

CLAIMS:

What is claimed is:

1. An isolated HA-1 (VLHDDLLEA) peptide-MHC (HLA-A*02) (pMHC) complex binding protein comprising:

a) a T cell receptor (TCR) alpha chain variable domain CDR sequence with at least about 80% identity to a TCR alpha chain CDR sequence selected from the group consisting of TCR alpha chain CDR sequences listed in Table 1; and/or

——— b) a TCR beta chain CDR sequence with at least about 80% identity to a TCR beta chain CDR sequence selected from the group consisting of TCR beta chain CDR sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-1 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about 5×10^{-4} M.

2. A binding protein comprising CDR1 having residues 46-51 of SEQ ID NO: 3, CDR2 having residues 69-75 of SEQ ID NO: 3, and CDR3 having residues 109-123 of SEQ ID NO: 3; and:

——— b) a TCR beta chain variable domain comprising CDR1 having residues 46-50 of SEQ ID NO: 4, CDR2 having residues 68-73 of SEQ ID NO: 4, and CDR3 having residues 111-123 of SEQ ID NO: 4.

2. The binding protein of claim 1 comprising:

a) a TCR alpha chain variable (V_α) domain sequence with at least about 80% identity to a TCR V_α domain sequence selected from the group consisting of TCR V_α domain sequences listed in Table 1; and/or

——— b) a TCR beta chain variable (V_β) domain sequence with at least about 80% identity to a TCR V_β domain sequence selected from the group consisting of TCR V_β domain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-1 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about 5×10^{-4} M.

3. A binding protein comprising:

——— a) a TCR alpha chain sequence with at least about 80% identity to a TCR alpha chain sequence selected from the group consisting of TCR alpha chain sequences listed in Table 1; and/or

~~—— b) a TCR beta chain sequence with at least about 80% identity to a TCR beta chain sequence selected from the group consisting of TCR beta chain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-1 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about 5×10^{-4} M.~~

4. ~~—— A binding protein comprising:~~

~~—— a) a TCR alpha chain CDR sequence selected from the group consisting of TCR alpha chain CDR sequences listed in Table 1; and/or~~

~~—— b) a TCR beta chain CDR sequence selected from the group consisting of TCR beta chain CDR sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-1 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about 5×10^{-4} M.~~

5. ~~—— A binding protein comprising residues 1-134 of SEQ ID NO: 3; and:~~

~~—— a) a TCR alpha chain variable (V_α) domain sequence selected from the group consisting of TCR V_α domain sequences listed in Table 1; and/or~~

~~b) a TCR beta chain variable (V_β) domain sequence selected from the group consisting of TCR V_β domain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-1 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about 5×10^{-4} M.~~

6. ~~—— A binding protein comprising residues 1-132 of SEQ ID NO: 4.:~~

3. The binding protein of claim 2 comprising:

a) a TCR alpha chain comprising the sequence of SEQ ID NO: 3 selected from the group consisting of TCR alpha chain sequences listed in Table 1; and/or

b) a TCR beta chain comprising the sequence sequence selected from the group consisting of TCR beta chain sequences listed in Table 1, wherein the binding protein is capable of SEQ ID NO: 4.

4. An isolated binding to an HA-1 (VLHDDLLEA) immunogenic peptide-MHC (HLA-A*02) (pMHC) complex binding protein comprising:

a) a TCR alpha chain variable domain comprising CDR1 having residues 46-51 of SEQ ID NO: 19, CDR2 having residues 69-75 of SEQ ID NO: 19, and CDR3 having residues 109-121 of SEQ ID NO: 19; and

b) a TCR beta chain variable domain comprising CDR1 having residues 46-50 of SEQ ID NO: 20, CDR2 having residues 68-73 of SEQ ID NO: 20, and CDR3 having residues 110-123 of SEQ ID NO: 20.

5. The ~~, optionally wherein the binding~~ protein of claim 4 comprising: affinity has a K_d less than or equal to about 5×10^{-4} M.

a) a TCR alpha chain variable (V_α) domain comprising residues 1-132 of SEQ ID NO: 19; and

b) a TCR beta chain variable (V_β) domain comprising residues 1-132 of SEQ ID NO: 20.

6. The binding protein of claim 5 comprising:

a) a TCR alpha chain comprising the sequence of SEQ ID NO: 19; and

b) a TCR beta chain comprising the sequence of SEQ ID NO: 20.

7. The binding protein of any one of claims 1-36, wherein 1) the TCR alpha chain CDR, TCR V_α domain, and/or TCR alpha chain is encoded by a TRAV21TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1, and/or 2) the TCR beta chain CDR, TCR V_β domain, and TRAJ40 gene, and 2) the TCR beta chain TCR V_β domain /or TCR beta chain is encoded by a TRBV7-9TRBV, TRBJ, and TRBJ2-3/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1, and/or 3) each CDR of the binding protein has up to five amino acid substitutions, insertions, deletions, or a combination thereof as compared to the cognate reference CDR sequence listed in Table 1.

8. The binding protein of any one of claims 4-6, wherein the TCR alpha chain TCR V_α domain or TCR alpha chain is encoded by a TRAV13-1 and TRAJ40 gene, and 2) the TCR beta chain TCR V_β domain or TCR beta chain is encoded by a TRBV7-9 and TRBJ2-1 gene1-7, wherein the HA-1 immunogenic peptide comprises the amino acid sequence VLHDDLLEA.

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, optionally wherein the binding domain comprises a transmembrane domain and an effector domain that is intracellular.
11. The binding protein of any one of claims 1-10, wherein the TCR alpha chain and the TCR beta chain are covalently linked, optionally wherein the TCR alpha chain and the TCR beta chain are covalently linked through a linker peptide.
12. The binding protein of any one of claims 1-11, wherein the TCR alpha chain and/or the TCR beta chain are covalently linked to a moiety, optionally wherein the covalently linked moiety comprises an affinity tag or a label.
13. The binding protein of claim 12, 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.
14. The binding protein of any one of claims 1-13, wherein the covalently linked moiety is selected from the group consisting of an inflammatory agent, cytokine, toxin, cytotoxic molecule, radioactive isotope, or antibody or antigen-binding fragment thereof.
15. The binding protein of any one of claims 1-14, wherein the binding protein binds to the pMHC complex on a cell surface.
16. The binding protein of any one of claims 1-15, wherein the MHC is a MHC multimer, optionally wherein the MHC multimer is a tetramer.
17. The binding protein of any one of claims 1-16, wherein the MHC is a MHC class I molecule.

18. The binding protein of any one of claims 1-17, wherein the MHC comprises an MHC alpha chain that is an HLA serotype HLA-A*02.

19. The binding protein of any one of claims 1-18, 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.

20. The binding protein of any one of claims 1-19, wherein binding of the binding protein to the HA-1 peptide-MHC (pMHC) complex elicits an immune response, optionally wherein the immune response is a T cell response.

21. The binding protein of any one of claims 1-20, wherein the T cell response is selected from the group consisting of T cell expansion, cytokine release, and/or cytotoxic killing.

22. The binding protein of any one of claims 1-21, wherein the binding protein is capable of specifically and/or selectively binding to the HA-1 immunogenic peptide-MHC (pMHC) complex with a K_d less than or equal to about 1×10^{-4} M, ~~less than or equal to about 5×10^{-5} M, less than or equal to about 1×10^{-5} M, less than or equal to about 5×10^{-6} M, less than or equal to about 1×10^{-6} M, less than or equal to about 5×10^{-7} M, less than or equal to about 1×10^{-7} M, less than or equal to about 5×10^{-8} M, less than or equal to about 1×10^{-8} M, less than or equal to about 5×10^{-9} M, less than or equal to about 1×10^{-9} M, less than or equal to about 5×10^{-10} M, less than or equal to about 1×10^{-10} M, less than or equal to about 5×10^{-11} M, less than or equal to about 1×10^{-11} M, less than or equal to about 5×10^{-12} M, or less than or equal to about 1×10^{-12} M.~~

23. ~~The binding protein of any one of claims 1-22, wherein the binding protein has a higher binding affinity to the peptide-MHC (pMHC) than does a known T-cell receptor.~~

24. ~~The binding protein of any one of claims 1-23, wherein the binding protein has at least 1.05 fold higher binding affinity to the peptide-MHC (pMHC) than does a known T-cell receptor.~~

25. ~~The binding protein of any one of claims 1-24, wherein the binding protein induces higher T-cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with a heterozygous expression of HA-1.~~

~~26. — The binding protein of any one of claims 1-25, wherein the binding protein induces at least 1.05 fold increase in T-cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with a heterozygous expression of HA-1.~~

~~27. — The binding protein of claim 25 or 26, wherein the target cell is THP-1 or TF1 cell line.~~

~~28. — The binding protein of claim 25 or 26, wherein the target cell is a cancer cell, optionally wherein the cancer cell is a hematopoietic cancer cell, a leukemia cell, a lymphoma cell, a myelodysplastic disorder cell, a myeloproliferative neoplasm cell, or a myeloma cell.~~

~~29. — The binding protein of any one of claims 22-28, wherein the binding protein does not bind to HA-1^R peptide-MHC (pMHC) complex, wherein the HA-1^R peptide comprises the amino acid sequence VLRDDLLEA.~~

~~2430. The binding protein of any one of claims 1-2322-29, wherein the binding protein does not bind to a CCDC114 peptide-MHC (pMHC) complex, optionally wherein the CCDC114 peptide is SMIDLLGV.~~

~~2531. — A TCR alpha chain and/or beta chain selected from the group consisting of TCR alpha chain and beta chain sequences listed in Table 1.~~

32. An isolated nucleic acid molecule that encodes ~~hybridizes, under stringent conditions, with the complement of a~~ binding protein of any one of claims 1-24 ~~nucleic acid encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1, or a sequence with at least about 80% homology to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences listed in Table 1, optionally wherein the isolated nucleic acid molecule comprises 1) a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1 and/or 2) a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1.~~

~~33.~~ The isolated nucleic acid of claim ~~of claim 32~~, wherein the nucleic acid is codon optimized for expression in a host cell.

~~26~~34. A vector comprising the isolated nucleic acid of claim ~~25~~32 or ~~33~~.

~~27~~35. The vector of claim ~~26~~, wherein the vector comprises the sequence of SEQ ID NO: ~~31~~ or the sequence of SEQ ID NO: ~~32~~.

~~28.~~ The vector of claim ~~27~~34, wherein the vector is a cloning vector, expression vector, or viral vector.

~~29~~36. The vector of claim ~~27~~34 or ~~28~~35, wherein the vector further comprises a nucleic acid sequence encoding CD8 α and/or CD8 β .

~~30~~37. The vector of ~~claim 29~~any one of claims ~~34-36~~, wherein the nucleic acid sequence encoding CD8 α or CD8 β is operably linked to a nucleic acid encoding a tag.

~~31~~38. The vector of ~~claim 30~~any one of claims ~~34-37~~, 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-terminal of CD8 α or CD8 β .

~~32~~39. The vector of ~~any one of claims 30 or 31~~34-38, wherein the tag is a CD34 enrichment tag.

~~33~~40. The vector of any one of claims ~~29-32~~34-39, wherein the ~~isolated nucleic acid encoding the binding protein of claim 23 or 24~~, 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.

~~34~~41. The vector of ~~claim 33~~any one of claims ~~34-40~~, wherein the self-cleaving peptide is P2A, E2A, F2A or T2A.

~~35~~42. A host cell which comprises the ~~isolated nucleic acid of claim 32 or 33~~, comprises the vector of any one of claims ~~26-34~~34-41, and/or expresses the binding protein of any one of claims 1-~~24~~30, optionally wherein the cell is genetically engineered.

3643. The host cell of claim 3542, wherein the host cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both.

3744. The host cell of claim 3542 or 3643, 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, and combinations thereof.

3845. The host cell of any one of claims 35-3742-44, 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, and combinations thereof.

3946. The host cell of any one claims 35-3842-45, wherein the host cell expresses CD8 α and/or CD8 β .

4047. The host cell of ~~claim 39~~claims 46, wherein the CD8 α and/or CD8 β is fused to a CD34 enrichment tag.

~~4148. The host cell of claim 47, wherein host cells are enriched using the CD34 enrichment tag.~~

49. The host cell of any one of claims 35-4042-48, wherein the host cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell.

4250. The host cell of ~~claim 41~~any one of claims 42-49, 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 combination thereof.

4351. The host cell of any one of claims 35-42-50, wherein the ~~host~~T cell is a naive T cell, central memory T cell, effector memory T cell, or a combination thereof.

4452. The host cell of any one of claims 35-4342-51, wherein the ~~host~~T cell is a primary T cell or a cell of a T cell line.

~~45~~53. The host cell of any one of claims ~~35-44~~42-52, wherein the ~~host~~T cell does not express or has a lower surface expression of an endogenous TCR.

~~46~~54. The host cell of any one of claims ~~35-45~~42-53, 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~~the HA-1 peptide epitope in the context of an MHC molecule.

~~47. 55.~~—The host cell of claim ~~46~~54, wherein the host cell is contacted with the target cell *in vitro*, *ex vivo*, or *in vivo*.

~~56.~~—The host cell of claim ~~54 or 55~~, wherein the cytokine is TNF- α , IL-2, and/or IFN- γ .

~~48~~57. The host cell of ~~claim 46 or 47~~any one of claims 54-56, wherein the cytotoxic molecule is perforins and/or granzymes, optionally wherein the cytotoxic molecule is granzyme B.

~~49~~58. The host cell of any one of claims ~~46-48~~54-57, 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-1.

~~50~~59. The host cell of claim ~~49~~58, wherein the host cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule.

~~51~~60. The host cell of any one of claims ~~46-50~~54-59, wherein the host cell is capable of killing a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-1 peptide epitope in the context of an MHC molecule.

~~52~~61. The host cell of claim ~~51~~61, wherein the killing is determined by a killing assay.

~~53~~62. The host cell of claim ~~51~~60 or ~~52~~61, wherein the ratio of the host cell and the target cell in the killing assay is from 20:1 to 0.625:1.

~~54~~63. The host cell of any one of claims ~~51-53~~60-62, wherein ~~the~~a target cell is a T2 cell pulsed with 1 μ g/mL to 50 pg/mL of HA-1 peptide.

5564. The host cell of any one of claims 51-54~~60-62~~, 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-1.

5665. The host cell of claim 5564, wherein the host cell is capable of killing an at least 1.05-fold higher number of target cells.

5766. The host cell of any one of claims 51, 52, 55~~60, 61, 64~~ and 5665, wherein the target cell is THP-1 or TF1 cell line.

5867. The host cell of any one of claims 46-57~~54-66~~, wherein the HA-1 ~~immunogenic~~ peptide epitope comprises the amino acid sequence VLHDDLLEA.

5968. The host cell of any one of claims 46-58~~54-67~~, wherein the MHC molecule is a MHC class I molecule.

6069. The host cell of any one of claims 46-59~~54-68~~, wherein the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02.

6170. The host cell of any one of claims 46-60~~54-69~~, wherein the HLA allele is selected from the group consisting of HLA-A*02:01, HLA-A*02:02, HLA-A*02:03, HLA-A*02:05, HLA-A*02:06, and HLA-A*02:07 allele.

6271. The host cell of any one of claims 46-61~~54-70~~, wherein the target cell is a cell line selected from the group consisting of SupM2, THP-1, and TF1 cell line, is a hematopoietic cancer cell expressing HA-1, or is not SU-DHL1.

6372. The host cell of claim 6271, wherein the cancer cell is of a hematological malignancy ~~selected~~~~selected~~ from the group consisting of a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, or myeloma.

6473. The host cell of any one of claims 46-63~~54-72~~, wherein a) the host cell does not induce T cell expansion, cytokine release, or cytotoxic killing when contacted with a target cell that comprises a peptide-MHC (pMHC) complex comprising a CCDC114 peptide epitope in the context of an MHC molecule and/or b) the host cell does not express HA-1 antigen, is not recognized by a binding protein of any one of claims 1-24~~30~~, is not of

serotype HLA-A*02, and/or does not express an HLA-A*02 allele, optionally wherein the HLA-A*02 allele is HLA-A*02:01 and/or HLA-A*02:06.

~~6574.~~ A population of host cells of any one of claims ~~35-6442-73~~.

~~6675.~~ A composition comprising: a) a binding protein according to any one of claims 1-~~2430~~, b) an isolated nucleic acid according to claim ~~2532-33~~, c) a vector according to any one of claims ~~26-34-41~~, d) a host cell according to any one of claims ~~35-6442-73~~, and/or e) a population of host cells according to claim ~~6574~~, and a carrier.

~~67.76.—~~ A device or kit comprising: a) a binding protein according to any one of claims 1-~~2430~~, b) an isolated nucleic acid according to claim ~~2532-33~~, c) a vector according to any one of claims ~~26-34-41~~, d) a host cell according to any one of claims ~~35-6442-73~~, and/or e) a population of host cells according to claim ~~6574~~, said device or kit optionally comprising a reagent to detect binding of a), d) and/or e) to a pMHC complex.

~~6877.~~ A method of producing a binding protein according to any one of claims 1-~~2430~~, 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-~~2430~~ under conditions suitable to allow expression of said binding protein; and (ii) recovering the expressed binding protein.

~~6978.~~ A method of producing a host cell expressing a binding protein according to any one of claims 1-~~2430~~, 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-~~2430~~ into the host cell; and (ii) culturing the transformed host cell under conditions suitable to allow expression of said binding protein.

~~79.—~~ A method of detecting the presence or absence of an HA-1 antigen and/or a cell expressing HA-1, optionally wherein the cell is a hyperproliferative cell, comprising detecting the presence or absence of said HA-1 antigen in a sample by use of at least one binding protein according to any one of claims 1-30, or at least one host cell according to any one of claims ~~42-73~~, wherein detection of the HA-1 antigen is indicative of the presence of an HA-1 antigen and/or cell expressing HA-1.

80. — ~~The method of claim 79, wherein the at least one binding protein, or the at least one host cell, forms a complex with the HA-1 peptide in the context of an MHC molecule, and the complex is detected in the form of fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay.~~

81. — ~~The method of claim 79 or 80, further comprising obtaining the sample from a subject.~~

82. — ~~The method of any one of claims 79-81, further comprising confirming cells expressing HA-1 by bone marrow biopsy.~~

83. — ~~A method of detecting the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in a subject, comprising:~~

~~a) contacting a sample obtained from the subject with at least one binding protein according to any one of claims 1-30, at least one host cell according to any one of claims 42-73, or a population of host cells according to claim 74; and~~

~~b) detecting the level of reactivity,~~

~~wherein a higher level of reactivity compared to a control level indicates the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in the subject.~~

84. — ~~The method of claim 83, wherein the control level is a reference number.~~

85. — ~~The method of claim 83, wherein the control level is a level of a subject without the non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen.~~

86. — ~~A method for monitoring the progression of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in a subject, the method comprising:~~

~~a) detecting in a subject sample at a first point in time the level of the HA-1 antigen or the cell of interest expressing HA-1, according to any one of claims 79-85;~~

~~b) repeating step a) at a subsequent point in time; and~~

c) comparing the level of HA-1 antigen or the cell of interest expressing HA-1 detected in steps a) and b) to monitor the progression of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in the subject, wherein an absent or reduced level of the HA-1 antigen or the cell of interest expressing HA-1 detected in step b) compared to step a) indicates an inhibited progression of the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in the subject.

87. — The method of claim 86, wherein between the first point in time and the subsequent point in time, the subject has undergone treatment to treat the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen.

88. — A method of assessing the efficacy of a therapy for a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen comprising:

—— a) determining the presence or level of reactivity between a sample obtained from the subject and at least one binding protein according to any one of claims 1-30, at least one host cell according to any one of claims 42-73, or a population of host cells according to claim 74, in a first sample obtained from a subject prior to providing at least a portion of the therapy for the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen to the subject, and

—— b) determining the presence or level of reactivity between a sample obtained from the subject and at least one binding protein according to any one of claims 1-30, at least one host cell according to any one of claims 42-73, or a population of host cells according to claim 74, in a second sample obtained from the subject following provision of the portion of the therapy for the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen;

wherein the absence or a reduced level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-1 antigen in the subject.

89. — ~~The method of any one of claims 83–89, wherein the level of reactivity is indicated by a) the presence of binding and/or b) T cell activation and/or effector function.~~

90. — ~~The method of claim 89, wherein the T cell activation or effector function is T cell proliferation, killing, or cytokine release.~~

91. — ~~The method of any one of claims 83–90, wherein the T cell binding, activation, and/or effector function is detected using fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay.~~

92. — ~~A method of preventing and/or treating a non-malignant disorder, a hyperproliferative disorder or a relapse of a hyperproliferative disorder characterized by expression of an HLA-1 antigen in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising cells expressing at least one binding protein of any one of claims 1–30.~~

93. — ~~The method of claim 92, wherein the cell is an allogeneic cell, syngeneic cell, or autologous cell.~~

94. — ~~The method of claim 92 or 93, wherein the cell is genetically modified.~~

95. — ~~The method of any one of claims 92–94, wherein the cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both a TCR gene and an HLA gene.~~

96. — ~~The method of any one of claims 92–95, wherein the cell comprises a knockout of an HLA gene selected from an α 1-macroglobulin gene, α 2-macroglobulin gene, α 3-macroglobulin gene, β 1-microglobulin gene, β 2-microglobulin gene, and a combination thereof.~~

97. — ~~The method of any one of claims 92–96, wherein the 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, and combinations thereof.~~

98.—~~The method of any one claims 92-97, wherein the cell expresses CD8 α and/or CD8 β ,~~

~~optionally wherein the CD8 α and/or CD8 β is fused to a CD34 enrichment tag.~~

99.—~~The method of claim 98, wherein cells are enriched using the CD34 enrichment tag.~~

100.—~~The method of any one of claims 92-99, wherein the cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell.~~

101.—~~The method of any one of claims 92-100, 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 combination thereof.~~

102.—~~The method of any one of claims 92-101, wherein the T cell is a naive T cell, central memory T cell, effector memory T cell, or combination thereof.~~

103.—~~The method of any one of claims 92-102, wherein the T cell is a primary T cell or a cell of a T cell line.~~

104.—~~The method of any one of claims 92-103, wherein the T cell does not express or has a lower surface expression of an endogenous TCR.~~

105.—~~The method of any one of claims 92-104, wherein the 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 the HA-1 peptide eiptope in the context of an MHC molecule.~~

106.—~~The method of any one of claims 92-105, wherein the cytokine is TNF- α , IL-2, and/or IFN- γ .~~

107.—~~The method of any one of claims 92-106, wherein the cytotoxic molecule is perforins and/or granzymes, optionally wherein the cytotoxic molecule is granzyme B.~~

~~108.—The method of any one of claims 92–107, wherein the 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-1.~~

~~109.—The method of claim 108, wherein the cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule.~~

~~110.—The method of any one of claims 92–109, wherein the host cell is capable of killing a target cell that comprises a peptide–MHC (pMHC) complex comprising an HA-1 peptide eiptope in the context of an MHC molecule.~~

~~111.—The method of any one of claims 92–110, 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-1.~~

~~112.—The method of claim 111, wherein the host cell is capable of killing an at least 1.05-fold higher number of target cells.~~

~~113.—The method of any one of claims 92–112, wherein the HA-1 immunogenic peptide comprises the amino acid sequence VLHDDLLEA.~~

~~114.—The method of any one of claims 92–113, wherein the MHC molecule is an MHC class I molecule.~~

~~115.—The method of any one of claims 92–114, wherein the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02.~~

~~116.—The method of any one of claims 92–115, wherein the HLA allele is selected from the group consisting of HLA-A*02:01, HLA-A*02:02, HLA-A*02:03, HLA-A*02:05, HLA-A*02:06, and HLA-A*02:07 allele.~~

~~117.—The method of any one of claims 92–116, wherein the target cell is a non-malignant cell or a hyperproliferating cell expressing the HA-1 antigen in the subject.~~

~~118.—The method of any one of claims 92–117, wherein the composition further comprises a pharmaceutically acceptable carrier.~~

~~119.—The method of any one of claims 92–118, wherein the composition induces an immune response against the non-malignant cells or the hyperproliferating cells expressing the HA-1 antigen in the subject.~~

~~120.—The method of any one of claims 92–119, wherein the composition induces an antigen-specific T-cell immune response against the non-malignant cells or the hyperproliferating cells expressing the HA-1 antigen in the subject.~~

~~121.—The method of any one of claims 92–120, wherein the antigen-specific T-cell immune response comprises at least one of a CD4⁺ helper T lymphocyte (Th) response and a CD8⁺ cytotoxic T lymphocyte (CTL) response.~~

~~122.—The method of any one of claims 83–121, wherein the hyperproliferative disorder comprises a hematological malignancy.~~

~~123.—The method of any one of claims 83–122, wherein the hematological malignancy comprises a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, or a myeloma.~~

~~124.—The method of any one of claims 83–123, wherein the hematological malignancy comprises a leukemia.~~

~~125.—The method of any one of claims 83–124, wherein the leukemia is selected from acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), mixed-phenotype acute leukemia (MPAL), chronic myeloid leukemia (CML), B-cell prolymphocytic leukemia, hairy-cell leukemia, or chronic lymphocytic leukemia (CLL).~~

~~126.—The method of any one of claims 83–125, wherein the hematological disorder comprises a lymphoma.~~

~~127.—The method of any one of claims 83–125, wherein the lymphoma is selected from Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), a central nervous system lymphoma, small lymphocytic lymphoma (SLL), CD37⁺ dendritic-cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle-cell lymphoma, diffuse large B-cell~~

lymphoma, mediastinal (thymic) large B-cell lymphoma, precursor B-lymphoblastic lymphoma, immunoblastic large cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, or Burkitt's lymphoma.

128.—The method of any one of claims 83–123, wherein the hematological malignancy comprises a myelodysplastic disorder (MDS), optionally wherein the MDS is selected from refractory cytopenia with unilineage dysplasia (refractory anemia, refractory neutropenia, and refractory thrombocytopenia), refractory anemia with ring sideroblasts (RARS), refractory anemia with ring sideroblasts–thrombocytosis (RARS-t), refractory cytopenia with multilineage dysplasia (RCMD), refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS), refractory anemia with excess blasts (RAEB), myelodysplasia unclassifiable, refractory cytopenia of childhood, or MDS with isolated del(5q).

129.—The method of any one of claims 83–123, wherein the non-malignant disorder is an immune deficiency disorder, optionally wherein the immune deficiency disorder is selected from the group consisting of severe combined immunodeficiency (SCID), Wiskott–Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, chronic granulomatous disease, leukocyte adhesion deficiency, DiGeorge syndrome, and indications for hematopoietic stem cell transplantation (HCT).

130.—The method of any one of claims 83–121, wherein the non-malignant disorder is a non-malignant hematology, optionally wherein the non-malignant hematology disorder is selected from the group consisting of sickle cell anemia, thalassemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), severe aplastic anemia, marrow failure syndromes, Fanconi anemia, Diamond–Blackfan anemia, and Shwachman–Diamond syndrome.

131.—The method of any one of claims 83–121, wherein the non-malignant disorder is an autoimmune disorder, optionally wherein the autoimmune disorder is systemic sclerosis or multiple sclerosis.

132.—The method of any one of claims 92–131, wherein the subject is receiving or previously received a hematopoietic cell transplant (HCT), optionally wherein the HCT

~~comprises cells that do not express HA-1 antigen, are not recognized by a binding protein of any one of claims 1-30, are not of serotype HLA-A*02, and/or do not express an HLA-A*02:01 allele.~~

~~133.—The method of claim 132, wherein the HCT comprises a donor hematopoietic cell comprising a chromosomal knockout of a gene that encodes an HLA component, a chromosomal knockout of a gene that encodes a TCR component, or both.~~

~~134.—The method of any one of claims 92-133, wherein the subject had previously received lymphodepleting chemotherapy.~~

~~135.—The method of claim 134, wherein the lymphodepleting chemotherapy comprised cyclophosphamide, fludarabine, anti-thymocyte globulin, or a combination thereof.~~

~~136.—The method of any one of claims 92-135, further comprising administering at least one additional treatment for the non-malignant disorder, the hyperproliferative disorder or the relapse of a hyperproliferative disorder to the subject.~~

~~137.—The method of any one of claims 92-136, wherein the at least one additional treatment for the non-malignant disorder, the hyperproliferative disorder or the relapse of a hyperproliferative disorder is administered concurrently or sequentially with the composition.~~

~~138.—The method of any one of claims 81-137, wherein the subject is an animal model of a disorder characterized by HA-1 expression and/or the mammal, optionally wherein the mammal is a human, a primate, or a rodent.~~

~~139.—An expression vector comprising a promoter operably linked to a nucleic acid sequence encoding CD8 α and/or CD8 β .~~

~~140.—The vector of claim 139, wherein the nucleic acid sequence encoding CD8 α or CD8 β is operably linked to a nucleic acid encoding a tag such that the tag is fused to the CD8 α or CD8 β .~~

141.—The vector of claim 139 or 140, 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-terminal of CD8 α or CD8 β .

142.—The vector of any one of claims 139–141, wherein the tag is a CD34 enrichment tag.

143.—The vector of any one of claims 139–142, wherein the vector further comprises a nucleic sequence encoding a TCR α and/or TCR β .

144.—The vector of any one of claims 139–143, wherein the TCR α and/or TCR β comprises a mutated transmembrane domain and/or a mutated constant domain.

145.—The vector of any one of claims 139–144, wherein the mutated transmembrane domain and/or mutated constant domain enhance cellular surface expression of TCR α and/or TCR β while decreasing expression of endogenous TCR α and/or TCR β .

146.—The vector of any one of claims 139–145, wherein the nucleic acid sequence encoding CD8 α and/or CD8 β and the nucleic sequence encoding TCR α and/ TCR β , are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide.

147.—The vector of any one of claims 139–146, wherein the self-cleaving peptide is P2A, E2A, F2A or T2A.

148.—The vector of any one of claims 139–147, wherein the vector further comprises a nucleic sequence encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1, or a sequence with at least about 80% homology to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences listed in Table 1, optionally wherein the isolated nucleic acid molecule comprises 1) a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1 and/or 2) a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1.

149.—The vector of any one of claims 139–148, wherein the vector has a nucleic sequence set forth in Table 3.