

Claims:

1. An HA-2 (YIGEVLVSV) peptide-MHC (HLA-A*02) (pMHC) complex binding protein comprising:
 - a) a T cell receptor (TCR) alpha chain variable domain comprising CDR1 having residues 47-53 of SEQ ID NO: 93, CDR2 having residues 71-78 of SEQ ID NO: 93, and CDR3 having residues 112-124 of SEQ ID NO: 93; and
 - b) a TCR beta chain variable domain comprising CDR1 having residues 44-49 of SEQ ID NO: 92, CDR2 having residues 67-71 of SEQ ID NO: 92, and CDR3 having residues 108-126 of SEQ ID NO: 92.
2. The binding protein of claim 1 comprising:
 - a) a TCR alpha chain variable (V_{α}) domain comprising residues 1-135 of SEQ ID NO: 93; and
 - b) a TCR beta chain variable (V_{β}) domain comprising residues 1-136 of SEQ ID NO: 92.
3. The binding protein of claim 1 or 2 comprising:
 - a) a TCR alpha chain variable (V_{α}) domain comprising residues 1-135 of SEQ ID NO: 93; and
 - b) a TCR beta chain sequence comprising i) the sequence of SEQ ID NO: 92 or ii) the sequence of SEQ ID NO: 92, except with the following five substitutions: E153K, S157A, F268I, V271A, and Q274H.
4. The binding protein of claim 1 or 2 comprising:
 - a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and
 - b) a TCR beta chain variable (V_{β}) domain comprising residues 1-136 of SEQ ID NO: 92.
5. The binding protein of claim 1 or 2 comprising:
 - a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and
 - b) a TCR beta chain sequence comprising the sequence of SEQ ID NO: 92.
6. The binding protein of claim 1 or 2 comprising:
 - a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and

b) a TCR beta chain sequence comprising the sequence of SEQ ID NO: 92, except with the following five substitutions: E153K, S157A, F268I, V271A, and Q274H.

7. The binding protein of any one of claims 1-6, wherein the TCR alpha chain or TCR V α domain is encoded by a TRAV38-2DV8 and TRAJ11 gene.

8. The binding protein of any one of claims 1-7, wherein the TCR beta chain or TCR V β domain is encoded by a TRBV30 and TRBJ2-3 gene.

9. The binding protein of any one of claims 1-8, wherein the binding protein is chimeric, humanized, or human.

10. The binding protein of any one of claims 1-9, wherein the binding protein is a TCR, an antigen-binding fragment of a TCR, a single chain TCR (scTCR), a chimeric antigen receptor (CAR), or a fusion protein comprising a TCR and an effector domain

11. The binding protein of claim 10, wherein the binding domain comprises a transmembrane domain and an effector domain that is intracellular.

12. The binding protein of any one of claims 1-11, wherein the TCR alpha chain and the TCR beta chain are covalently linked.

13. The binding protein of claim 12, wherein the TCR alpha chain and the TCR beta chain are covalently linked through a linker peptide.

14. The binding protein of any one of claims 1-13, wherein the TCR alpha chain and/or the TCR beta chain are covalently linked to a moiety.

15. The binding protein of claim 14, wherein the covalently linked moiety comprises an affinity tag or a label.

16. The binding protein of claim 15, wherein the affinity tag is selected from the group consisting of CD34 enrichment tag, Glutathione-S-Transferase (GST), calmodulin

binding protein (CBP), protein C tag, Myc tag, HaloTag, HA tag, Flag tag, His tag, biotin tag, and V5 tag, and/or wherein the label is a fluorescent protein.

17. The binding protein of claim 15 or 16, wherein the covalently linked moiety is selected from the group consisting of an inflammatory agent, cytokine, toxin, cytotoxic molecule, radioactive isotope, and antibody or antigen-binding fragment thereof.

18. The binding protein of any one of claims 1-17, wherein the binding protein binds to the pMHC complex on a cell surface.

19. The binding protein of any one of claims 1-18, wherein the MHC is a MHC multimer.

20. The binding protein of claim 19, wherein the MHC multimer is a tetramer.

21. The binding protein of any one of claims 1-20, wherein the MHC is a MHC class I molecule.

22. The binding protein of any one of claims 1-21, wherein the MHC comprises an MHC alpha chain that is an HLA serotype HLA-A*02.

23. The binding protein of any one of claims 1-22, wherein the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele.

24. The binding protein of claim 23, wherein the HLA allele is HLA-A*0201.

25. The binding protein of any one of claims 1-24, wherein binding of the binding protein to the HA-2 peptide-MHC (pMHC) complex elicits an immune response.

26. The binding protein of claim 25, wherein the immune response is a T cell response.

27. The binding protein of claim 25 or 26, wherein the T cell response is selected from the group consisting of T cell expansion, cytokine release, and cytotoxic killing.

28. The binding protein of any one of claims 1-27, wherein the binding protein is capable of specifically binding to the HA-2 (YIGEVLVSV)peptide-MHC (HLA-A*02) (pMHC) complex with a K_d less than or equal to about 1×10^{-4} M.
29. An isolated nucleic acid molecule that encodes a binding protein of any one of claims 1-28.
30. The isolated nucleic acid of claim 29, wherein the nucleic acid is codon optimized for expression in a host cell.
31. A vector comprising the isolated nucleic acid of claim 29 or 30.
32. The vector of claim 31 comprising the sequence of SEQ ID NO: 106.
33. The vector of claim 31 or 32, wherein the vector is a cloning vector, expression vector, or viral vector.
34. The vector of any one of claims 31-33, wherein the vector further comprises a nucleic acid sequence encoding CD8 α and/or CD8 β .
35. The vector of claim 34, wherein the nucleic acid sequence encoding CD8 α or CD8 β is operably linked to a nucleic acid encoding a tag.
36. The vector of claim 35, wherein the nucleic acid encoding a tag is at the 5' upstream of the nucleic acid sequence encoding CD8 α or CD8 β such that the tag is fused to the N-terminus of CD8 α or CD8 β .
37. The vector of claim 35 or 36, wherein the tag is a CD34 enrichment tag.
38. The vector of any one of claims 31-37, wherein the isolated nucleic acid of claim 29 or 30, and the nucleic acid sequence encoding CD8 α and/or CD8 β are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide.
39. The vector of claim 38, wherein the self-cleaving peptide is P2A, E2A, F2A or T2A.

40. A host cell which comprises the isolated nucleic acid of claim 29 or 30, comprises the vector of any one of claims 31-39, and/or expresses the binding protein of any one of claims 1-28.
41. The host cell of claim 40, wherein the cell is genetically engineered.
42. The host cell of claim 40 or 41, wherein the host cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both.
43. The host cell of any one of claims 40-42, wherein the host cell comprises a knockout of an HLA gene selected from an $\alpha 1$ macroglobulin gene, $\alpha 2$ macroglobulin gene, $\alpha 3$ macroglobulin gene, $\beta 1$ microglobulin gene, $\beta 2$ microglobulin gene, or a combination thereof.
44. The host cell of any one of claims 40-43, wherein the host cell comprises a knockout of a TCR gene selected from a TCR α variable region gene, TCR β variable region gene, TCR constant region gene, or a combination thereof.
45. The host cell of any one of claims 40-44, wherein the host cell expresses CD8 α and/or CD8 β .
46. The host cell of claim 45, wherein the CD8 α and/or CD8 β is fused to a CD34 enrichment tag.
47. The host cell of any one of claims 40-46, wherein the host cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell.
48. The host cell of claim 47, wherein the immune cell is a cytotoxic lymphocyte, cytotoxic lymphocyte precursor cell, cytotoxic lymphocyte progenitor cell, cytotoxic lymphocyte stem cell, CD4⁺ T cell, CD8⁺ T cell, CD4/CD8 double negative T cell, gamma delta ($\gamma\delta$) T cell, natural killer (NK) cell, NK-T cell, dendritic cell, or a combination thereof.
49. The host cell of any one of claims 40-48, wherein the host cell is a naive T cell, central memory T cell, effector memory T cell, or a combination thereof.

50. The host cell of any one of claims 40-49, wherein the host cell is a primary T cell or a cell of a T cell line.
51. The host cell of any one of claims 40-50, wherein the host cell does not express or has a lower surface expression of an endogenous TCR.
52. The host cell of any one of claims 40-51, wherein the host cell is capable of producing a cytokine or a cytotoxic molecule when contacted with a target cell that comprises a peptide-MHC (pMHC) complex comprising an HA-2 peptide epitope in the context of an MHC molecule.
53. The host cell of claim 52, wherein the cytokine is TNF- α , IL-2, and/or IFN- γ .
54. The host cell of claim 52 or 53, wherein the cytotoxic molecule is perforins and/or granzymes.
55. The host cell of claim 54, wherein the cytotoxic molecule is granzyme B.
56. The host cell of any one of claims 52-55, wherein the host cell is capable of producing a higher level of cytokine or a cytotoxic molecule when contacted with a target cell with a heterozygous expression of HA-2.
57. The host cell of claim 56, wherein the host cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule.
58. The host cell of any one of claims 52-57, wherein the host cell is capable of killing a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-2 peptide epitope in the context of an MHC molecule.
59. The host cell of claim 58, wherein the killing is determined by a killing assay.
60. The host cell of claim 58 or 59, wherein the ratio of the host cell and the target cell in the killing assay is from 20:1 to 0.625:1.

61. The host cell of any one of claims 58-60, wherein the target cell is a T2 cell pulsed with 1 µg/mL to 50 pg/mL of HA-2 peptide.
62. The host cell of any one of claims 58-61, wherein the host cell is capable of killing a higher number of target cells when contacted with target cells with a heterozygous expression of HA-2.
63. The host cell of claim 62, wherein the host cell is capable of killing an at least 1.05-fold higher number of target cells.
64. The host cell of any one of claims 58, 59, 62, and 63, wherein the target cell is a DEL, THP-1, or TF-1 cell line.
65. The host cell of any one of claims 52-64, wherein the HA-2 peptide epitope comprises the amino acid sequence YIGEVLVSV.
66. The host cell of any one of claims 52-64, wherein the HA-2 peptide epitope comprises the amino acid sequence YIGEVLVSM.
67. The host cell of any one of claims 52-66, wherein the MHC molecule is a MHC class I molecule.
68. The host cell of any one of claims 52-67, wherein the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02.
69. The host cell of any one of claims 52-68, wherein the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele.
70. The host cell of claim 69, wherein the HLA allele is HLA-A*0201.
71. The host cell of any one of claims 52-70, wherein the target cell is a cell line selected from the group consisting of Del, THP-1, and TF-1 cell lines, is a hematopoietic cancer cell expressing HA-2, or is not NB4.

72. The host cell of claim 71, wherein the cancer cell is of a hematological malignancy selected from the group consisting of a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, and myeloma.

73. The host cell of any one of claims 52-72, wherein the host cell does not express HA-2 antigen, is not recognized by a binding protein of any one of claims 1-28, is not of serotype HLA-A*02, and/or does not express an HLA-A*02 allele.

74. A population of host cells of any one of claims 40-73.

75. A composition comprising: a) a binding protein according to any one of claims 1-28, b) an isolated nucleic acid according to claim 29 or 30, c) a vector according to any one of claims 31-39, d) a host cell according to any one of claims 40-73, and/or e) a population of host cells according to claim 74, and a carrier.

76. A device or kit comprising: a) a binding protein according to any one of claims 1-28, b) an isolated nucleic acid according to claim 29 or 30, c) a vector according to any one of claims 31-39, d) a host cell according to any one of claims 40-73, and/or e) a population of host cells according to claim 74.

77. The device or kit of claim 76, wherein said device or kit further comprises a reagent to detect binding of a), d) and/or e) to a pMHC complex.

78. A method of producing a binding protein according to any one of claims 1-28, wherein the method comprises the steps of: (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding a binding protein according to any one of claims 1-28 under conditions suitable to allow expression of said binding protein; and (ii) recovering the expressed binding protein.

79. A method of producing a host cell expressing a binding protein according to any one of claims 1-28, wherein the method comprises the steps of: (i) introducing a nucleic acid comprising a sequence encoding a binding protein according to any one of claims 1-28 into the

host cell; (ii) culturing the transformed host cell under conditions suitable to allow expression of said binding protein.