

Claims

1. A nucleic acid molecule comprising (i) a first nucleotide sequence encoding a recombinant T cell receptor (TCR) or an antigen binding portion thereof that specifically binds a target human protein; and (ii) a second nucleotide sequence, wherein the second nucleotide sequence or the polypeptide encoded by the second nucleotide sequence inhibits the expression of an endogenous TCR; wherein:
 - (a) the target human protein is tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR cross competes for binding to human tyrosinase with a reference anti-tyrosinase TCR, wherein the reference anti-tyrosinase TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1 ("anti-MAGE-A1 TCR"), wherein the anti-MAGE-A1 TCR cross competes for binding to human MAGE-A1 with a reference anti-MAGE-A1 TCR, wherein the reference anti-MAGE-A1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;
 - (c) the target human protein is MART1 ("anti-MART1 TCR"), wherein the anti-MART1 TCR cross competes for binding to human MART1 with a reference anti-MART1 TCR, wherein the reference anti-MART1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 21, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3 ("anti-MAGE-A3 TCR"), wherein the anti-MAGE-A3 TCR cross competes for binding to human MAGE-A3 with a reference anti-MAGE-A3 TCR, wherein the reference anti-MAGE-A3 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or

- (e) the target human protein is SSX2 ("anti-SSX2 TCR"), wherein the anti-SSX2 TCR cross competes for binding to human SSX2 with a reference anti-SSX2 TCR, wherein the reference anti-SSX2 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.
2. A nucleic acid molecule comprising (i) a first nucleotide sequence encoding a recombinant T cell receptor (TCR) or an antigen binding portion thereof that specifically binds a target human protein; and (ii) a second nucleotide sequence, wherein the second nucleotide sequence or the polypeptide encoded by the second nucleotide sequence inhibits the expression of an endogenous TCR; wherein:
- (a) target human protein is tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR binds the same epitope or an overlapping epitope of human tyrosinase as a reference anti-tyrosinase TCR, wherein the reference anti-tyrosinase TCR comprises an alpha chain and a beta chain, wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1 and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1 ("anti-MAGE-A1 TCR"), wherein the anti-MAGE-A1 TCR binds the same epitope or an overlapping epitope of human MAGE-A1 as a reference anti-MAGE-A1 TCR, wherein the reference anti-MAGE-A1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;
 - (c) the target human protein is MART1 ("anti-MART1 TCR"), wherein the anti-MART1 TCR binds the same epitope or an overlapping epitope of human MART1 as a reference anti-MART1 TCR, wherein the reference anti-MART1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 21, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;

- (d) the target human protein is MAGE-A3 ("anti-MAGE-A3 TCR"), wherein the anti-MAGE-A3 TCR binds the same epitope or an overlapping epitope of human MAGE-A3 as a reference anti-MAGE-A3 TCR, wherein the reference anti-MAGE-A3 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or
 - (e) the target human protein is SSX2 ("anti-SSX2 TCR"), wherein the anti-SSX2 TCR binds the same epitope or an overlapping epitope of human SSX2 as a reference anti-SSX2 TCR, wherein the reference anti-SSX2 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.
3. The nucleic acid molecule of claim 1 or 2, wherein:
- (a) the anti-tyrosinase TCR binds to an epitope of tyrosinase consisting of an amino acid sequence as set forth in SEQ ID NO: 51;
 - (b) the anti-MAGE-A1 TCR binds to an epitope of MAGE-A1 consisting of an amino acid sequence as set forth in SEQ ID NO: 52;
 - (c) the anti-MART1 TCR binds to an epitope of MART1 consisting of an amino acid sequence as set forth in SEQ ID NO: 53;
 - (d) the anti-MAGE-A3 TCR binds to an epitope of MAGE-A3 consisting of an amino acid sequence as set forth in SEQ ID NO: 54; or
 - (e) the anti-SSX2 TCR binds to an epitope of SSX2 consisting of an amino acid sequence as set forth in SEQ ID NO: 55.
4. The nucleic acid molecule of claim 2 or 3, wherein the epitope is complexed with an HLA class I molecule.
5. The nucleic acid molecule of claim 4, wherein the HLA class I molecule is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G allele.

6. The nucleic acid molecule of claim 4, wherein:
- (a) the target human protein is tyrosinase, and the HLA class I molecule is an HLA-C*05 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is an HLA-B*07 allele;
 - (c) the target human protein is MART1, and the HLA class I molecule is an HLA-B*18 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is an HLA-B*18 allele; or
 - (e) the target human protein is SSX2, and the HLA class I molecule is an HLA-A*02 allele.
7. The nucleic acid molecule of any one of claims 4 to 6, wherein:
- (a) the target human protein is tyrosinase, and the HLA class I molecule is selected from an HLA-C*05:01 allele, an HLA-C*05:03 allele, an HLA-C*05:04 allele, an HLA-C*05:05 allele, and an HLA-C*05:06 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is selected from an HLA-B*07:02 allele, an HLA-B*07:03 allele, an HLA-B*07:04 allele, an HLA-B*07:05 allele, and an HLA-B*07:06 allele;
 - (c) the target human protein is MART1, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele; or

- (e) the target human protein is SSX2, and the HLA class I molecule is selected from an HLA-A*02:01 allele, an HLA-A*02:02 allele, an HLA-A*02:03 allele, an HLA-A*02:04 allele, and an HLA-A*02:05 allele.
8. The nucleic acid molecule of any one of claims 4 to 7, wherein:
- (a) the target human protein is tyrosinase, and the HLA class I molecule is an HLA-C*05:01 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is an HLA-B*07:02 allele;
 - (c) the target human protein is MART1, and the HLA class I molecule is an HLA-B*18:01 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is an HLA-B*18:01 allele; or
 - (e) the target human protein is SSX2, and the HLA class I molecule is an HLA-A*02:01 allele.
9. The nucleic acid molecule of any one of claims 1 to 8, wherein the recombinant TCR or an antigen binding portion thereof that specifically binds the target human protein comprises an alpha chain and a beta chain; wherein the alpha chain comprises a variable region comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; wherein the beta chain comprises variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:
- (a) the target human protein is tyrosinase, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 7;
 - (b) the target human protein is MAGE-A1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 17;
 - (c) the target human protein is MART1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 27;

- (d) the target human protein is MAGE-A3, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 37; or
 - (e) the target human protein is SSX2, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 47.
10. The nucleic acid molecule of claim 9, wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 10;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 20;
 - (c) the target human protein is MART1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 30;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 40; or
 - (e) the target human protein is SSX2, and the alpha beta CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 50.
11. The nucleic acid molecule of any one of claims 1 to 8, wherein the recombinant TCR or an antigen binding portion thereof that specifically binds the target human protein comprises an alpha chain and a beta chain, wherein the alpha chain comprises a variable region comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; wherein the beta chain comprises variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 10;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 20;

- (c) the target human protein is MART1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 30;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 40; or
 - (e) the target human protein is SSX2, and the alpha beta CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 50.
12. The nucleic acid molecule of claim 11, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 7;
 - (b) the target human protein is MAGE-A1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 17;
 - (c) the target human protein is MART1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 27;
 - (d) the target human protein is MAGE-A3, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 37; or
 - (e) the target human protein is SSX2, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 47.
13. The nucleic acid molecule of any one of claims 9 to 12, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 5;
 - (b) the target human protein is MAGE-A1, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 15;
 - (c) the target human protein is MART1, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 25;

- (d) the target human protein is MAGE-A3, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 35; or
 - (e) the target human protein is SSX2, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 45.
14. The nucleic acid molecule of any one of claims 9 to 13, wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 8;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 18;
 - (c) the target human protein is MART1, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 28;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 38; or
 - (e) the target human protein is SSX2, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 48.
15. The nucleic acid molecule of any one of claims 9 to 14, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 6;
 - (b) the target human protein is MAGE-A1, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 16;
 - (c) the target human protein is MART1, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 26;
 - (d) the target human protein is MAGE-A3, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 36; or

- (e) the target human protein is SSX2, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 46.
16. The nucleic acid molecule of any one of claims 9 to 15, wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 9;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 19;
 - (c) the target human protein is MART1, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 29;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 39; or
 - (e) the target human protein is SSX2, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 49.
17. The nucleic acid molecule of any one of claims 9 to 16, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 1;
 - (b) the target human protein is MAGE-A1, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 11;
 - (c) the target human protein is MART1, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 31; or

- (e) the target human protein is SSX2, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 41.
18. The nucleic acid molecule of any one of claims 9 to 17, wherein:
- (a) the target human protein is tyrosinase, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 12;
 - (c) the target human protein is MART1, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 32; or
 - (e) the target human protein is SSX2, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 42.
19. The nucleic acid molecule of any one of claims 9 to 18, wherein the alpha chain further comprises a constant region, wherein the constant region is different from endogenous constant region of the alpha chain.
20. The nucleic acid molecule of any one of claims 9 to 19, wherein the alpha chain further comprises a constant region, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or

at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 1;

- (b) the target human protein is MAGE-A1, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 11;
- (c) the target human protein is MART1, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 21;
- (d) the target human protein is MAGE-A3, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 31; or
- (e) the target human protein is SSX2, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 41.

21. The nucleic acid molecule of claim 19 or 20, wherein:

- (a) the target human protein is tyrosinase, and the alpha chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 1;

- (b) the target human protein is MAGE-A1, and the alpha chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 11;
 - (c) the target human protein is MART1, and the alpha chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 31; or
 - (e) the target human protein is SSX2, and the alpha chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 41.
22. The nucleic acid molecule of any one of claims 9 to 21, wherein the beta chain further comprises a constant region, wherein the constant region is different from endogenous constant regions of the beta chain.
23. The nucleic acid molecule of any one of claims 9 to 22, wherein the beta chain further comprises a constant region, and wherein:
- (a) the target human protein is tyrosinase, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%,

at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 12;

- (c) the target human protein is MART1, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 22;
- (d) the target human protein is MAGE-A3, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 32; or
- (e) the target human protein is SSX2, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 42.

24. The nucleic acid molecule of claim 22 or 23, wherein:

- (a) the target human protein is tyrosinase, and the beta chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 2;
- (b) the target human protein is MAGE-A1, and the beta chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 12;

- (c) the target human protein is MART1, and the beta chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3, and the beta chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 32; or
 - (e) the target human protein is SSX2, and the beta chain constant region comprises an amino acid sequence comprising at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to a constant region present in the amino acid sequence set forth SEQ ID NO: 42.
25. The nucleic acid molecule of any one of claims 9 to 24, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1;
 - (b) the target human protein is MAGE-A1, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11;
 - (c) the target human protein is MART1, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31; or
 - (e) the target human protein is SSX2, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41.
26. The nucleic acid molecule of any one of claims 9 to 25, wherein:
- (a) the target human protein is tyrosinase, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;

- (b) the target human protein is MAGE-A1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;
 - (c) the target human protein is MART1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or
 - (e) the target human protein is SSX2, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.
27. The nucleic acid molecule of any one of claims 1 to 26, wherein the second nucleotide sequence is one or more siRNAs that reduce the expression of endogenous TCRs.
28. The nucleic acid molecule of claim 27, wherein the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the endogenous TCRs.
29. The nucleic acid molecule of claim 27 or 28, wherein the one or more siRNAs comprise one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 57-60.
30. The nucleic acid molecule of any one of claims 1 to 29, wherein the second nucleotide sequence encodes Cas9.
31. The nucleic acid molecule of any one of claims 1 to 30, wherein the recombinant TCR or an antigen binding portion thereof comprises an alpha chain constant region, a beta chain constant region, or both; and wherein the alpha chain constant region, the beta chain constant region, or both comprises an amino acid sequence having at least 1, at least 2, at least 3, at least 4, or at least 5 substitutions within the target sequence relative to the corresponding amino acid sequence of an endogenous TCR.
32. A vector comprising the nucleic acid molecule of any one of claims 1 to 31.
33. The vector of claim 32, which is a viral vector, a mammalian vector, or bacterial vector.

34. The vector of claim 32 or 33, which is a retroviral vector.
35. The vector of any one of claims 32 to 34, which is selected from the group consisting of an adenoviral vector, a lentivirus, a Sendai virus vector, a baculoviral vector, an Epstein Barr viral vector, a papovaviral vector, a vaccinia viral vector, a herpes simplex viral vector, a hybrid vector, and an adeno associated virus (AAV) vector.
36. The vector of any one of claims 32 to 35, which is a lentivirus.
37. A T cell receptor (TCR) or an antigen binding portion thereof comprising the alpha chain variable domain of the recombinant TCR or an antigen binding portion thereof of any one of claims 9 to 31 and the beta chain variable domain of the recombinant TCR or an antigen binding portion thereof of any one of claims 9 to 31.
38. A recombinant T cell receptor (TCR) or an antigen binding portion thereof ("recombinant TCR") that specifically binds a target human protein, wherein:
 - (a) the target human protein is tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR cross competes for binding to human tyrosinase with a reference anti-tyrosinase TCR, wherein the reference anti-tyrosinase TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1 ("anti-MAGE-A1 TCR"), wherein the anti-MAGE-A1 TCR cross competes for binding to human MAGE-A1 with a reference anti-MAGE-A1 TCR, wherein the reference anti-MAGE-A1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;
 - (c) the target human protein is MART1 ("anti-MART1 TCR"), wherein the anti-MART1 TCR cross competes for binding to human MART1 with a reference anti-MART1 TCR, wherein the reference anti-MART1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence

as set forth in SEQ ID NO: 21, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;

- (d) the target human protein is MAGE-A3 ("anti-MAGE-A3 TCR"), wherein the anti-MAGE-A3 TCR cross competes for binding to human MAGE-A3 with a reference anti-MAGE-A3 TCR, wherein the reference anti-MAGE-A3 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or
- (e) the target human protein is SSX2 ("anti-SSX2 TCR"), wherein the anti-SSX2 TCR cross competes for binding to human SSX2 with a reference anti-SSX2 TCR, wherein the reference anti-SSX2 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.

39. A recombinant T cell receptor (TCR) or an antigen binding portion thereof ("recombinant TCR") that specifically binds a target human protein, wherein:

- (a) target human protein is tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR binds the same epitope or an overlapping epitope of human tyrosinase as a reference anti-tyrosinase TCR, wherein the reference anti-tyrosinase TCR comprises an alpha chain and a beta chain, wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1 and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;
- (b) the target human protein is MAGE-A1 ("anti-MAGE-A1 TCR"), wherein the anti-MAGE-A1 TCR binds the same epitope or an overlapping epitope of human MAGE-A1 as a reference anti-MAGE-A1 TCR, wherein the reference anti-MAGE-A1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;

- (c) the target human protein is MART1 ("anti-MART1 TCR"), wherein the anti-MART1 TCR binds the same epitope or an overlapping epitope of human MART1 as a reference anti-MART1 TCR, wherein the reference anti-MART1 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 21, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3 ("anti-MAGE-A3 TCR"), wherein the anti-MAGE-A3 TCR binds the same epitope or an overlapping epitope of human MAGE-A3 as a reference anti-MAGE-A3 TCR, wherein the reference anti-MAGE-A3 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or
 - (e) the target human protein is SSX2 ("anti-SSX2 TCR"), wherein the anti-SSX2 TCR binds the same epitope or an overlapping epitope of human SSX2 as a reference anti-SSX2 TCR, wherein the reference anti-SSX2 TCR comprises an alpha chain and a beta chain, and wherein the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.
40. The recombinant TCR of claim 38 or 39, wherein:
- (a) the anti-tyrosinase TCR binds to an epitope of tyrosinase consisting of an amino acid sequence as set forth in SEQ ID NO: 51;
 - (b) the anti-MAGE-A1 TCR binds to an epitope of MAGE-A1 consisting of an amino acid sequence as set forth in SEQ ID NO: 52;
 - (c) the anti-MART1 TCR binds to an epitope of MART1 consisting of an amino acid sequence as set forth in SEQ ID NO: 53;
 - (d) the anti-MAGE-A3 TCR binds to an epitope of MAGE-A3 consisting of an amino acid sequence as set forth in SEQ ID NO: 54; or

- (e) the anti-SSX2 TCR binds to an epitope of SSX2 consisting of an amino acid sequence as set forth in SEQ ID NO: 55.
- 41. The recombinant TCR of claim 39 or 40, wherein the epitope is complexed with an HLA class I molecule.
 - 42. The recombinant TCR of claim 41, wherein the HLA class I molecule is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G allele.
 - 43. The recombinant TCR of claim 41, wherein:
 - (a) the target human protein is tyrosinase, and the HLA class I molecule is an HLA-C*05 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is an HLA-B*07 allele;
 - (c) the target human protein is MART1, and the HLA class I molecule is an HLA-B*18 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is an HLA-B*18 allele; or
 - (e) the target human protein is SSX2, and the HLA class I molecule is an HLA-A*02 allele.
 - 44. The recombinant TCR of any one of claims 41 to 43, wherein:
 - (a) the target human protein is tyrosinase, and the HLA class I molecule is selected from an HLA-C*05:01 allele, an HLA-C*05:03 allele, an HLA-C*05:04 allele, an HLA-C*05:05 allele, and an HLA-C*05:06 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is selected from an HLA-B*07:02 allele, an HLA-B*07:03 allele, an HLA-B*07:04 allele, an HLA-B*07:05 allele, and an HLA-B*07:06 allele;

- (c) the target human protein is MART1, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele; or
 - (e) the target human protein is SSX2, and the HLA class I molecule is selected from an HLA-A*02:01 allele, an HLA-A*02:02 allele, an HLA-A*02:03 allele, an HLA-A*02:04 allele, and an HLA-A*02:05 allele.
45. The recombinant TCR of any one of claims 41 to 44, wherein:
- (a) the target human protein is tyrosinase, and the HLA class I molecule is an HLA-C*05:01 allele;
 - (b) the target human protein is MAGE-A1, and the HLA class I molecule is an HLA-B*07:02 allele;
 - (c) the target human protein is MART1, and the HLA class I molecule is an HLA-B*18:01 allele;
 - (d) the target human protein is MAGE-A3, and the HLA class I molecule is an HLA-B*18:01 allele; or
 - (e) the target human protein is SSX2, and the HLA class I molecule is an HLA-A*02:01 allele.
46. The recombinant TCR of any one of claims 38 to 45, wherein the recombinant TCR or an antigen binding portion thereof that specifically binds the target human protein comprises an alpha chain and a beta chain; wherein the alpha chain comprises a variable region comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; wherein the beta chain comprises variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:

- (a) the target human protein is tyrosinase, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 7;
- (b) the target human protein is MAGE-A1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 17;
- (c) the target human protein is MART1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 27;
- (d) the target human protein is MAGE-A3, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 37; or
- (e) the target human protein is SSX2, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 47.

47. The recombinant TCR of claim 46, wherein:

- (a) the target human protein is tyrosinase, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 10;
- (b) the target human protein is MAGE-A1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 20;
- (c) the target human protein is MART1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 30;
- (d) the target human protein is MAGE-A3, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 40; or
- (e) the target human protein is SSX2, and the alpha beta CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 50.

48. The recombinant TCR of any one of claims 38 to 45, wherein the recombinant TCR or an antigen binding portion thereof that specifically binds the target human protein comprises an alpha chain and a beta chain, wherein the alpha chain comprises a variable region comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3;

wherein the beta chain comprises variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:

- (a) the target human protein is tyrosinase, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 10;
- (b) the target human protein is MAGE-A1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 20;
- (c) the target human protein is MART1, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 30;
- (d) the target human protein is MAGE-A3, and the beta chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 40; or
- (e) the target human protein is SSX2, and the alpha beta CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 50.

49. The recombinant TCR of claim 48, wherein:

- (a) the target human protein is tyrosinase, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 7;
- (b) the target human protein is MAGE-A1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 17;
- (c) the target human protein is MART1, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 27;
- (d) the target human protein is MAGE-A3, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 37; or
- (e) the target human protein is SSX2, and the alpha chain CDR3 comprises an amino acid sequence as set forth in SEQ ID NO: 47.

50. The recombinant TCR of any one of claims 46 to 49, wherein:

- (a) the target human protein is tyrosinase, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 5;
 - (b) the target human protein is MAGE-A1, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 15;
 - (c) the target human protein is MART1, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 25;
 - (d) the target human protein is MAGE-A3, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 35; or
 - (e) the target human protein is SSX2, and the alpha chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 45.
51. The recombinant TCR of any one of claims 46 to 50, wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 8;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 18;
 - (c) the target human protein is MART1, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 28;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 38; or
 - (e) the target human protein is SSX2, and the beta chain CDR1 comprises an amino acid sequence as set forth in SEQ ID NO: 48.
52. The recombinant TCR of any one of claims 46 to 51, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 6;

- (b) the target human protein is MAGE-A1, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 16;
 - (c) the target human protein is MART1, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 26;
 - (d) the target human protein is MAGE-A3, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 36; or
 - (e) the target human protein is SSX2, and the alpha chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 46.
53. The recombinant TCR of any one of claims 46 to 52, wherein:
- (a) the target human protein is tyrosinase, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 9;
 - (b) the target human protein is MAGE-A1, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 19;
 - (c) the target human protein is MART1, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 29;
 - (d) the target human protein is MAGE-A3, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 39; or
 - (e) the target human protein is SSX2, and the beta chain CDR2 comprises an amino acid sequence as set forth in SEQ ID NO: 49.
54. The recombinant TCR of any one of claims 46 to 53, wherein:
- (a) the target human protein is tyrosinase, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 1;
 - (b) the target human protein is MAGE-A1, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 11;

- (c) the target human protein is MART1, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 31; or
 - (e) the target human protein is SSX2, and the alpha chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 41.
55. The recombinant TCR of any one of claims 46 to 54, wherein:
- (a) the target human protein is tyrosinase, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 12;
 - (c) the target human protein is MART1, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 32; or
 - (e) the target human protein is SSX2, and the beta chain variable domain comprises an amino acid sequence of a variable domain present in the amino acid sequence set forth SEQ ID NO: 42.
56. The recombinant TCR of any one of claims 46 to 55, wherein the alpha chain further comprises a constant region, wherein:

- (a) the target human protein is tyrosinase, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 1;
 - (b) the target human protein is MAGE-A1, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 11;
 - (c) the target human protein is MART1, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 31; or
 - (e) the target human protein is SSX2, and the alpha chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 41.
57. The recombinant TCR of any one of claims 9 to 54, wherein the beta chain further comprises a constant region, and wherein:
- (a) the target human protein is tyrosinase, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%,

at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 2;

- (b) the target human protein is MAGE-A1, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 12;
- (c) the target human protein is MART1, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 22;
- (d) the target human protein is MAGE-A3, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 32; or
- (e) the target human protein is SSX2, and the beta chain constant region comprises an amino acid sequence having at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity to a constant region present in the amino acid sequence set forth SEQ ID NO: 42.

58. The recombinant TCR of any one of claims 46 to 57, wherein:

- (a) the target human protein is tyrosinase, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 1;
- (b) the target human protein is MAGE-A1, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 11;

- (c) the target human protein is MART1, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 21;
 - (d) the target human protein is MAGE-A3, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 31; or
 - (e) the target human protein is SSX2, and the alpha chain comprises an amino acid sequence as set forth in SEQ ID NO: 41.
59. The recombinant TCR of any one of claims 46 to 58, wherein:
- (a) the target human protein is tyrosinase, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2;
 - (b) the target human protein is MAGE-A1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 12;
 - (c) the target human protein is MART1, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 22;
 - (d) the target human protein is MAGE-A3, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 32; or
 - (e) the target human protein is SSX2, and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 42.
60. A bispecific TCR comprising a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen-binding domain comprises the TCR or an antigen-binding portion thereof of claim 37 or the recombinant TCR of any one of claims 38 to 59.
61. The bispecific TCR of claim 60, wherein the first antigen-binding domain comprises a single chain variable fragment ("scFv").
62. The bispecific TCR of claim 60 or 61, wherein the second antigen-binding domain binds specifically to a protein expressed on the surface of a T cell.

63. The bispecific TCR of any one of claims 60 to 62, wherein the second antigen-binding domain binds specifically to CD3.
64. The bispecific TCR of any one of claims 60 to 63, wherein the second antigen-binding domain comprises an scFv.
65. The bispecific TCR of any one of claims 60 to 64, wherein the first antigen-binding domain and the second antigen-binding domain are linked or associated by a covalent bond.
66. The bispecific TCR of any one of claims 60 to 65, wherein the first antigen-binding domain and the second antigen-binding domain are linked by a peptide bond.
67. A cell comprising the nucleic acid molecule of any one of claims 1 to 31, the vector of any one of claims 32 to 36, the TCR of claim 37, the recombinant TCR of any one of claims 38 to 59, or the bispecific TCR of any one of claims 60 to 66.
68. The cell of claim 67, which further expresses CD3.
69. The cell of claim 67 or 68, which is selected from the group consisting of a T cell, a natural killer (NK) cell, an natural killer T (NKT) cell, or an ILC cell.
70. A method of treating a cancer in a subject in need thereof, comprising administering to the subject the cell of any one of claims 67 to 69.
71. The method of claim 70, wherein the cancer is selected from the group consisting of melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma (NHL), primary mediastinal large B cell lymphoma (PMBC), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), transformed follicular lymphoma, splenic marginal zone lymphoma (SMZL), cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemia, acute

myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, other B cell malignancies, and combinations of said cancers.

72. The method of claim 70 or 71, wherein the cancer is relapsed or refractory.
73. The method of any one of claims 70 to 72, wherein the cancer is locally advanced.
74. The method of any one of claims 70 to 73, wherein the cancer is advanced.
75. The method of any one of claims 70 to 74, wherein the cancer is metastatic.
76. The method of any one of claims 70 to 75, wherein the cells are obtained from the subject.
77. The method of any one of claims 70 to 76, wherein the cells are obtained from a donor other than the subject.
78. The method of any one of claims 70 to 77, wherein the subject is preconditioned prior to the administering of the cells.
79. The method of any one of claims 68 to 78, wherein the preconditioning comprises administering to the subject a chemotherapy, a cytokine, a protein, a small molecule, or any combination thereof.
80. The method of claim 78 or 79, wherein the preconditioning comprises administering an interleukin.
81. The method of any one of claims 78 to 80, wherein the preconditioning comprises administering IL-2, , IL-4, IL-7, IL-9, IL-15, IL-21, or any combination thereof.

82. The method of any one of claims 78 to 81, wherein the preconditioning comprises administering a preconditioning agent selected from the group consisting of cyclophosphamide, fludarabine, vitamin C, an AKT inhibitor, ATRA, Rapamycin, or any combination thereof.
83. The method of any one of claims 78 to 82, wherein the preconditioning comprises administering cyclophosphamide, fludarabine, or both.
84. A method of engineering an antigen-targeting cell, comprising transducing a cell collected from a subject in need of a T cell therapy with the nucleic acid molecule of any one of claims 1 to 31 or the vector of any one of claims 32 to 36.
85. The method of claim 84, wherein the antigen-targeting cell further expresses CD3.
86. The method of claim 84 or 85, wherein the cell is a T cell or a natural killer (NK) cell.
87. An HLA class I molecule complexed to a peptide, wherein the HLA class I molecule comprises an $\alpha 1$ domain, an $\alpha 2$ domain, an $\alpha 3$ domain and a $\beta 2m$, and wherein the peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof.
88. The HLA class I molecule of claim 87, which is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G.
89. The HLA class I molecule of claim 87 or 88, wherein:
- (a) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 51, and the HLA class I molecule is an HLA-C;
 - (b) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 52, and the HLA class I molecule is an HLA-B;
 - (c) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 53, and the HLA class I molecule is an HLA-B;
 - (d) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 54, and the HLA class I molecule is an HLA-B; or

- (e) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 55, and the HLA class I molecule is an HLA-A.
90. The HLA class I molecule of any one of claims 87 to 89, wherein:
- (a) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 51, and the HLA class I molecule is an HLA-C*05;
 - (b) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 52, and the HLA class I molecule is an HLA-B*07;
 - (c) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 53, and the HLA class I molecule is an HLA-B*18;
 - (d) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 54, and the HLA class I molecule is an HLA-B*18; or
 - (e) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 55, and the HLA class I molecule is an HLA-A*02.
91. The HLA class I molecule of any one of claims 87 to 90, wherein:
- (a) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 51, and the HLA class I molecule is selected from an HLA-C*05:01 allele, an HLA-C*05:03 allele, an HLA-C*05:04 allele, an HLA-C*05:05 allele, and an HLA-C*05:06 allele;
 - (b) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 52, and the HLA class I molecule is selected from an HLA-B*07:02 allele, an HLA-B*07:03 allele, an HLA-B*07:04 allele, an HLA-B*07:05 allele, and an HLA-B*07:06 allele;
 - (c) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 53, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele;

- (d) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 54, and the HLA class I molecule is selected from an HLA-B*18:01 allele, an HLA-B*18:02 allele, an HLA-B*18:03 allele, an HLA-B*18:04 allele, and an HLA-B*18:05 allele; or
 - (e) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 55, and the HLA class I molecule is selected from an HLA-A*02:01 allele, an HLA-A*02:02 allele, an HLA-A*02:03 allele, an HLA-A*02:04 allele, and an HLA-A*02:05 allele.
92. The HLA class I molecule of any one of claims 87 to 91, wherein:
- (a) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 51, and the HLA class I molecule is an HLA-C*05:01;
 - (b) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 52, and the HLA class I molecule is an HLA-B*07:02;
 - (c) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 53, and the HLA class I molecule is an HLA-B*18:01;
 - (d) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 54, and the HLA class I molecule is an HLA-B*18:01; or
 - (e) the peptide consists of an amino acid sequence set forth in SEQ ID NO: 55, and the HLA class I molecule is an HLA-A*02:01.
93. The HLA class I molecule of any one of claims 87 to 92, which is a monomer.
94. The HLA class I molecule of any one of claims 87 to 92, which is a dimer.
95. The HLA class I molecule of any one of claims 87 to 92, which is a trimer.
96. The HLA class I molecule of any one of claims 87 to 92, which is a tetramer.
97. The HLA class I molecule of any one of claims 87 to 92, which is a pentamer.

98. An antigen presenting cell (APC), comprising the HLA class I molecule of any one of claims 87 to 97.
99. The APC of claims 98, wherein the HLA class I molecule is expressed on the surface of the APC.
100. A method of enriching a target population of T cells obtained from a human subject, comprising contacting the T cells with the HLA class I molecule of any one of claims 87 to 97 or the APC of claim 98 or 99, wherein following the contacting, the enriched population of T cells comprises a higher number of T cells capable of binding the HLA class I molecule relative to the number of T cells capable of binding the HLA class I molecule prior to the contacting.
101. A method of enriching a target population of T cells obtained from a human subject, comprising contacting the T cells *in vitro* with a peptide; wherein the peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof; wherein following the contacting, the enriched population of T cells comprises a higher number of T cells capable of targeting a tumor cell relative to the number of T cells capable of targeting a tumor cell prior to the contacting.
102. The method of claim 100 or 101, wherein the T cells obtained from the human subject are tumor infiltrating lymphocytes (TIL).
103. A method of treating a tumor in a subject in need thereof, comprising administering to the subject the enriched T cells of claim 100 or 101.
104. A method of enhancing cytotoxic T cell-mediated targeting of cancer cells in a subject afflicted with a cancer, comprising administering to the subject a peptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof.
105. A cancer vaccine comprising a peptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof.

106. A method of selecting a T cell capable of targeting a tumor cell, comprising contacting a population of isolated T cells *in vitro* with a peptide, wherein the peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof.
107. The method of claim 106, wherein the T cell is a tumor infiltrating lymphocytes (TIL).