

(see, e.g., U.S. Pat. Nos. 7,342,092; 7,608,685; 7,622,119). In addition, WT-1 expression has been reported to be a marker of minimal residual disease because increased transcript levels in patients with AML in morphologic remission were predictive of overt clinical relapse (Inoue *et al.*, *Blood* 84:3071, 1994; Ogawa *et al.*, *Blood* 101:1698, 2003).

Since WT-1 is an intracellular (usually nuclear) protein, immunotherapies targeting WT-1 have used cellular approaches aimed at generating WT-1-specific CD8⁺ cytotoxic T lymphocyte (CTL) responses that recognize peptides presented on the cell surface by MHC class I molecules. For induction of a CTL response, intracellular proteins are usually degraded by the proteasome or endo/lysosomes, with the resulting peptide fragments binding to MHC class I or class II molecules. These peptide-MHC complexes are displayed on the cell surface where they are bound by T cells via the peptide-MHC-TCR interaction. Peptides derived from the WT-1 protein can theoretically be used in a vaccine in humans to induce human leukocyte antigen (HLA)-restricted cytotoxic CD8⁺ T cells that are capable of killing tumor cells. However, because WT-1 is a self-protein, immunization may only elicit responses by T cells with low affinity TCRs. In addition, antibodies against WT-1 are detectable in patients with hematopoietic malignancies and solid tumors, which show that WT-1 can be a highly immunogenic antigen (Gaiger *et al.*, *Clin. Cancer Res.* 7 (Suppl. 3):761, 2001).

Clearly there is a need for alternative gene therapies for use as highly specific, WT-1 targeted immunotherapies directed against various cancers, such as leukemia and tumors. The presently disclosed embodiments address this need and provide other related advantages.

~~BRIEF~~ SUMMARY

In one aspect, the present disclosure refers to a modified immune cell, comprising a heterologous polynucleotide that encodes a binding protein, wherein the encoded binding protein comprises:

(a) a T cell receptor (TCR) α chain variable ($V\alpha$) domain comprising the CDR1 amino acid sequence (CDR1 α) according to SEQ ID NO.:26, the CDR2 amino

acid sequence (CDR2 α) according to SEQ ID NO.:27, and the CDR3 amino acid sequence (CDR3 α) according to SEQ ID NO.:28; and

(b) a TCR β chain variable (V β) domain comprising the CDR1 amino acid sequence (CDR1 β) according to SEQ ID NO.:38, the CDR2 amino acid sequence (CDR2 β) according to SEQ ID NO.:39, and the CDR3 amino acid sequence (CDR3 β) according to SEQ ID NO.:40,

wherein the encoded binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):human leukocyte antigen (HLA) complex, wherein, optionally, the HLA comprises HLA-A*0201.

In another aspect, the present disclosure refers to a binding protein comprising a T cell receptor (TCR) α chain variable (V α) domain and a TCR β chain variable (V β) domain, wherein the V α and V β domains comprise CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:26-28 and 38-40, respectively, and wherein the binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):HLA complex.

In another aspect, the present disclosure refers to an isolated polynucleotide encoding the binding protein as disclosed herein.

In another aspect, the present disclosure refers to a vector, comprising the polynucleotide as disclosed herein, wherein, optionally, the vector is a lentiviral vector or a retroviral vector.

In another aspect, the present disclosure refers to a host cell, comprising the polynucleotide as disclosed herein and capable of expressing the encoded binding protein.

In another aspect, the present disclosure refers to a composition, comprising:

(i) the modified immune cell as disclosed herein;

(ii) the binding protein as disclosed herein;

(iii) the polynucleotide as disclosed herein;

(iv) the vector as disclosed herein; and/or

(v) the host cell as disclosed herein;

and a pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the present disclosure refers to the use of: (i) the modified immune cell as disclosed herein; (ii) the binding protein as disclosed herein; (iii) the polynucleotide as disclosed herein; (iv) the vector as disclosed herein; (v) the host cell as disclosed herein; and/or (vi) the composition as disclosed herein in the manufacture of a medicament for treating a subject having a disease or disorder associated with WT-1 expression, wherein the disease or disorder is a hematological malignancy or a solid cancer.

In another aspect, the present disclosure refers to a composition, comprising:

- (i) the modified immune cell as disclosed herein;
- (ii) the binding protein as disclosed herein;
- (iii) the polynucleotide as disclosed herein;
- (iv) the vector as disclosed herein; and/or
- (v) the host cell as disclosed herein,

for use in therapy.

The present disclosure provides, according to certain ~~embodiment~~examples, binding proteins that are capable of binding to a RMFPNAPYL (SEQ ID NO:94):human leukocyte antigen (HLA) complex, wherein the binding proteins comprise (a) a T cell receptor (TCR) α chain variable ($V\alpha$) domain comprising the CDR3 amino acid sequence ($CDR3\alpha$) according to any one of SEQ ID NOs.:19, 22, 25, or 28, or a variant thereof, and a TCR β chain variable ($V\beta$) domain, wherein the $V\beta$ optionally comprises

or consists of an amino acid sequence having at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) identity to the amino acid sequence set forth in any one of SEQ ID NOs.:5-8 or 13-16; (b) a TCR V β domain comprising the CDR3 amino acid sequence (CDR3 β) according to any one of SEQ ID NOs.:31, 34, 37, or 40, or a variant thereof, and a TCR V α domain, wherein the V α optionally comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.: 1-4 or 9-12; or (c) a TCR V α domain of (a), and a TCR V β domain of (b).

In certain [embodimentexamples](#), a binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):human leukocyte antigen (HLA) complex with an IFN γ production pEC₅₀ of 4.0, 4.5, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, or higher (*e.g.*, an immune cell (such as, for example, a T cell, a NK-T cell, or a NK cell) comprising the binding protein has a SEQ ID NO.:94:HLA IFN γ production pEC₅₀ of 4.0, 4.5, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, or higher).

In certain [embodimentexamples](#), the HLA comprises HLA-A*0201.

In certain [embodimentexamples](#), the binding protein is human, humanized, or chimeric.

In any of the herein disclosed [embodimentexamples](#), a binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):human leukocyte antigen (HLA) complex, wherein the binding protein comprises a TCR V β domain and a TCR V α domain, wherein: (i) the V β domain comprises or consists of an amino acid sequence having at least 90% identity (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) to the amino acid sequence of any one of SEQ ID NOs.: 5-8 or 13-16; and/or (ii) the V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence of any one of SEQ ID NOs.:1- 4 or 9-12.

In certain [embodimentexamples](#), the encoded binding protein is a TCR, a CAR, or a scTCR.

Also provided herein modified immune cells that comprise a heterologous polynucleotide that encodes a binding protein as disclosed herein. In certain [embodimentexamples](#), the immune cell comprises a T cell, a NK cell, a NK-T cell, or any combination thereof. In certain [embodimentexamples](#), an immune cell encoding a binding

protein as disclosed herein is activated in the presence of a peptide according to SEQ ID NO.:94 (*e.g.*, comprised in a peptide:HLA complex). In certain [embodimentexamples](#), an immune cell encoding a binding protein as disclosed herein is capable of killing a target cell expressing a SEQ ID NO: 94:HLA complex.

Also provided are isolated polynucleotides that encode a binding protein according to the present disclosure. In certain [embodimentexamples](#), the encoded binding protein comprises: (i) the amino acid sequence set forth in any one of SEQ ID NOs.: 19, 22, 25, 28, 31, 34, 37, or 40; (ii) the amino acid sequence set forth in any one of SEQ ID NOs.: 17, 20, 23, 26, 29, 32, 35, or 38; (iii) the amino acid sequence set forth in any one of SEQ ID NOs.: 18, 21, 24, 27, 30, 33, 36, or 39; (iv) an amino acid sequence comprising, consisting of, or having at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to the amino acid sequence set forth in any one of SEQ ID NOs: 1-4 or 9-12; (v) an amino acid sequence comprising, consisting of, or having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 5-8 or 13-16; (vi) an amino acid sequence comprising, consisting of, or having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.: 46-53; (vii) an amino acid sequence comprising, consisting of, or having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.: 54-61; or (viii) any combination of (i)-(vii).

In certain [embodimentexamples](#), the polynucleotide comprises or consists of a polynucleotide having at least 75% (*e.g.*, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%) identity to the nucleotide sequence set forth in any one of SEQ ID NOs.: 62-81. In certain [embodimentexamples](#), the polynucleotide is codon-optimized for expression in a host cell, such an immune cell (*e.g.*, human T cell).

Vectors that contain a polynucleotide as described herein are also provided, as well as compositions that comprise a presently disclosed modified cell, binding protein, polynucleotide, and/or vector.

Also provided are methods for treating a subject having a disease or disorder associated with WT-1 expression or activity, wherein the methods comprise administering to the subject an effective amount of a modified immune cell, binding protein, polynucleotide, or vector as disclosed herein.

In certain [embodimentexamples](#), the disease or disorder is a hematological malignancy or a solid cancer. For example, the hematological malignancy to be treated may be acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloid leukemia (AML, including refractory and relapsed AML, and including acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelocytic leukemia, acute myelomonocytic leukemia (*e.g.*, with or without eosinophilia), acute monocytic leukemia, acute erythroid leukemia, and acute megakaryoblastic leukemia), chronic myelogenous leukemia (CML), chronic myelocytic leukemia, chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM, including refractory and relapsed MM). Exemplary solid cancer to be treated may be biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, breast cancer, breast carcinoma, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, glioblastoma, melanoma, diffuse peritoneal mesothelioma, malignant pleural mesothelioma, glioma, astrocytoma, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, hepatocellular carcinoma, lung cancer, non small-cell lung cancer, malignant melanoma, osteosarcoma, ovarian cancer (*e.g.*, epithelial ovarian cancer, ovarian carcinoma), fallopian tube cancer, endometrial carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, osteogenic sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, uterine carcinosarcoma, or uterine cancer.

These and other aspects and [embodimentexamples](#) of the present disclosure will be further understood upon reference to the following detailed description and attached drawings. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference in their entirety, as if each was incorporated individually. Aspects and [embodimentexamples](#) of the disclosure can be modified, if necessary,

to employ concepts of the various patents, applications and publications to provide yet further [embodiment examples](#).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows identification of WT-1-specific T cell lines. Briefly, WT-1-specific polyclonal T cell lines (CD8+) obtained from 4 healthy donors were cultured with peptide-pulsed autologous dendritic cells, stained with CD8-independent (CD8i) WT-1 peptide/HLA-A tetramer, and sorted for high tetramer staining cells. Twenty-four (24) WT-1-specific clonotypes were identified. TCR repertoire analysis was performed by sequencing. The fold-enrichment of each clonotype within the sorted versus unsorted populations (y-axis) and the CD3 surface expression (x-axis) of each clonotype are shown.

Figures 2A-2C show that exemplary WT-1-specific binding proteins are expressed in transduced host cells. Ten (10) WT-1 specific TCRs from the 24 clonotypes shown in Figure 1 were used to transduce TCR α /TCR β -deficient J76 Jurkat T cells. WT-1:HLA-A tetramer binding and CD3 expression of the transduced cells (shown in light grey) was compared to cells transduced with a reference WT-1-specific TCR (shown in dark grey) having an α chain according to SEQ ID NO.:82 and a β chain according to SEQ ID NO.:83 and described by Schmitt *et al.* (*Nat. Biotechnol.* 35:1188, 2017).

Figures 3A and 3B show that binding proteins of the present disclosure are functional in transduced host cells. (A) Jurkat cells expressing *Nur77*-dtTomato reporter (reporting antigen-specific signaling in human T cells; *see* Ahsouri and Weiss, *J Immunol* 198(2):657-668 (2017)) were transduced with WT-1-specific TCR and incubated for 24h with APCs loaded with WT-1 peptide at the indicated concentrations. (B) *Nur77* activation peptide EC₅₀ values of the indicated TCRs.

Figures 4A-4C show further functional characterization of exemplary binding proteins of the present disclosure. (A) Peptide/MHC tetramer binding by CD8+ T cells that were transduced to express a WT-1-specific TCR as indicated. (B) IFN γ production (as determined by flow cytometry) by expanded antigen-specific CD8+ T cells in a 4 hour co-culture with T2 target cells pulsed with titrated concentrations of

CLAIMS

What is claimed is:

1. A modified immune cell, comprising a heterologous polynucleotide that encodes a binding protein, wherein the encoded binding protein comprises:

(a) a T cell receptor (TCR) α chain variable ($V\alpha$) domain comprising the CDR1 amino acid sequence (CDR1 α) according to SEQ ID NO.:26, the CDR2 amino acid sequence (CDR2 α) according to SEQ ID NO.:27, and the CDR3 amino acid sequence (CDR3 α) according to ~~any one of SEQ ID NOs.:28, 19, 22, or 25, or a variant thereof, and a TCR β chain variable ($V\beta$) domain; or~~ and

(b) a TCR β chain variable ($V\beta$) domain comprising the CDR1 amino acid sequence (CDR1 β) according to SEQ ID NO.:38, the CDR2 amino acid sequence (CDR2 β) according to SEQ ID NO.:39, and the CDR3 amino acid sequence (CDR3 β) according to ~~any one of SEQ ID NOs.:40, 31, 34, or 37, or a variant thereof, and a TCR $V\alpha$ domain; or~~

~~(c) — a TCR $V\alpha$ domain of (a), and a TCR $V\beta$ domain of (b),~~

wherein the encoded binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):human leukocyte antigen (HLA) complex, wherein, optionally, the HLA comprises HLA-A*0201.

2. The modified immune cell of claim 1, wherein the encoded binding protein is capable of binding to the RMFPNAPYL (SEQ ID NO.:94):HLA complex with an IFN γ production pEC₅₀ of 4.0 or higher, ~~or 4.5 or higher,~~ 5.0 or higher, 5.5 or higher, 6.0 or higher, or 6.5 or higher.

~~3. — The modified immune cell of claim 1 or 2, wherein the encoded binding protein is capable of binding to the RMFPNAPYL (SEQ ID NO.:94):HLA complex with an IFN γ production pEC₅₀ of 5.0 or higher.~~

~~4. The modified immune cell of any one of claims 1-3, wherein the encoded binding protein is capable of binding to the RMFPNAPYL (SEQ ID NO.:94):HLA complex with an IFN γ production pEC₅₀ of 5.5 or higher.~~

~~5. The modified immune cell of any one of claims 1-4, wherein the encoded binding protein is capable of binding to the RMFPNAPYL (SEQ ID NO.:94):HLA complex with an IFN γ production pEC₅₀ of 6.0 or higher.~~

~~6. The modified immune cell of any one of claims 1-5, wherein the encoded binding protein is capable of binding to the RMFPNAPYL (SEQ ID NO.:94):HLA complex with an IFN γ production pEC₅₀ of 6.5 or higher.~~

~~3-7.~~ The modified immune cell of ~~any one of claims 1~~ or 2-6, wherein the HLA comprises HLA-A*201.

~~48.~~ The modified immune cell of any one of claims 1-~~37~~, wherein ~~50%~~ or more of the modified immune cells in a population produce IFN- γ when the population of the modified immune cells is co-cultured for 4 hours with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻⁴ μ M, 10⁻⁵ μ M, or 10⁻⁶ μ M in the co-culture, wherein the antigen-presenting cells optionally comprise T2 cells.

~~59.~~ The modified immune cell of any one of claims 1-~~48~~, ~~1~~ wherein:

~~(i)~~ -10% or more of the modified immune cells in a population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻² μ M in the co-culture, wherein the antigen-presenting cells optionally comprise T2 cells, Jurkat cells, or both:

~~10(ii): The modified immune cell of claim 9, wherein~~ 15% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻² μM in the co-culture;~~;~~

~~11(iii): The modified immune cell of claim 9 or 10, wherein~~ 20% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻² μM in the co-culture;~~;~~

~~12(iv): The modified immune cell of any one of claims 9-11, wherein~~ 40% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻² μM in the co-culture;~~;~~ or

~~13(v): The modified immune cell of any one of claims 9-12, wherein~~ 50% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻² μM in the co-culture.

~~614.~~ The modified immune cell of any one of claims 1-~~513~~, wherein:

(i) ~~_____~~ 10% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻³ μM in the co-culture; and/or:

(ii) ~~15.~~—~~The modified immune cell of claim 14, wherein~~ 15% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.:94) at a peptide concentration of 10⁻³ μM in the co-culture; ~~and/or~~

(iii) ~~16.~~—~~The modified immune cell of claim 14 or 15, wherein~~ 20% or more of the modified immune cells in the population are Nur77⁺ when the population of the modified immune cells is co-cultured with antigen-presenting cells pulsed with a peptide comprising or consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO.: 94) at a peptide concentration of ~~about~~ 10⁻³ μM in the co-culture.

~~17.~~ The modified immune cell of any one of claims 1-~~16~~, wherein:

(i) ~~the modified immune cell is capable of killing 11% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1;~~

(ii) ~~18.~~—~~The modified immune cell of claim 17, wherein~~ the modified immune cell is capable of killing 12% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1;

(iii) ~~19.~~—~~The modified immune cell of claim 17 or 18, wherein~~ the modified immune cell is capable of killing 14% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1;

(iv) ~~20.~~—~~The modified immune cell of any one of claims 17-19, wherein~~ the modified immune cell is capable of killing 15% or more of HLA-A*0201⁺ MDA-

MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1; and/or-

(v) 21.—~~The modified immune cell of any one of claims 17-20, wherein~~ the modified immune cell is capable of killing 20% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1; or-

(vi) 22.—~~The modified immune cell of any one of claims 17-21, wherein~~ the modified immune cell is capable of killing 25% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 30:1.

823. The modified immune cell of any one of claims 1-~~227~~, wherein the modified immune cell is capable of killing 10% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 10:1.

924. The modified immune cell of any one of claims 1-~~823~~, wherein the modified immune cell is capable of killing ~~about~~ 5% or more of HLA-A*0201⁺ MDA-MB-468 cells in a sample when the modified immune cell and the MDA-MB-468 cells are present in the sample at a ratio of 1:1.

1025. The modified immune cell of any one of claims 1-~~924~~, wherein the modified immune cell is capable of killing 21% or more, 22% or more, 23% or more, 24% or more, or 25% or more-of Panc1 cells in a sample when the modified immune cell and the Panc1 cells are present at a ratio of 30:1.

26.—~~The modified immune cell of claim 25, wherein the modified immune cell is capable of killing 22% or more of Panc1 cells in a sample when the modified immune cell and the Panc1 cells are present at a ratio of 30:1.~~

~~27. The modified immune cell of claim 25 or 26, wherein the modified immune cell is capable of killing 23% or more of Panc1 cells in a sample when the modified immune cell and the Panc1 cells are present at a ratio of 30:1.~~

~~28. The modified immune cell of any one of claims 25-27, wherein the modified immune cell is capable of killing 24% or more of Panc1 cells in a sample when the modified immune cell and the Panc1 cells are present at a ratio of 30:1.~~

~~29. The modified immune cell of any one of claims 25-28, wherein the modified immune cell is capable of killing 25% or more of Panc1 cells in a sample when the modified immune cell and the Panc1 cells are present at a ratio of 30:1.~~

1130. The modified immune cell of any one of claims 1-~~1029~~, wherein the modified immune cell has increased killing activity against HLA-A*0201⁺ MDA-MB-468 cells and/or against Panc1 cells in a 4-hour co-culture as compared to a reference immune cell comprising a polynucleotide that encodes a T cell receptor comprising a TCR α chain having the amino acid sequence set forth in SEQ ID NO.:82 and a TCR β chain having the amino acid sequence set forth in SEQ ID NO.:83.

1231. The modified immune cell of any one of claims 1-~~1130~~, wherein the encoded binding protein is capable of binding to a WT-1 peptide:HLA complex on a cell surface independent of CD8 or in the absence of CD8.

1332. The modified immune cell of any one of claims 1-~~1231~~, wherein:

(i) the encoded V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence ~~set forth in of any one of~~ SEQ ID NOs.:16, ~~or 5, 6, 7, 8, 13, 14, or 15~~; and/or

(ii) the encoded V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence ~~set forth in of any one of~~ SEQ ID NOs.:12, ~~or 1, 2, 3, 4, 9, 10, or 11~~.

14. The modified immune cell of claim 13, wherein:

(i) the encoded V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:16; and

(ii) the encoded V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth-in SEQ ID NO.:12.

15. The modified immune cell of claim 13, wherein:

(i) the encoded V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:8; and

(ii) the encoded V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:4.

~~33.—The modified immune cell of any one of claims 1–32, wherein the encoded V β domain comprises or consists of an amino acid sequence having at least 90% identity to any one of SEQ ID NOs.: 16, 5, 6, 7, 8, 13, 14, or 15, and/or the encoded V α domain comprises or consists of an amino acid sequence having at least 90% identity to any one of SEQ ID NOs.:12, 1, 2, 3, 4, 9, 10, or 11, provided that:~~

~~(i) —at least three or four of the CDRs have no mutations;~~

~~(ii) —the CDRs that do have mutations have only up to two amino acid substitutions, up to a contiguous five amino acid deletion, or a combination thereof; and~~

~~(iii) —the encoded binding protein retains its ability to bind to a RMFPNAPYL (SEQ ID NO.:94):HLA complex, optionally with an interferon gamma (IFN γ) production pEC50 of 4.0 or higher.~~

~~34.—The modified immune cell of any one of claims 1–33, wherein:~~

~~(i) —the encoded CDR3 β comprises or consists of the amino acid sequence set forth in SEQ ID NO.:40, and the encoded CDR3 α comprises or consists of the amino acid sequence set forth in SEQ ID NO.:28;~~

(ii) ~~the encoded CDR3 β comprises or consists of the amino acid sequence set forth in SEQ ID NO: 31, and the encoded CDR3 α comprises or consists of the amino acid sequence set forth in SEQ ID NO: 19;~~

(iii) ~~the encoded CDR3 β comprises or consists of the amino acid sequence set forth in SEQ ID NO: 34, and the encoded CDR3 α comprises or consists of the amino acid sequence set forth in SEQ ID NO: 22; or~~

(iv) ~~the encoded CDR3 β comprises or consists of the amino acid sequence set forth in SEQ ID NO: 37, and the encoded CDR3 α comprises or consists of the amino acid sequence set forth in SEQ ID NO: 25.~~

~~35. The modified immune cell of any one of claims 1-34, wherein:~~

(i) ~~the encoded V β domain comprises the CDR1 β amino acid sequence of any one of SEQ ID NOs.:38, 29, 32, or 35 and/or the CDR2 β amino acid sequence of any one of SEQ ID NOs.: 39, 30, 33, or 36; and/or~~

(ii) ~~the encoded V α domain comprises the CDR1 α amino acid sequence of any one of SEQ ID NOs.:26, 17, 20, or 23, and/or the CDR2 α amino acid sequence of any one of SEQ ID NOs.:27, 18, 21, or 24.~~

~~36. The modified immune cell of any one of claims 1-35, wherein the encoded TCR V α and V β domains comprise CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of:~~

(i) ~~SEQ ID NOs.:26-28 and 38-40, respectively;~~

(ii) ~~SEQ ID NOs.:23, 27, 28, and 38-40, respectively;~~

(iii) ~~SEQ ID NOs.: 17-19 and 29-31, respectively;~~

(iv) ~~SEQ ID NOs.: 20-22 and 32-34, respectively; or~~

(v) ~~SEQ ID NOs.: 23-25 and 35-37, respectively.~~

~~37~~16. The modified immune cell of any one of claims 1-~~36~~15, wherein:

(a) the encoded TCR V β domain comprises:

(i) an amino acid sequence according to a TRBJ02-03 gene segment; and/or

(ii) ~~an amino acid sequence according to a TRBV06-05 gene segment; an amino acid sequence according to a TRBV07-09 gene segment; or~~ an amino acid sequence according to a TRBV20-01 gene segment;

(b) _____;

~~38. The modified immune cell of any one of claims 1-37, wherein the~~
encoded TCR V α domain comprises:

~~(i) an amino acid sequence according to a TRAJ43 gene segment;~~
and/or

~~(ii) an amino acid sequence according to a TRAV20-02 gene segment; an amino acid sequence according to a TRAV38DV08 gene segment;~~
~~or~~ an amino acid sequence according to a TRAV38-01 gene segment; or

~~39. The modified immune cell of claim 38, wherein:~~

~~(i) the encoded TCR V β domain comprises an amino acid sequence according to a TRBJ02-03 gene segment; and~~

~~(ii) the encoded TCR V α domain comprises an amino acid sequence according to a TRAJ43 gene segment.~~

~~40. The modified immune cell of claim 38, wherein:~~

~~(i) the encoded TCR V β domain comprises an amino acid sequence according to a TRBV06-05 gene segment; and~~

~~(ii) the encoded TCR V α domain comprises an amino acid sequence according to a TRAV20 gene segment.~~

~~41. The modified immune cell of claim 38, wherein:~~

~~(i) the encoded TCR V β domain comprises an amino acid sequence according to a TRBV07-09 gene segment; and~~

~~(ii) the encoded TCR V α domain comprises an amino acid sequence according to a TRAV38DV08 gene segment.~~

~~(c) The modified immune cell of claim 38, wherein:~~

- (i) the encoded TCR V β domain comprises an amino acid sequence according to a TRBV20-01 gene segment; and
- (ii) the encoded TCR V α domain comprises an amino acid sequence according to a TRAV38-01 gene segment.

~~4317. The modified immune cell of any one of claims 1-4216, wherein:~~

- ~~(i) —the encoded V β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:16 or 8, and the encoded V α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:12 or 4;~~
- ~~(ii) —the encoded V β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:13 or 5, and the encoded V α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:9 or 1;~~
- ~~(iii) —the encoded V β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:14 or 6, and the encoded V α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:10 or 2; or~~
- ~~(iv) —the encoded V β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:15 or 7, and the encoded V α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:11 or 3.~~

18. The modified immune cell of claim 17, wherein the encoded V β domain comprises the amino acid sequence set forth in SEQ ID NO.:16, and the encoded V α domain comprises the amino acid sequence set forth in SEQ ID NO.:12.

19. The modified immune cell of claim 17, wherein the encoded V β domain consists of the amino acid sequence set forth in SEQ ID NO.:16, and the encoded V α domain consists of the amino acid sequence set forth in SEQ ID NO.:12.

~~4420. The modified immune cell of any one of claims 1-4319, wherein the encoded binding protein further comprises:~~

- (i) a TCR α chain constant domain (C α), or a fragment thereof; and/or

- (ii) a TCR β chain constant domain (C β), or a fragment thereof.

~~45~~21. The modified immune cell of claim ~~44~~20, wherein the encoded C α comprises or consists of an amino acid sequence having at least 90% identity to ~~any one of~~ SEQ ID NOs.:~~41~~44.

~~46~~22. The modified immune cell of claim ~~44 or 45~~20 or 21, wherein the encoded C β comprises or consists of an amino acid sequence having at least 90% identity to SEQ ID NO.:45.

23. The modified immune cell of claim 22, wherein the encoded binding comprises:

- (i) a C α comprising the amino acid sequence of SEQ ID NO.:44; and
(ii) a C β comprising the amino acid sequence of SEQ ID NO.:45.

24. The modified immune cell of claim 22, wherein the encoded binding comprises:

- (i) a C α consisting of the amino acid sequence of SEQ ID NO.:44; and
(ii) a C β consisting of the amino acid sequence of SEQ ID NO.:45.

~~47~~25. The modified immune cell of any one of claims ~~44-46~~20-24, wherein the encoded binding protein comprises:

~~(i)~~—a TCR β chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:61 or 57, and a TCR α chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:53 or 49;

~~(ii)~~—a TCR β chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:58 or 54, and a TCR α chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:50 or 46;

~~(iii) — a TCR β chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:59 or 55, and a TCR α chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:51 or 47; or~~

~~(iv) — a TCR β chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:60 or 56, and a TCR α chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:52 or 48.~~

26. The modified immune cell of claim 25, wherein the encoded binding protein comprises:

(i) a TCR β chain comprising the amino acid sequence set forth in SEQ ID NO.:61; and

(ii) a TCR α chain comprising the amino acid sequence set forth in SEQ ID NO.:53.

27. The modified immune cell of claim 25, wherein the encoded binding protein comprises:

(i) a TCR β chain consisting of the amino acid sequence set forth in SEQ ID NO.:57; and

(ii) a TCR α chain consisting of the amino acid sequence set forth in SEQ ID NO.:49.

28. The modified immune cell of claim 25, wherein the heterologous polynucleotide encoding a binding protein encodes (i) the amino acid sequence set forth in SEQ ID NO.:61 and (ii) the amino acid sequence set forth in SEQ ID NO.:53.

29. The modified immune cell of claim 25, wherein the heterologous polynucleotide encoding a binding protein encodes (i) the amino acid sequence set forth in SEQ ID NO.:57 and (ii) the amino acid sequence set forth in SEQ ID NO.:49.

[4830](#). The modified immune cell of any one of claims 1-[4729](#), wherein the encoded binding protein is a TCR, a chimeric antigen receptor (CAR), or a single-chain TCR (scTCR).

[4931](#). The modified immune cell of any one of claims 1-[4830](#), wherein the immune cell is a human immune system cell, [wherein, optionally,](#)

~~50. The modified immune cell of any one of claims 1-49, wherein~~ the immune cell is a T cell, optionally a CD4⁺ T cell, a CD8⁺ T cell, a CD4⁺CD8⁻ double negative T cell, or a $\gamma\delta$ T cell, a natural killer cell, a NK-T cell, a dendritic cell, or any combination thereof, [wherein, further optionally,](#)

~~51. The modified immune cell of claim 50, wherein~~ the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, a stem cell memory T cell, or any combination thereof.

[5232](#). The modified immune cell of any one of claims 1-[5131](#), wherein the polynucleotide encoding the binding protein is codon-optimized for expression in the immune cell.

[5333](#). The modified immune cell of any one of claims 1-[5232](#), wherein the polynucleotide encoding the binding protein comprises a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in any one of SEQ ID NOs.:[65](#), [69](#), [73](#), and [7762-77](#), [wherein, optionally,](#)

~~54. The modified immune cell of claim 53, wherein~~ the polynucleotide encoding the binding protein comprises:

(i) —a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:77, and a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:[69](#);

(ii) ~~—a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:74, and a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:66;~~

(iii) ~~—a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:75, and a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:67; or~~

(iv) ~~—a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:76, and a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in SEQ ID NO.:68.~~

5534. The modified immune cell of any one of claims 1-~~5433~~, wherein the polynucleotide encoding a binding protein further comprises a polynucleotide encoding a self-cleaving peptide disposed between the V β -encoding polynucleotide and the V α -encoding polynucleotide, wherein:

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(i) ~~56. —The modified immune cell of claim 55, wherein~~ the encoded self-cleaving peptide comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.:84-88; and/or-

(ii) ~~57. —The modified immune cell of claim 55 or 56, wherein~~ the polynucleotide encoding a self-cleaving peptide comprises or consists of a polynucleotide sequence having at least 75% identity to the polynucleotide sequence set forth in any one of SEQ ID NOs.:89-93; and/or-

(iii) ~~58. —The modified immune cell of any one of claims 55-57, wherein~~ the polynucleotide encoding a binding protein has a structure from 5'-end to 3'-end of (TCR β chain-encoding polynucleotide)-(self-cleaving peptide-encoding polynucleotide)-(TCR α chain-encoding polynucleotide); and/or-

(iv) ~~59.~~ ~~The modified immune cell any one of claims 55-58, wherein the~~
polynucleotide encoding a binding protein comprises a polynucleotide having at least
75% identity to the polynucleotide sequence set forth in ~~any one of~~ SEQ ID NOs.:81-
~~or 78-80.; and/or~~

(v) ~~60.~~ ~~The modified immune cell of claim 53, wherein the~~
polynucleotide encoding a binding protein comprises a polynucleotide comprising or
consisting of the polynucleotide sequence set forth in ~~any one of~~ SEQ ID NOs.:81-
~~78-80.~~

35. The modified immune cell of claim 34, comprising a polynucleotide that
comprises the polynucleotide sequence set forth in SEQ ID NO.:81.

~~61~~36. The modified immune cell of any one of claims 1-~~60~~35, further
comprising:

(i) a heterologous polynucleotide encoding a polypeptide that comprises an
extracellular portion of a CD8 co-receptor α chain, wherein, optionally, the encoded
polypeptide is or comprises a CD8 co-receptor α chain;

(ii) a heterologous polynucleotide encoding a polypeptide that comprises an
extracellular portion of a CD8 co-receptor β chain, wherein, optionally, the encoded
polypeptide is or comprises a CD8 co-receptor β chain; or

(iii) the polynucleotide of (i) and the polynucleotide of (ii),
wherein, optionally, the host cell comprises a CD4+ T cell.

~~62~~37. The host cell of claim ~~61~~36, comprising:

(a) the heterologous polynucleotide encoding a polypeptide comprising an
extracellular portion of a CD8 co-receptor α chain wherein, optionally, the encoded
polypeptide is or comprises a CD8 co-receptor α chain;

(b) the heterologous polynucleotide encoding a polypeptide comprising an
extracellular portion of a CD8 co-receptor β chain, wherein, optionally, the encoded
polypeptide is or comprises a CD8 co-receptor β chain; and

(c) a polynucleotide encoding a self-cleaving peptide disposed between the polynucleotide of (a) and the polynucleotide of (b).

38. The modified immune cell of claim 36 or 37, comprising:

(a) the heterologous polynucleotide encoding a CD8 co-receptor β -chain;

and

(b) the heterologous polynucleotide encoding a CD8 co-receptor α -chain.

39. The modified immune cell of any one of claims 1-38, wherein the immune cell comprises a chromosomal gene knockout of a PD-1 gene; a LAG3 gene; a TIM3 gene; a CTLA4 gene; an HLA component gene; a TCR component gene; or any combination thereof, wherein, optionally,

64. The modified immune cell of claim 63, wherein (i) the chromosomal gene knockout comprises a knockout of an HLA component gene selected from an $\alpha 1$ macroglobulin gene; an $\alpha 2$ macroglobulin gene; an $\alpha 3$ macroglobulin gene; a $\beta 1$ microglobulin gene; or a $\beta 2$ microglobulin gene; or any combination thereof, and/or

65. The modified immune cell of claim 63 or 64, wherein (ii) the chromosomal gene knockout comprises a knockout of a TCR component gene selected from a TCR α variable region gene; a TCR β variable region gene; a TCR constant region gene; or any combination thereof.

40. A binding protein comprising a T cell receptor (TCR) α chain variable ($V\alpha$) domain and a TCR β chain variable ($V\beta$) domain,

wherein the $V\alpha$ and $V\beta$ domains comprise CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:26-28 and 38-40, respectively,

and wherein the binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):HLA complex.

41. The binding protein of claim 40, wherein, the HLA comprises HLA-A*0201.

42. The binding protein of claim 40 or 41, wherein:

(i) the V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:16, or 8; and/or

(ii) the V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:12, or 4.

43. The binding protein of claim 42, wherein:

(i) the V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:16; and

(ii) the V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:12.

44. The binding protein of claim 42, wherein:

(i) the V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:8; and

(ii) the V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:4.

45. The binding protein of any one of claims 40-44, wherein:

(a) the TCR V β domain comprises:

(i) an amino acid sequence according to a TRBJ02-03 gene segment; and/or

(ii) an amino acid sequence according to a TRBV20-01 gene segment;

(b) the TCR V α domain comprises an amino acid sequence according to a TRAV38-01 gene segment; or

(c)

- (i) the TCR V β domain comprises an amino acid sequence according to a TRBV20-01 gene segment, and
- (ii) the TCR V α domain comprises an amino acid sequence according to a TRAV38-01 gene segment.

46. The binding protein of any one of claims 40-45, the V β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:16 or 8, and the V α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:12 or 4.

47. The binding protein of claim 46, wherein the V β domain comprises the amino acid sequence set forth in SEQ ID NO.:16, and the V α domain comprises the amino acid sequence set forth in SEQ ID NO.:12.

48. The binding protein of claim 46, wherein the V β domain consists of the amino acid sequence set forth in SEQ ID NO.:16, and the V α domain consists of the amino acid sequence set forth in SEQ ID NO.:12.

49. The binding protein of any one of claims 40-48, further comprising:

- (i) a TCR α chain constant domain (C α), or a fragment thereof; and/or
- (ii) a TCR β chain constant domain (C β), or a fragment thereof.

50. The binding protein of claim 49, wherein the C α comprises or consists of an amino acid sequence having at least 90% identity to SEQ ID NO.:44.

51. The binding protein of claim 49 or 50, wherein the C β comprises or consists of an amino acid sequence having at least 90% identity to SEQ ID NO.:45.

52. The binding protein of claim 51, comprising:

- (i) a C α comprising the amino acid sequence of SEQ ID NO.:44; and
- (ii) a C β comprising the amino acid sequence of SEQ ID NO.:45.

53. The binding protein of claim 51, comprising:

- (i) a C α consisting of the amino acid sequence of SEQ ID NO.:44; and
- (ii) a C β consisting of the amino acid sequence of SEQ ID NO.:45.

54. The binding protein of any one of claims 49-53, comprising a TCR β chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:61 or 57, and a TCR α chain having at least 90% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:53 or 49.

55. The binding protein of claim 54, comprising:

- (i) a TCR β chain comprising the amino acid sequence set forth in SEQ ID NO.:61; and
- (ii) a TCR α chain comprising the amino acid sequence set forth in SEQ ID NO.:53.

56. The binding protein of claim 54, comprising:

- (i) a TCR β chain consisting of the amino acid sequence set forth in SEQ ID NO.:61; and
- (ii) a TCR α chain consisting of the amino acid sequence set forth in SEQ ID NO.:53.

6657. An isolated polynucleotide encoding ~~a~~the binding protein; ~~of any one of claims 50-56~~ wherein the encoded binding protein comprises a TCR V α domain and a TCR V β domain and is capable of binding to a RMFPNAPYL (SEQ ID NO.:94):HLA complex, wherein the HLA optionally comprises HLA A*0201, and wherein:

- (i) —the encoded V α domain comprises the CDR3 amino acid sequence set forth in any one of SEQ ID NOs.:28, 19, 22, or 25;
- (ii) —the encoded V β domain comprises the CDR3 amino acid sequence set forth in any one of SEQ ID NOs.:40, 31, 34, or 37;

- (iii) ~~the encoded V α domain comprises the CDR1 amino acid sequence set forth in any one of SEQ ID NOs.:26, 17, 20, or 23;~~
- (iv) ~~the encoded V β domain comprises the CDR1 amino acid sequence set forth in any one of SEQ ID NOs.:38, 32, or 35;~~
- (v) ~~the encoded V α domain comprises the CDR2 amino acid sequence set forth in any one of SEQ ID NOs.:27, 18, 21, or 24;~~
- (vi) ~~the encoded V β domain comprises the CDR2 amino acid sequence set forth in any one of SEQ ID NOs.:39, 30, 33, or 36;~~
- (vii) ~~the encoded V α domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.:4, 1-3, 12, or 9-11;~~
- (viii) ~~the encoded V β domain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.:8, 5-7, 16, or 13-15;~~
- (ix) ~~the encoded TCR V α is comprised in a TCR α chain, wherein the TCR α chain comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.:53 and 46-52;~~
- (x) ~~the encoded TCR V β is comprised in a TCR β chain, wherein the TCR β chain comprises an amino acid sequence comprising, consisting of, or having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs.:61 and 54-60; or~~
- (xi) ~~any combination of (i)-(x).~~

~~67~~58. The isolated polynucleotide of claim ~~66~~57, wherein the polynucleotide is codon-optimized for expression in a host cell, wherein, optionally, the host cell is a human T cell, NK cell, or NK-T cell~~-, and/or~~

~~68.~~ ~~The isolated polynucleotide of claim 66 or 67,~~ wherein the polynucleotide comprises a polynucleotide having at least 75% identity to the polynucleotide sequence set forth in any one of SEQ ID NOs.: ~~65, 69, 73, 77, and 81~~62-84.

~~69~~59. A vector, comprising the polynucleotide of ~~any one of claims 66-68~~claim 57 or 58; ~~wherein, optionally,~~

~~70.~~ ~~The vector of claim 69, wherein~~ the vector is a lentiviral vector or a retroviral vector.

~~71~~60. A host cell, comprising the polynucleotide of ~~any one of claims 66-68~~claim 57 or 58 and capable of expressing the encoded binding protein.

~~72~~61. A composition, comprising:

- (i) the modified immune cell of any one of claims 1-~~65~~39;
- ~~(ii)~~ the binding protein of any one of claims 40-56;
- ~~(iii)~~ the polynucleotide of ~~any one of claims 66-68~~claim 57 or 58;
- ~~(iiiiv)~~ the vector of claim ~~69 or 70~~59 or 60; and/or
- ~~(iv)~~ the host cell of claim ~~71~~61;

and a pharmaceutically acceptable carrier, excipient, or diluent.

~~73.~~ ~~The composition of claim 72, comprising:~~

- ~~(i)~~ ~~the modified immune cell of any one of claims 1-65; and~~
- ~~(ii)~~ ~~an immune cell comprising a polynucleotide that encodes a binding protein that comprises a TCR V α and a TCR V β and is capable of specifically binding to a VLDFAPPGA (SEQ ID NO.:100):HLA complex, wherein, optionally, the HLA comprises HLA A*0201, and wherein, optionally, the modified immune cell of (i) and the immune cell of (ii) are each independently selected from a T cell, a NK cell, and NK T cell.~~

~~74.~~ ~~The composition of claim 73, wherein the binding protein of the immune cell in (ii) comprises:~~

- ~~(a)~~ ~~CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:101-103 and 105-107, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino~~

acid sequence set forth in SEQ ID NO.:104 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:108;

(b)——CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:109-110 and 113-115, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:112 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:116; or

(c)——CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:117-119 and 121-123, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:120 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:124.

7562. Use of A method for treating a subject having a disease or disorder associated with WT-1 expression, comprising administering to the subject an effective amount of: (i) the modified immune cell of any one of claims 1-6539; (ii) the binding protein of any one of claims 40-56; (iii) (ii) the polynucleotide of any one of claims 66-68claim 57 or 58; (iii) (iv) the vector of claim 69 or 7059 or 60; (iv) the host cell of claim 7160; and/or (vi) the composition of any one of claim 61 in the manufacture of a medicament for treating a subject having a disease or disorder associated with WT-1 expressions 72-74, wherein the disease or disorder is a hematological malignancy or a solid cancer.

76.——The method of claim 75, comprising administering the modified immune cell of any one of claims 1-65 to a subject who has received, is receiving, or will receive an immune cell comprising a polynucleotide that encodes a binding protein that comprises a TCR V α and a TCR V β and is capable of specifically binding to a VLDFAPPGA (SEQ ID NO.:100):HLA complex, wherein, optionally, the HLA comprises HLA A*0201, and wherein, optionally, the modified immune cell and the immune cell are each independently selected from a T cell, a NK cell, and NK-T cell.

~~77. The method of claim 76, wherein the binding protein that is capable of specifically binding to the VLDFAPPGA (SEQ ID NO.:100):HLA complex comprises:~~

~~(a) CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:101-103 and 105-107, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:104 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:108;~~

~~(b) CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:109-110 and 113-115, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:112 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:116; or~~

~~(c) CDR1 α , CDR2 α , CDR3 α , CDR1 β , CDR2 β , and CDR3 β amino acid sequences of SEQ ID NOs.:117-119 and 121-123, respectively, and wherein, optionally, (1) the V α has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:120 and/or (2) the V β has at least 90% identity to, comprises, or consists of the amino acid sequence set forth in SEQ ID NO.:124.~~

~~78. The method of any one of claims 75-77, wherein the disease or disorder is a hematological malignancy or a solid cancer.~~

7963. The ~~method-use~~ of claim 7862, wherein the hematological malignancy is selected from acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloid leukemia (AML, including refractory and relapsed AML, and including acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelocytic leukemia, acute myelomonocytic leukemia (*e.g.*, with or without eosinophilia), acute monocytic leukemia, acute erythroid leukemia, and acute megakaryoblastic leukemia), chronic myelogenous leukemia (CML), chronic myelocytic leukemia, chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM, including refractory and relapsed MM)~~-, or~~

~~80.—The method of claim 78,~~ wherein the solid cancer is selected from biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, breast cancer, breast carcinoma, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, glioblastoma, melanoma, diffuse peritoneal mesothelioma, malignant pleural mesothelioma, glioma, astrocytoma, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, hepatocellular carcinoma, lung cancer, non small-cell lung cancer, malignant melanoma, osteosarcoma, ovarian cancer (*e.g.*, epithelial ovarian cancer, ovarian carcinoma), fallopian tube cancer, endometrial carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, osteogenic sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, uterine carcinosarcoma, or uterine cancer.

~~81.—The method according to any one of claims 75–80, wherein the modified immune cell is modified *ex vivo* to comprise the heterologous polynucleotide.~~

~~82.—The method according to any one of claims 75–81, wherein the modified immune cell is allogeneic, syngeneic, or autologous to the subject.~~

~~8364.~~ The ~~method according to any one of claims 75–82~~according to claim 62 or 63, wherein the modified immune cell is a hematopoietic progenitor cell or a human immune system cell~~;~~ wherein, optionally,

~~84.—The method according to claim 83, wherein~~ the immune system cell is a CD4⁺ T cell, a CD8⁺ T cell, a CD4[−] CD8[−] double negative T cell, a $\gamma\delta$ T cell, a natural killer cell, a dendritic cell, or any combination thereof~~;~~ wherein, further optionally,

~~85.—The method according to claim 84, wherein~~ the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, or any combination thereof.

~~86~~65. The ~~method-use~~ according to any one of claims ~~75-85~~~~62-64~~, wherein:
(i) ~~the method-use~~ comprises ~~administering~~ a plurality of doses of the modified immune cell ~~to the subject, wherein, optionally,~~

~~87. The method according to claim 86, wherein~~ the plurality of doses are to be administered at intervals between administrations of about two to about four weeks; and/or

~~88. The method according to any one of claims 75-87, wherein (ii)~~ the modified immune cell is to be administered to the subject at a dose of about 10^4 cells/kg to about 10^{11} cells/kg; and/or

~~89. The method according to any one of claims 75-88, wherein (iii)~~ the ~~method-use~~ further comprises ~~administering~~ a cytokine ~~to the subject, wherein,~~ optionally,

~~90. The method according to claim 89, wherein~~ the cytokine is IL-2, IL-15, IL-21, or any combination thereof; wherein, further optionally,

~~91. The method according to claim 90, wherein~~ the cytokine is IL-2 and is to be administered concurrently or sequentially with the modified immune cell; wherein, even further optionally,

~~92. The method according to claim 91, wherein~~ the cytokine is to be administered sequentially, provided that the subject ~~was~~ has been administered the modified immune cell at least three or four times before cytokine administration; and/or

~~93. The method according to any one of claims 89-92, wherein~~ the cytokine is IL-2 and is to be administered subcutaneously; and/or

~~94. The method according to any one of claims 75-93, wherein (iv)~~ the subject is further receiving immunosuppressive therapy; wherein, optionally,

~~95. The method according to claim 94, wherein~~ the immunosuppressive therapy is selected from calcineurin inhibitors, corticosteroids, microtubule inhibitors, low dose of a mycophenolic acid prodrug, or any combination thereof; and/or

~~96. The method according to any one of claims 75-95, wherein (v)~~ the subject has received a non-myeloablative or a myeloablative hematopoietic cell transplant; wherein, optionally,

~~97. The method according to claim 96, wherein~~ the subject is to be administered the modified immune cell at least three months after the non-myeloablative hematopoietic cell transplant; wherein, further optionally,

~~98. The method according to claim 97, wherein~~ the subject is to be administered the modified immune cell at least two months after the myeloablative hematopoietic cell transplant; and/or

~~99. The method of any one of claims 75-98, wherein (vi)~~ the subject has previously received therapy for AML.

~~100~~66. A composition, comprising:

- (i) the modified immune cell of any one of claims 1-~~65~~39;
- (ii) the binding protein of any one of claims 40-56;
- (iii) the polynucleotide of any one of claims 66-68claim 57 or 58;
- ~~(iiiiv)~~ the vector of claim ~~69 or 70~~59; and/or
- ~~(iv)~~ the host cell of claim ~~71~~60,

for use in ~~the treatment of a disease or disorder associated with WT 1~~
expressiontherapy.

~~101.—A composition, comprising:~~

- ~~(i) —the modified immune cell of any one of claims 1-65;~~
- ~~(ii) —the polynucleotide of any one of claims 66-68;~~
- ~~(iii) —the vector of claim 69 or 70; and/or~~
- ~~(iv) —the host cell of claim 71;~~

~~for use in the manufacture of a medicament for the treatment of a disease or disorder associated with WT-1 expression.~~

~~102.—The composition for use according to claim 100 or 101, wherein the disease or disorder is a hematological malignancy or a solid cancer.~~

~~103.—The composition for use according to claim 102, wherein the hematological malignancy is selected from acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloid leukemia (AML, including refractory and relapsed AML, and including acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelocytic leukemia, acute myelomonocytic leukemia (e.g., with or without eosinophilia), acute monocytic leukemia, acute erythroid leukemia, and acute megakaryoblastic leukemia), chronic myelogenous leukemia (CML), chronic myelocytic leukemia, chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non Hodgkin's lymphoma (NHL), or multiple myeloma (MM, including refractory and relapsed MM).~~

~~104.—The composition for use according to claim 102, wherein the solid cancer is selected from biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, breast cancer, breast carcinoma, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, glioblastoma, melanoma, diffuse peritoneal mesothelioma, malignant pleural mesothelioma, glioma, astrocytoma, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, hepatocellular carcinoma, lung cancer, non small cell lung cancer, malignant melanoma, osteosarcoma, ovarian cancer (e.g.,~~

~~epithelial ovarian cancer, ovarian carcinoma), fallopian tube cancer, endometrial carcinoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, osteogenic sarcoma, testicular germ cell tumor, urothelial cancer, uterine sarcoma, uterine carcinosarcoma, or uterine cancer.~~

~~105.—A binding protein comprising a T cell receptor (TCR) α chain variable ($V\alpha$) domain and a TCR β chain variable ($V\beta$) domain, wherein:~~

~~the $V\alpha$ domain comprises:~~

~~(i) —the CDR3 amino acid sequence ($CDR3\alpha$) according to any one of SEQ ID NOs: 28, 19, 22, or 25, or 28, or a variant thereof;~~

~~(ii) —the CDR1 amino acid sequence ($CDR1\alpha$) of any one of SEQ ID NOs: 26, 17, 20, or 23;~~

~~(iii) —the CDR2 amino acid sequence ($CDR2\alpha$) of any one of SEQ ID NOs: 27, 18, 21, or 24;~~

~~(iv) —an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 1-4 or 9-12; or~~

~~(v) —any combination of (i)–(iv); and~~

~~the $V\beta$ domain comprises:~~

~~(vi) —the CDR3 amino acid sequence ($CDR3\beta$) according to any one of SEQ ID NOs: 40, 31, 34, or 37, or a variant thereof;~~

~~(vii) —the CDR1 amino acid sequence ($CDR1\beta$) of any one of SEQ ID NOs: 38, 29, 32, or 35;~~

~~(viii) —the CDR2 amino acid sequence ($CDR2\beta$) of any one of SEQ ID NOs: 39, 30, 33, or 36;~~

~~(ix) —an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any one of SEQ ID NOs: 5-8 or 13-16; or~~

~~(x) —any combination of (vi)–(x);~~

~~wherein the binding protein is capable of binding to a RMFPNAPYL (SEQ ID NO: 94):HLA complex, wherein, optionally, the HLA comprises HLA-A*0201.~~

~~106.—The binding protein of claim 105, further comprising:~~

~~(1)—a TCR α chain constant domain ($C\alpha$), or a fragment thereof; and/or~~

~~(2)—a TCR β chain constant domain ($C\beta$), or a fragment thereof.~~

~~107.—The binding protein of claim 106, wherein the $C\alpha$ comprises or consists of the amino acid sequence of any one of SEQ ID NOs.:41-44.~~

~~108.—The binding protein of claim 106 or 107, wherein the $C\beta$ comprises or consists of the amino acid sequence of SEQ ID NO.:45.~~

~~109.—An isolated polynucleotide encoding the binding protein of any one of claims 105-108.~~

~~110.—The polynucleotide of claim 109, which is codon optimized for expression in a host cell.~~

~~111.—A modified immune cell, comprising the polynucleotide of any one of claims 109-110, wherein the polynucleotide is heterologous to the immune cell.~~