

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 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
 - (b) a TCR $V\beta$ domain comprising 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.
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.
7. The modified immune cell of any one of claims 1-6, wherein the HLA comprises HLA-A*201.
8. The modified immune cell of any one of claims 1-7, 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.
9. The modified immune cell of any one of claims 1-8, wherein 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. 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 μ M in the co-culture.

11. 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. 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.

13. 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.

14. The modified immune cell of any one of claims 1-13, wherein 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.

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.

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 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.

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.

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.

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.

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.

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.

23. The modified immune cell of any one of claims 1-22, 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.

24. The modified immune cell of any one of claims 1-23, 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.

25. The modified immune cell of any one of claims 1-24, wherein the modified immune cell is capable of killing 21% 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.

30. The modified immune cell of any one of claims 1-29, 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.

31. The modified immune cell of any one of claims 1-30, 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.

32. The modified immune cell of any one of claims 1-31, 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 of any one of SEQ ID NOs.:16, 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 of any one of SEQ ID NOs.:12, 1, 2, 3, 4, 9, 10, or 11.

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. The modified immune cell of any one of claims 1-36, wherein 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.

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.

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.

42. 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.

43. The modified immune cell of any one of claims 1-42, 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.

44. The modified immune cell of any one of claims 1-43, 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. The modified immune cell of claim 44, 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. The modified immune cell of claim 44 or 45, wherein the encoded C β comprises or consists of an amino acid sequence having at least 90% identity to SEQ ID NO.:45.

47. The modified immune cell of any one of claims 44-46, 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.

48. The modified immune cell of any one of claims 1-47, wherein the encoded binding protein is a TCR, a chimeric antigen receptor (CAR), or a single-chain TCR (scTCR).

49. The modified immune cell of any one of claims 1-48, wherein the immune cell is a human immune system cell.

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.

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.

52. The modified immune cell of any one of claims 1-51, wherein the polynucleotide encoding the binding protein is codon-optimized for expression in the immune cell.

53. The modified immune cell of any one of claims 1-52, 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.:62-77.

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.

55. The modified immune cell of any one of claims 1-54, 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.

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.

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.

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).

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.

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 or 78-80.

61. The modified immune cell of any one of claims 1-60, 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. The host cell of claim 61, 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).

63. The modified immune cell of any one of claims 1-62, 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.

64. The modified immune cell of claim 63, wherein the chromosomal gene knockout comprises a knockout of an HLA component gene selected from an α 1 macroglobulin gene; an α 2 macroglobulin gene; an α 3 macroglobulin gene; a β 1 microglobulin gene; or a β 2 microglobulin gene; or any combination thereof.

65. The modified immune cell of claim 63 or 64, wherein 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.

66. An isolated polynucleotide encoding a binding protein, 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 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. The isolated polynucleotide of claim 66, 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.

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: 62-81.

69. A vector, comprising the polynucleotide of any one of claims 66-68.

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

71. A host cell, comprising the polynucleotide of any one of claims 66-68 and capable of expressing the encoded binding protein.

72. 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;
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.

75. 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 1-65; (ii) the polynucleotide of any one of claims 66-68; (iii) the vector of claim 69 or 70; (iv) the host cell of claim 71; and/or (v) the composition of any one of claims 72-74.

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.

79. The method of claim 78, 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).

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.

83. The method according to any one of claims 75-82, wherein the modified immune cell is a hematopoietic progenitor cell or a human immune system cell.

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.

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. The method according to any one of claims 75-85, wherein the method comprises administering a plurality of doses of the modified immune cell to the subject.

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

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

89. The method according to any one of claims 75-88, wherein the method further comprises administering a cytokine to the subject.

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

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

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

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

94. The method according to any one of claims 75-93, wherein the subject is further receiving immunosuppressive therapy.

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.

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

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

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

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

100. 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 treatment of a disease or disorder associated with WT-1 expression.

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 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.