

specific T cell lines representing thousands of individual T cell clones from the peripheral repertoires of greater than 75 normal donors, a very time and labor intensive process (Chapuis *et al.*, 2013; Schmitt *et al.*, *Hum. Gene Ther.* 20:1240, 2009; Ho *et al.*, *J. Immunol. Methods* 310:40, 2006).

There is a need for alternative antigen-specific TCR immunotherapies directed against various cancers, such as leukemia and tumors. Presently disclosed embodiments address these needs and provide other related advantages.

SUMMARY

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

- (a) a V_{α} domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS:50, 32, 38, 44, 26, or 51, and a V_{β} domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS:47, 23, 29, 35, or 41;
- (b) a T cell receptor (TCR) α -chain variable (V_{α}) domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS.:50, 26, 32, 38, 44, or 51, and a TCR β -chain variable (V_{β}) domain; or
- (c) a V_{β} domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS.:47, 23, 29, 35, or 41, and a V_{α} domain; ; and

wherein the binding protein is capable of specifically binding to a MAGE-A1 peptide:HLA complex on a cell surface independent of CD8 or in the absence of CD8.

In another aspect, the present disclosure refers to a composition comprising a modified cell as disclosed herein and a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect, the present disclosure refers to a unit dose, comprising an effective amount of (i) the modified cell as disclosed herein or (ii) a composition as disclosed herein.

In another aspect, the present disclosure refers to an isolated polynucleotide encoding a binding protein having a TCR V_{α} domain and a TCR V_{β} domain, wherein the encoded binding protein is capable of specifically binding to a MAGE-A1 peptide:HLA

complex on a cell surface independent of CD8 or in the absence of CD8, the isolated polynucleotide comprising:

(a) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:121, 97, 103, 109, or 115 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:118, 94, 100, 106, or 112;

(b) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:121, 97, 103, 109, or 115, and a V_{β} -encoding polynucleotide; or

(c) a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:118, 94, 100, 106, or 112, and a V_{α} -encoding polynucleotide.

In yet another aspect, the present disclosure refers to an expression vector, comprising a polynucleotide as disclosed herein operably linked to an expression control sequence.

In yet another aspect, the present disclosure refers to a use of a modified cell as disclosed herein, a composition as disclosed herein, or a unit dose as disclosed herein in the manufacture of a medicament for treating a hyperproliferative disorder associated with MAGE-A1 expression in a human subject.

In yet another aspect, the present disclosure refers to a modified CD4⁺ T cell, comprising a heterologous polynucleotide encoding a TCR from a CD8⁺ T cell that is capable of specifically binding to a peptide antigen.

In yet another aspect, the present disclosure refers to a method for making a modified CD4⁺ T cell, comprising transducing a CD4⁺ T cell with a heterologous polynucleotide encoding a TCR from a CD8⁺ T cell that is capable of specifically binding a peptide antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B show representative data illustrating that high-affinity T cells for viral antigens are found at higher frequencies (A) than high-affinity T cells for self-antigens, which are found at very low frequencies (B).

Figures 2A and 2B show, respectively, (A) a schematic of a T cell enrichment assay performed by the inventors of the present disclosure, (B) flow cytometry data from a series of sorting experiments used to enrich for antigen-specific CD8⁺ T cells.

Figure 3 shows exemplary data from a TCR β CDR3 enrichment scheme of the present disclosure using MAGE-A1:HLA tetramers.

Figures 4A and 4B show, respectively, (A) specific binding of MAGE-A1:HLA tetramers by TCRs identified using methods of the present disclosure and (B) enrichment of MAGE-A1-specific TCRs.

Figures 5A-5C provide, respectively, (A) flow cytometry data showing MAGE-A1-specific CD8⁺ T cells of the present disclosure binding MAGE-A1:HLA tetramers, (B) cytokine production by MAGE-A1-specific CD8⁺ T cells in the absence (left) or presence (right) of antigen-expressing U266 myeloma cells, and (C) specific lysis data showing that high-affinity MAGE-A1 TCR-transduced CD8⁺ T cells of this disclosure bind antigen:MHC tetramers and kill cells presenting MAGE-A1: MHC (A*0201). Data in (C) was from a standard Cr⁵¹-release assay in which the CD8⁺ T cells were co-cultured with U266 cells alone, with exogenous interferon-gamma (IFN γ) or with exogenous MAGE-A1 peptide.

Figure 6A illustrates an immunotherapy approach according to the present disclosure in which CD4⁺ T cells are transduced to express a TCR and a CD8 co-

CLAIMS

What is claimed is:

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

(a) a V_α domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS:50, 32, 38, 44, 26, or 51, and a V_β domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS:47, 23, 29, 35, or 41;

(b) a T cell receptor (TCR) α -chain variable (V_α) domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS.:50, 26, 32, 38, 44, or 51, and a TCR β -chain variable (V_β) domain; or

(c) a V_β domain having a CDR3 amino acid sequence according to any one of SEQ ID NOS.:47, 23, 29, 35, or 41, and a V_α domain; ; and

wherein the binding protein is capable of specifically binding to a MAGE-A1 peptide:HLA complex on a cell surface independent of CD8 or in the absence of CD8.

2. The modified cell according to claim 1, wherein the encoded binding protein is capable of specifically binding to a KVLEYVIKV (SEQ ID NO.:123):human leukocyte antigen (HLA) complex with a K_d less than or equal to about 10^{-8} M.

3. The modified cell of claim 1 or 2, wherein the V_β domain of (a) is derived from a TRBV30 allele, a TRBV29 allele, or a TRBV9 allele.

4. The modified cell of claim 1 or 2, wherein the V_α domain of (b) is derived from a TRAV38-1 allele, a TRAV34 allele, a TRAV16 allele, or a TRAV5 allele.

5. The modified cell according to any one of claims 1-4, wherein the encoded V_α domain comprises an amino acid sequence that is at least about 90% identical to an amino acid sequence according to any one of SEQ ID NOS.:19, 3, 7, 11, and 15, and the encoded V_β domain

comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence according to any one of SEQ ID NOS:17, 1, 5, 9, and 13, provided that (a) at least three or four of the CDRs have no change in sequence, wherein the CDRs that do have sequence changes have only up to two amino acid substitutions, up to a contiguous five amino acid deletion, or a combination thereof, and (b) the encoded binding protein remains capable of specifically binding to a MAGE-A1 peptide:HLA cell surface complex independent, or in the absence, of CD8.

6. The modified cell according to any one of claims 1-5, wherein:

(a) the encoded V_{α} domain comprises (i) a CDR1 amino acid sequence according to any one of SEQ ID NOS:48, 24, 30, 36, and 42, and/or (ii) a CDR2 amino acid sequence according to any one of SEQ ID NOS:49, 25, 31, 37, and 43; and/or

(b) the encoded V_{β} domain comprises (iii) a CDR1 amino acid sequence according to any one of SEQ ID NOS:45, 21, 27, 33, and 39, and/or (iv) a CDR2 amino acid sequence according to any one of SEQ ID NOS:46, 22, 28, 34, and 40.

7. The modified cell according to any one of claims 1-6, wherein the encoded binding protein comprises:

(a) V_{α} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:48-50, respectively, and V_{β} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:45-47, respectively;

(b) V_{α} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:30-32, respectively, and V_{β} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:27-29, respectively;

(c) V_{α} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:36-38, respectively, and V_{β} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:33-35, respectively;

(d) V_{α} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:42-44, respectively, and V_{β} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:39-41, respectively; or

(e) V_{α} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:24-26, respectively, and V_{β} CDR1, CDR2, and CDR3 amino acid sequences according to SEQ ID NOS:21-23, respectively.

8. The modified cell according to any one of claims 1-7, wherein the encoded binding protein specifically binds to a KVLEYVIKV (SEQ ID NO.:123):HLA-A*201 complex.

9. The modified cell according to any one of claims 1-8, wherein the encoded V_{α} domain comprises or consists of an amino acid sequence according to SEQ ID NO.:19, 3, 7, 11, or 15.

10. The modified cell according to any one of claims 1-9, wherein the encoded V_{β} domain comprises or consists of an amino acid sequence according to SEQ ID NO.:17, 1, 5, 9, or 13.

11. The modified cell according to any one of claims 1-10, further comprising a heterologous polynucleotide encoding a TCR α -chain constant (C_{α}) domain having at least 90% sequence identity to an amino acid sequence according to SEQ ID NO.:20, 4, 8, 12, or 16.

12. The modified cell according to any one of claims 1-11, further comprising a heterologous polynucleotide encoding a TCR β -chain constant (C_{β}) domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence according to SEQ ID NO.:18, 2, 6, 10, or 14.

13. The modified cell according to any one of claims 1-12, wherein the encoded binding protein comprises a V_{α} domain comprising or consisting of SEQ ID NO.: 19, a V_{β} domain comprising or consisting of SEQ ID NO.: 17, a C_{α} domain comprising or consisting of SEQ ID NO.: 20, and a C_{β} domain comprising or consisting of SEQ ID NO.: 18.

14. The modified cell according to any one of claims 1-12, wherein the encoded binding protein comprises a V_{α} domain comprising or consisting of SEQ ID NO.: 7, a V_{β} domain comprising or consisting of SEQ ID NO.: 5, a C_{α} domain comprising or consisting of SEQ ID NO.: 8, and a C_{β} comprising or consisting of SEQ ID NO.: 6.

15. The modified cell according to any one of claims 1-14, wherein the encoded binding protein comprises a V_{α} domain comprising or consisting of SEQ ID NO.: 11, a V_{β} domain comprising or consisting of SEQ ID NO.: 9, a C_{α} domain comprising or consisting of SEQ ID NO.: 12, and a C_{β} domain comprising or consisting of SEQ ID NO.: 10.

16. The modified cell according to any one of claims 1-12, wherein the encoded binding protein comprises a V_{α} domain comprising or consisting of SEQ ID NO.: 15, a V_{β} domain comprising or consisting of SEQ ID NO.: 13, a C_{α} comprising or consisting of SEQ ID NO.: 16, and a C_{β} domain comprising or consisting of SEQ ID NO.: 14.

17. The modified cell according to any one of claims 1-12, wherein the encoded binding protein comprises a V_{α} domain comprising or consisting of SEQ ID NO.: 3, a V_{β} domain comprising or consisting of SEQ ID NO.: 1, a C_{α} domain comprising or consisting of SEQ ID NO.: 4, and a C_{β} domain comprising or consisting of SEQ ID NO.: 2.

18. The modified cell according to any one of claims 1-17, wherein the binding protein is a T cell receptor (TCR), an antigen-binding fragment of a TCR, or a chimeric antigen receptor.

19. The modified cell according to claim 18, wherein the TCR, the chimeric antigen receptor, or the antigen-binding fragment of the TCR is chimeric, humanized or human.

20. The modified cell according to claim 18 or 19, wherein the antigen-binding fragment of the TCR comprises a single chain TCR (scTCR).

21. The modified cell according to any one of claims 18-20, wherein the binding protein is a chimeric antigen receptor, optionally a TCR-CAR.

22. The modified cell according to any one of claims 18-20, wherein the binding protein is a TCR.

23. The modified cell according to any one of claims 1-22, wherein the modified cell is a human immune cell.

24. The modified cell according to claim 23, wherein the immune cell is a T cell, a NK cell, or a NK-T cell.

25. The modified cell according to claim 24, wherein the immune cell is a CD4⁺ T cell, a CD8⁺ T cell, or both.

26. The modified cell according to any one of claims 23-25, wherein the modified 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.

27. The modified cell according to claim 26, 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.

28. The modified cell according to claim 26, 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 a combination thereof.

29. The modified cell according to any one of claims 25-28, wherein the modified cell is a CD4+ T cell and further comprises a heterologous polynucleotide encoding at least an extracellular portion of a CD8 co-receptor.

30. The modified cell according to claim 29, wherein the polynucleotide encoding the binding protein and/or the polynucleotide encoding the at least an extracellular portion of a CD8 co-receptor is codon-optimized for expression by the modified cell.

31. A composition comprising a modified cell according to any one of claims 1-30 and a pharmaceutically acceptable carrier, diluent, or excipient.

32. A unit dose, comprising an effective amount of (i) the modified cell according to any one of claims 1-30 or (ii) a composition according to claim 31.

33. The unit dose according to claim 32, comprising at least about 30% modified CD4+ T cells, combined with (ii) a composition comprising at least about 30% modified CD8+ T cells, in about a 1:1 ratio.

34. The unit dose according to claim 33, wherein the unit dose contains substantially no naïve T cells.

35. An isolated polynucleotide encoding a binding protein having a TCR V_α domain and a TCR V_β domain, wherein the encoded binding protein is capable of specifically binding to a MAGE-A1 peptide:HLA complex on a cell surface independent of CD8 or in the absence of CD8, the isolated polynucleotide comprising:

(a) a V_α CDR3-encoding polynucleotide according to SEQ ID NO:121, 97, 103, 109, or 115 and a V_β CDR3-encoding polynucleotide according to SEQ ID NO:118, 94, 100, 106, or 112;

(b) a V_α CDR3-encoding polynucleotide according to SEQ ID NO:121, 97, 103, 109, or 115, and a V_β-encoding polynucleotide; or

(c) a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:118, 94, 100, 106, or 112, and a V_{α} -encoding polynucleotide.

36. The isolated polynucleotide of claim 35, wherein the V_{β} -encoding polynucleotide of (b) is derived from a TRBV30 allele, a TRBV29 allele, or a TRBV9 allele.

37. The isolated polynucleotide of claim 35, wherein the V_{α} -encoding polynucleotide of (c) is derived from a TRAV38-1 allele, a TRAV34 allele, a TRAV16 allele, or a TRAV5 allele.

38. The isolated polynucleotide according to any one of claims 35-37, comprising:

(a) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:121 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:118;

(b) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:103 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:100;

(c) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:109 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:106;

(d) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:115 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:112; or

(e) a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:97 and a V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:94.

39. The isolated polynucleotide according to any one of claims 35-38, further comprising:

(a) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:119, 95, 101, 107, or 113;

(b) a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:120, 96, 102, 108, or 114;

(c) a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:116, 92, 98, 104, or 110; and/or

(d) a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:117, 93, 99, 105, or 111.

40. The isolated polynucleotide according to any one of claims 35-39, comprising:

(a) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:119, a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:120, a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:121, a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:116, a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:117, and V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:118;

(b) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:101, a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:102, a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:103, a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:98, a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:99, and V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:100;

(c) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:107, a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:108, a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:109, a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:104, a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:105, and V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:106;

(d) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:113, a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:114, a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:115, a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:110, a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:111, and V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:112; or

(e) a V_{α} CDR1-encoding polynucleotide according to SEQ ID NO:95, a V_{α} CDR2-encoding polynucleotide according to SEQ ID NO:96, a V_{α} CDR3-encoding polynucleotide according to SEQ ID NO:97, a V_{β} CDR1-encoding polynucleotide according to SEQ ID NO:92, a V_{β} CDR2-encoding polynucleotide according to SEQ ID NO:93, and V_{β} CDR3-encoding polynucleotide according to SEQ ID NO:94.

41. The isolated polynucleotide according to any one of claims 35-40, wherein the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:90, 58, 66, 74, or 82, and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:88, 56, 64, 72, or 80.

42. The isolated polynucleotide according to any one of claims 35-41, wherein:

(a) the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:90 and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:88;

(b) the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:66 and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:64;

(c) the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:74 and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:72;

(d) the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:82 and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:80; or

(e) the V_α-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:58 and the V_β-encoding polynucleotide comprises a nucleotide sequence having at least 80% identity to SEQ ID NO:56.

43. The isolated polynucleotide according to claim 42, wherein:

(a) the V_α-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:90 and the V_β-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:88;

(b) the V_α-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:66 and the V_β-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:64;

(c) the V_{α} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:74 and the V_{β} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:72;

(d) the V_{α} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:82 and the V_{β} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:80; or

(e) V_{α} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:58 and the V_{β} -encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:56.

44. The isolated polynucleotide according to any one of claims 35-43, further comprising:

(a) a C_{α} -domain-encoding polynucleotide having at least 80% identity to SEQ ID NO:91, 59, 67, 75, or 83; and/or

(b) a C_{β} -domain-encoding polynucleotide having at least 80% identity to SEQ ID NO:89, 57, 65, 73, or 81.

45. The isolated polynucleotide according to claim 44, wherein the C_{α} -domain-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:91, 59, 67, 75, or 83, and the C_{β} -domain-encoding polynucleotide comprises or consists of a nucleotide sequence according to SEQ ID NO:89, 57, 65, 73, or 81.

46. The isolated polynucleotide according to claim 45, comprising:

(a) a V_{α} -encoding polynucleotide according to SEQ ID NO:90, a V_{β} -encoding polynucleotide according to SEQ ID NO:88, a C_{α} -domain-encoding polynucleotide according to SEQ ID NO:91, and a C_{β} -domain-encoding polynucleotide according to SEQ ID NO:89;

(b) a V_{α} -encoding polynucleotide according to SEQ ID NO:66, a V_{β} -encoding polynucleotide according to SEQ ID NO:64, a C_{α} -domain-encoding polynucleotide according to SEQ ID NO:67, and a C_{β} -domain-encoding polynucleotide according to SEQ ID NO:65;

- (c) a V_α-encoding polynucleotide according to SEQ ID NO:74, a V_β-encoding polynucleotide according to SEQ ID NO:72, a C_α-domain-encoding polynucleotide according to SEQ ID NO:75, and a C_β-domain-encoding polynucleotide according to SEQ ID NO:73;
- (d) a V_α-encoding polynucleotide according to SEQ ID NO:82, a V_β-encoding polynucleotide according to SEQ ID NO:80, a C_α-domain-encoding polynucleotide according to SEQ ID NO:83, and a C_β-domain-encoding polynucleotide according to SEQ ID NO:81; or
- (e) a V_α-encoding polynucleotide according to SEQ ID NO:58, a V_β-encoding polynucleotide according to SEQ ID NO:56, a C_α-domain-encoding polynucleotide according to SEQ ID NO:59, and a C_β-domain-encoding polynucleotide according to SEQ ID NO:57.

47. The isolated polynucleotide according to any one of claims 44-46, further comprising a polynucleotide encoding a self-cleaving peptide disposed between a TCR α-chain-encoding polynucleotide and a TCR β-chain-encoding polynucleotide.

48. The isolated polynucleotide according to claim 47, wherein the polynucleotide encoding a self-cleaving peptide comprises or consists of a nucleotide sequence according to any one of SEQ ID NOS.:128-132.

49. The isolated polynucleotide according to claim 47, wherein the polynucleotide encodes a self-cleaving peptide comprising or consisting of an amino acid sequence according to any one of SEQ ID NOS.:124-127.

50. An expression vector, comprising a polynucleotide according to any one of claims 35-49 operably linked to an expression control sequence.

51. The expression vector according to claim 50, wherein the vector is capable of delivering the polynucleotide to a host cell.

52. The expression vector according to claim 51, wherein the host cell is a hematopoietic progenitor cell or a human immune system cell.

53. The expression vector according to claim 52, wherein the human 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.

54. The expression vector according to claim 53, wherein the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, or any combination thereof.

55. The expression vector according to any one of claims 50-54, wherein the vector is a viral vector.

56. The expression vector according to claim 55, wherein the viral vector is a lentiviral vector or a γ -retroviral vector.

57. Use of a modified cell according to any one of claims 1-30, a composition according to claim 31, or a unit dose according to claim any one of claims 3-34 in the manufacture of a medicament for treating a hyperproliferative disorder associated with MAGE-A1 expression in a human subject.

58. The use according to claim 57, wherein the hyperproliferative disorder is a hematological malignancy or a solid cancer.

59. The use according to claim 60, wherein the hematological malignancy is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM).

60. The use according to claim 58, wherein the solid cancer is selected from non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC), ovarian cancer, malignant melanoma, colon cancer, colorectal adenocarcinoma, colorectal cancer, biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, breast cancer, cervical cancer,

desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, lung cancer, mesothelioma, osteosarcoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, or uterine cancer.

61. The use according to any one of claims 57-60, wherein the modified cell is capable of promoting an antigen-specific T cell response against a MAGE-A1 in a class I HLA-restricted manner.

62. The use according to claim 61, wherein the class I HLA-restricted response is transporter-associated with antigen processing (TAP)-independent.

63. The use according to claim 61 or 62, wherein the antigen-specific T cell response comprises at least one of a CD4+ helper T lymphocyte (Th) response and a CD8+ cytotoxic T lymphocyte (CTL) response.

64. The use according to claim 63, wherein the CTL response is directed against a cell having aberrant MAGE-A1 expression.

65. The use according to any one of claims 57-64, wherein the modified cell is modified *ex vivo*.

66. The use according to claim 65, wherein the modified cell is an allogeneic cell, a syngeneic cell, or an autologous cell.

67. The use according to claim any one of claims 57-66, wherein the modified cell is a modified human immune cell, wherein the immune cell is selected from 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.

68. The use according to claim 67, wherein the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, or any combination thereof.

69. The use according to claim 67 or 68, wherein the T cell is a CD4+ T cell.

70. The use according to claim 69, wherein the CD4+ T cell further comprises a heterologous polynucleotide encoding at least an extracellular portion of a CD8 co-receptor.

71. The use according to claim 69 or 70, further comprising that a CD8+ T cell is to be administered to the subject that is capable of specifically binding to a MAGE-A1 peptide:HLA complex on a cell surface.

72. The use according to claim 71, wherein the CD8+ T cell comprises a modified cell according to any one of claims 1-30.

73. The use according to any one of claims 57-72, wherein the modified cell is to be administered parenterally.

74. The use according to any one of claims 57-73, wherein the method comprises that a plurality of doses of the modified cell is to be administered to the subject.

75. The use according to claim 74, wherein the plurality of doses are to be administered at intervals between administrations of about two to about four weeks.

76. The use according to any one of claims 57-75, wherein the modified cell is to be administered to the subject at a dose of about 10^7 cells/m² to about 10^{11} cells/m².

77. The use according to any one of claims 57-76, wherein the method further comprises that a cytokine is to be administered.

78. The use according to claim 77, wherein the cytokine is IL-2, IL-15, IL-21, or any combination thereof.

79. The use according to claim 78, wherein the cytokine is IL-2 and is to be administered concurrently or sequentially with the modified cell.

80. The use according to claim 79, wherein the cytokine is to be administered sequentially, provided that the subject was administered the modified cell at least three or four times before cytokine administration.

81. The use according to any one of claims 78-80, wherein the cytokine is IL-2 and is to be administered subcutaneously.

82. The use according to any one of claims 57-81, wherein the subject is further receiving immunosuppressive therapy.

83. The use according to claim 82, wherein the immunosuppressive therapy is selected from calcineurin inhibitors, corticosteroids, microtubule inhibitors, low dose of a mycophenolic acid prodrug, an immune checkpoint inhibitor, or any combination thereof.

84. The use according to any one of claims 57-83, wherein a stimulatory immune checkpoint molecule is to be administered to the subject.

85. The use according to any one of claims 57-84, wherein the subject has received a non-myeloablative or a myeloablative hematopoietic cell transplant.

86. The use according to claim 85, wherein the subject is to be administered the modified cell at least three months after the non-myeloablative hematopoietic cell transplant.

87. The use according to claim 86, wherein the subject is to be administered the modified cell at least two months after the myeloablative hematopoietic cell transplant.

88. The use according to any one of claims 57-87, wherein the subject has been administered one or more of a DNA hypomethylation agent and a HDAC inhibitor.

89. A modified CD4+ T cell, comprising a heterologous polynucleotide encoding a TCR from a CD8+ T cell that is capable of specifically binding to a peptide antigen.

90. The modified CD4+ T cell according to claim 89, wherein the TCR is a high-affinity TCR.

91. The modified CD4+ T cell according to claim 89 or 90, wherein the TCR is capable of specifically binding to a peptide:antigen HLA complex on a cell surface independent of CD8 or in the absence of CD8.

92. The modified CD4+ T cell according to any one of claims 89-91, further comprising a heterologous polynucleotide encoding at least an extracellular portion of a CD8 co-receptor molecule.

93. The modified CD4+ T cell according to claim 92, wherein the heterologous polynucleotide encodes a CD8 α and a CD8 β from the CD8+ T cell.

94. The modified CD4+ T cell according to claim 92 or 93, wherein the modified CD4+ T cell is capable of eliciting a CTL response when bound to the peptide:antigen HLA complex.

95. The modified CD4+ T cell according to any one of claims 89-94, wherein the peptide antigen is from MAGE-A1.

96. A method for making a modified CD4+ T cell, comprising transducing a CD4+ T cell with a heterologous polynucleotide encoding a TCR from a CD8+ T cell that is capable of specifically binding a peptide antigen.

97. The method according to claim 96, wherein the TCR is a naturally occurring TCR.

98. The method according to claim 96 or claim 97, further comprising transducing the CD4+ T cell with a heterologous polynucleotide encoding at least an extracellular portion of a CD8 co-receptor.

99. The method according to claim 98, wherein the CD8 co-receptor comprises a CD8 α and a CD8 β from the CD8+ T cell.

100. The use of any one of claims 57-88, wherein the human subject is further receiving an anti-PD-1 antibody or an anti-PD-L1 antibody.