene.
72. A method of lengthening survival of a subject having a neoplasm, the method comprising administering to the subject an effective amount of the immunoresponsive cells of any one of claims 31-51 or the pharmaceutical composition of claim 52 or 53.
73. A nucleotide acid encoding a recombinant TCR of any one of claims 1-30.
74. A nucleic acid composition comprising a recombinant TCR of any one of claims 1-30.
75. The nucleic acid composition of claim 74, wherein the nucleic acid sequences are comprised in a vector.
76. A vector comprising the nucleic acid composition of claim 74 or 75.
77. A kit comprising a recombinant TCR of any one of claims 1-30, an immunoresponsive cell of any one of claims 31-51, a pharmaceutical composition of claim 52 or 53, a nucleic acid composition of claim 74 or 75, or a vector of claim 76.

78. The kit of claim 77, wherein the kit further comprises written instructions for treating and/or preventing a neoplasm, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.
79. The recombinant TCR of any one of claims 1-30 for use in a therapy.
- 5 80. The pharmaceutical composition of claim 51 or 52 for used in a therapy.
81. The immunoresponsive cell of any one of claims 31-51 for used in a therapy.
82. Use of the immunoresponsive cells of any one of claims 31-51 or the pharmaceutical composition of claim 52 or 53 for reducing tumor burden in a subject.
83. Use of the immunoresponsive cells of any one of claims 31-51 or the
10 pharmaceutical composition of claim 52 or 53 for treating or preventing a neoplasm.
84. Use of the immunoresponsive cells of any one of claims 31-51 or the pharmaceutical composition of claim 52 or 53 for lengthening survival of a subject having neoplasm (e.g., cancer).