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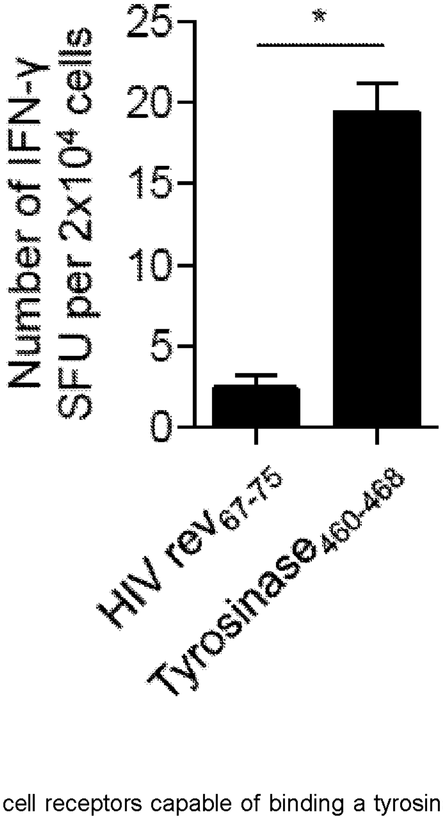
(54) Titre : RECEPTEURS DE LYMPHOCYTES T ET LEURS PROCEDES D'UTILISATION
(54) Title: T CELL RECEPTORS AND METHODS OF USE THEREOF

FIG. 2



(57) Abrégé/Abstract:
The present disclosure is directed recombinant T cell receptors capable of binding a tyrosinase epitope, a MAGA-A1 epitope, a MART1 epitope, a MAGE-A3 epitope, or an SSX2 epitope and nucleic acid molecules encoding the same. In some embodiments, the nucleic acid molecules further comprise 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. Other aspects of the disclosure are directed to vectors comprising the nucleic acid molecule and cells comprising the recombinant TCR, the nucleic acid molecule, or the vector. Still other aspects of the disclosure are directed to methods of using the same. In some embodiments, the methods comprise treating a cancer in a subject in need thereof.

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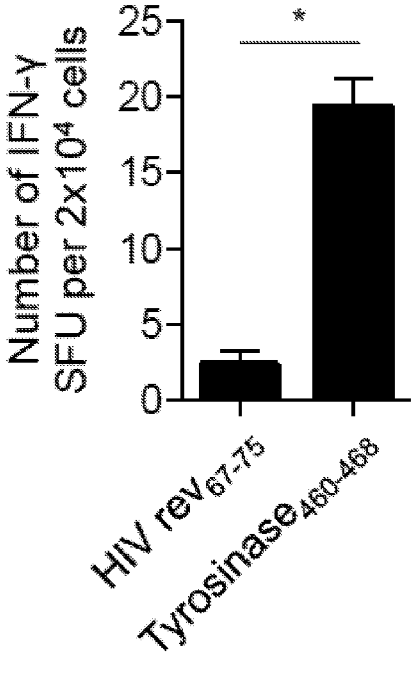
FIG. 2



(57) **Abstract:** The present disclosure is directed recombinant T cell receptors capable of binding a tyrosinase epitope, a MAGA-A1 epitope, a MART1 epitope, a MAGE-A3 epitope, or an SSX2 epitope and nucleic acid molecules encoding the same. In some embodiments, the nucleic acid molecules further comprise 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. Other aspects of the disclosure are directed to vectors comprising the nucleic acid molecule and cells comprising the recombinant TCR, the nucleic acid molecule, or the vector. Still other aspects of the disclosure are directed to methods of using the same. In some embodiments, the methods comprise treating a cancer in a subject in need thereof.

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[Continued on next page]

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T CELL RECEPTORS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the priority benefit of U.S. Provisional Application No. 62/823,487, filed March 25, 2019, which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

[0002] The content of the electronically submitted sequence listing (Name: 4285_008PC01_SeqListing_ST25.txt, Size: 69,638 bytes; and Date of Creation: March 23, 2020) is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure provides recombinant T cell receptors ("TCRs") that specifically bind a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2 and uses thereof.

BACKGROUND OF THE DISCLOSURE

[0004] Immunotherapy has immerged as a critical tool in the battle against a variety of diseases, including cancer. T cell therapies are at the forefront of immunotherapeutic development, and adoptive transfer of antitumor T cells has been shown induce clinical responses in cancer patients. Though many T cell therapies target mutated tumor antigens, the vast majority of neoantigens are not shared and are unique to each patient.

[0005] Potential non-mutated antigens out number mutated antigens by multiple orders of magnitude. The elucidation of T cell epitopes derived from shared antigens may facilitate the robust development of efficacious and safe adoptive T cell therapies that are readily available to a larger cohort of cancer patients. However, the sheer number of non-mutated antigens and the high polymorphism of HLA genes may have hampered comprehensive analyses of the specificity of antitumor T cell responses toward non-mutated antigens.

[0006] The present disclosure provides novel epitopes for the non-mutated antigens tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2 and TCRs capable of specifically binding the epitopes. These novel epitopes are associated with associated with particular HLA alleles. The use of these tumor-reactive HLA-restricted TCRs stand to widen the applicability of TCR gene therapy, particularly in immuno-oncology.

SUMMARY OF THE DISCLOSURE

[0007] Certain aspects of the present disclosure are directed to 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.

[0008] Certain aspects of the present disclosure are directed to 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.

[0009] In some embodiments, (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.

[0010] In some embodiments, the epitope is complexed with an HLA class I molecule. In some embodiments, the HLA class I molecule is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G allele. In some embodiments, (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.

[0011] In some embodiments, (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.

[0012] In some embodiments, (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.

[0013] In some embodiments, 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.

[0014] In some embodiments, (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.

[0015] In some embodiments, 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.

[0016] In some embodiments, (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.

[0017] In some embodiments, (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.

[0018] In some embodiments, (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.

[0019] In some embodiments, (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.

[0020] In some embodiments, (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.

[0021] In some embodiments, (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.

[0022] In some embodiments, (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. In some embodiments, the alpha chain further comprises a constant region, wherein the constant region is different from endogenous constant region of the alpha chain.

[0023] In some embodiments, 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.

[0024] In some embodiments, (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. In some embodiments, the beta chain further comprises a constant region, wherein the constant region is different from endogenous constant regions of the beta chain.

[0025] In some embodiments, the beta chain further comprises a constant region, 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.

[0026] In some embodiments, (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.

[0027] In some embodiments, (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.

[0028] In some embodiments, (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.

[0029] In some embodiments, the second nucleotide sequence is one or more siRNAs that reduce the expression of endogenous TCRs. In some embodiments, the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the endogenous TCRs. In some embodiments, the one or more siRNAs comprise one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 57-60. In some embodiments, the second nucleotide sequence encodes Cas9.

[0030] In some embodiments, 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.

[0031] Certain aspects of the present disclosure are directed to a vector comprising a nucleic acid molecule disclosed herein. In some embodiments, the vector is a viral vector, a mammalian vector, or bacterial vector. In some embodiments, the vector is a retroviral vector. In some embodiments, the vector 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. In some embodiments, the vector is a lentivirus.

[0032] Certain aspects of the present disclosure are directed to 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 disclosed herein and the beta chain variable domain of the recombinant TCR or an antigen binding portion thereof disclosed herein.

[0033] Certain aspects of the present disclosure are directed to 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.

[0034] Certain aspects of the present disclosure are directed to 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.

[0035] In some embodiments, (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.

[0036] In some embodiments, the epitope is complexed with an HLA class I molecule. In some embodiments, the HLA class I molecule is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G allele. In some embodiments: (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.

[0037] In some embodiments, (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.

[0038] In some embodiments, (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.

[0039] In some embodiments, 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.

[0040] In some embodiments, (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.

[0041] In some embodiments, 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.

[0042] In some embodiments, (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.

[0043] In some embodiments, (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.

[0044] In some embodiments, (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.

[0045] In some embodiments, (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.

[0046] In some embodiments, (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.

[0047] In some embodiments, (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.

[0048] In some embodiments, (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.

[0049] In some embodiments, 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.

[0050] In some embodiments, 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.

[0051] In some embodiments, (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.

[0052] In some embodiments, (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.

[0053] Certain aspects of the present disclosure are directed to a bispecific TCR comprising a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen-binding domain comprises a TCR or an antigen-binding portion thereof disclosed herein or a recombinant TCR of disclosed herein. In some embodiments, the first antigen-binding domain comprises a single chain variable fragment ("scFv"). In some embodiments, the second antigen-binding domain binds specifically to a protein expressed on the surface of a T cell. In some embodiments, the second antigen-binding domain binds specifically to CD3. In some embodiments, the second antigen-binding domain comprises an scFv. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are linked or associated by a covalent bond.In some embodiments, the first antigen-binding domain and the second antigen-binding domain are linked by a peptide bond.

[0054] Certain aspects of the present disclosure are directed to a cell comprising a nucleic acid molecule disclosed herein, a vector disclosed herein, a TCR disclosed herein, a recombinant TCR disclosed herein, or a bispecific TCR disclosed herein. In some embodiments, the cell further expresses CD3. In some embodiments, the cell 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.

[0055] Certain aspects of the present disclosure are directed to a method of treating a cancer in a subject in need thereof, comprising administering to the subject a cell disclosed herein. In some embodiments, 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.

[0056] In some embodiments, the cancer is relapsed or refractory. In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is advanced. In some embodiments, the cancer is metastatic.

[0057] In some embodiments, the cells are obtained from the subject. In some embodiments, the cells are obtained from a donor other than the subject. In some embodiments, the subject is preconditioned prior to the administering of the cells. In some embodiments, the preconditioning comprises administering to the subject a chemotherapy, a cytokine, a protein, a small molecule, or any combination thereof. In some embodiments, the preconditioning comprises administering an interleukin. In some embodiments, the preconditioning comprises administering IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, or any combination thereof. In some embodiments, 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. In some embodiments, the preconditioning comprises administering cyclophosphamide, fludarabine, or both.

[0058] Certain aspects of the present disclosure are directed to a method of engineering an antigen-targeting cell, comprising transducing a cell collected from a subject in need of a T cell therapy with a nucleic acid molecule disclosed herein or a vector disclosed herein. In some embodiments, the antigen-targeting cell further expresses CD3. In some embodiments, the cell is a T cell or a natural killer (NK) cell.

[0059] Certain aspects of the present disclosure are directed to an HLA class I molecule complexed to a peptide, wherein the HLA class I molecule comprises an α1 domain, an α2 domain, an α3 domain and a β2m, 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. In some embodiments, the HLA class I molecule is an HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, or HLA-G. In some embodiments, (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.

[0060] In some embodiments, (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.

[0061] In some embodiments, (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.

[0062] In some embodiments, (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.

[0063] In some embodiments, the HLA class I molecule is a monomer. In some embodiments, the HLA class I molecule is a dimer. In some embodiments, the HLA class I molecule is a trimer. In some embodiments, the HLA class I molecule is a tetramer. In some embodiments, the HLA class I molecule is a pentamer.

[0064] Certain aspects of the present disclosure are directed to an antigen presenting cell (APC), comprising an HLA class I molecule disclosed herein. In some embodiments, the HLA class I molecule is expressed on the surface of the APC.

[0065] Certain aspects of the present disclosure are directed to a method of enriching a target population of T cells obtained from a human subject, comprising contacting the T cells with an HLA class I molecule disclosed herein or an APC disclosed herein, 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.

[0066] Certain aspects of the present disclosure are directed to 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. In some embodiments, the T cells obtained from the human subject are tumor infiltrating lymphocytes (TIL).

[0067] Certain aspects of the present disclosure are directed to a method of treating a tumor in a subject in need thereof, comprising administering to the subject enriched T cells disclosed herein.

[0068] Certain aspects of the present disclosure are directed to 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.

[0069] Certain aspects of the present disclosure are directed to 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.

[0070] Certain aspects of the present disclosure are directed to 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. In some embodiments, the T cell is a tumor infiltrating lymphocytes (TIL).

BRIEF DESCRIPTION OF THE DRAWINGS

[0071] FIGs. 1A-1D are graphical representations of C*05:01/tyrosinase$_{460-468}$ multimer staining of melanoma TILs. The TILs were stimulated once with C*05:01-artificial APCs pulsed with the tyrosinase$_{460-468}$ peptide. Data on C*05:01/tyrosinase$_{460-468}$ (FIGs. 1A-1B) or control C*05:01/HIV rev$_{67-75}$ multimer (FIGs. 1C-1D) staining before stimulation (day 0; FIGs. 1A and 1C) and 14 days after stimulation (day 14; FIGs. 1B and 1D) are shown. The percentage of multimer$^+$ cells in CD8$^+$ T cells is shown.

[0072] FIG. 2 is a bar graph illustrating the functional assessment of C*05:01/tyrosinase$_{460-468}$ multimer-positive melanoma TILs. IFN-γ production by C*05:01-positive TILs in an HLA-C*05:01-restricted peptide-specific manner. The TILs were employed as responder cells in IFN-γ ELISPOT analysis. C*05:01-artificial APCs pulsed with the indicated peptides were used as stimulator cells. The HIV rev$_{67-75}$ peptide was employed as a control. Experiments were carried out in triplicate, and error bars depict standard deviation (SD). $^{*}P < 0.05$.

[0073] FIGs. 3A-3I are graphical representations of positive staining of Jurkat 76/CD8 cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes with a cognate multimer. Jurkat 76/CD8 cells transduced with the C*05:01/tyrosinase$_{460-468}$ TCR (FIGs. 3B, 3E, and 3H) were stained with the C*05:01/tyrosinase$_{460-468}$ multimer (FIG. 3B). The C*05:01/HIV rev$_{67-75}$ multimer (FIGs. 3D, 3E, and 3F), C*05:01/unexchanged multimer (FIGs. 3G, 3H, and 3I), and C*07:02/MAGE-A1$_{289-297}$ TCR (clone CL2; FIGs. 3C, 3F, and 3I) were used as controls, as well as Jurkat 76/CD8 not transduced with a TCR (FIGs. 3A, 3D, and 3G). The percentage of multimer^{+} CD8^{+} T cells is shown.

[0074] FIGs. 4A-4D are graphical representations of positive staining of human primary T cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes (FIGs. 4B and 4D) with a cognate multimer. Primary T cells transduced with the C*05:01/tyrosinase$_{460-468}$ TCR were stained with the C*05:01/tyrosinase$_{460-468}$ (FIG. 4B) or C*05:01/HIV rev$_{67-75}$ control multimer (FIG. 4D). Untransduced primary T cells were employed as negative controls (FIGs. 4A and 4C). The percentage of multimer^{+} CD8^{+} T cells is shown.

[0075] FIG. 5 is a bar graph illustrating that human primary T cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes react strongly with the cognate peptide presented by the target class I molecule. Primary T cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes or untransduced primary T cells (x-axis) were used as responder cells in IFN-γ ELISPOT analysis. HLA-C*05:01-transduced T2 cells (T2-C*05:01) were generated. T2 or T2-C05:01 cells pulsed with the tyrosinase$_{460-468}$ or HIV rev$_{67-75}$ peptide (control) were used as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{***}P < 0.001$.

[0076] FIG. 6A is a graphical representation illustrating that primary T cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes recognize tumor cells. Primary T cells transduced with C*05:01/tyrosinase$_{460-468}$ TCR genes or untransduced primary T cells were employed as responder cells in IFN-γ ELISPOT analysis. Malme-3M, Me275, and MCF7 cells that were either untransduced or transduced with HLA-C*05:01 or tyrosinase , as indicated, were employed as stimulator cells following treatment with 100 ng/ml IFNγ for 48 hours. Experiments were carried out in triplicate, and error bars depict SD. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

[0077] FIGs. 7A-7D are graphical representations of the expression of endogenous or transduced tyrosinase gene. The expression of endogenous or transduced tyrosinase gene in target cells was analyzed via intracellular flow cytometry following staining with anti-tyrosinase mAb (open curve) and an isotype control (filled curve).

[0078] FIGs. 8A-8D are graphical representations of the expression of ΔNGFR in target cells transduced with the full-length HLA-C*05:01 gene tagged with ΔNGFR (FIGs. 8B and 8D). Surface expression of ΔNGFR in target cells transduced with the full-length HLA-C*05:01 gene tagged with ΔNGFR was analyzed by flow cytometry following staining with an anti-NGFR mAb (open curve) and an isotype control (filled curve). ΔNGFR alone was used as a control (FIGs. 8A and 8C).

[0079] FIGs. 9A-9B are graphical representations of B*07:02/MAGE-A$1_{289\text{-}297}$ multimer staining of melanoma TILs. FIG. 9A shows staining of the TILs with B*07:02/MAGE-A$1_{289\text{-}297}$ multimer. B*07:02/EBV EBNA3$A_{379\text{-}387}$ (FIG. 9B) multimer was used as a negative control. The percentage of multimer$^+$ cells in CD8$^+$ T cells is shown.

[0080] FIG. 10 is a bar graph illustrating the functional assessment of B*07:02/MAGE-A$1_{289\text{-}297}$ multimer-positive melanoma TILs. IFN-γ production by the TILs in a B*07:02/MAGE-A$1_{289\text{-}297}$-specific manner. The TILs were employed as responder cells in IFN-γ ELISPOT analysis. B*07:02-artificial APCs pulsed with the indicated peptides were used as stimulator cells. The HIV nef$_{128\text{-}137}$ peptide was employed as a control. Experiments were carried out in triplicate, and error bars depict standard deviation (SD). $*P < 0.05$.

[0081] FIGs. 11A-11I are graphical representations of positive staining of Jurkat 76/CD8 cells transduced with B*07:02/MAGE-A$1_{289\text{-}297}$ TCR genes with a cognate multimer. Jurkat 76/CD8 cells transduced with the B*07:02/MAGE-A$1_{289\text{-}297}$ TCR (FIGs. 11B, 11E, and 11H) were stained with the B*07:02/MAGE-A$1_{289\text{-}297}$ multimer (FIG. 11B). The B*07:02/NY-ESO-$1_{60\text{-}72}$ multimer (FIGs. 11D, 11E, and 11F), B*07:02/unexchanged multimer (FIGs. 11G, 11H, and 11I), and B*07:02/NY-ESO-$1_{60\text{-}72}$ TCR (FIGs. 11C, 11F, and 11I) were employed as controls, as well as Jurkat 76/CD8 not transduced with a TCR (FIGs. 11A, 11D, and 11G). The percentage of multimer$^+$ CD8$^+$ cells is shown.

[0082] FIGs. 12A-12D are graphical representations of positive staining of human primary T cells transduced with B*07:02/MAGE-A1$_{289-297}$ TCR genes (FIGs. 12B and 12D) with a cognate multimer. Primary T cells transduced with the B*07:02/MAGE-A1$_{289-297}$ TCR were stained with the B*07:02/MAGE-A1$_{289-297}$ (FIG. 12B) or B*07:02/HIV nef$_{128-137}$ control multimer (FIG. 12D). Untransduced primary T cells were employed as negative controls (FIGs. 12A and 12C). The percentage of multimer$^+$ CD8$^+$ T cells is shown.

[0083] FIG. 13 is a bar graph illustrating that human primary T cells transduced with B*07:02/MAGE-A1$_{289-297}$ TCR genes react strongly with the cognate peptide presented by the target class I molecule. Primary T cells transduced with B*07:02/MAGE-A1$_{289-297}$ TCR genes or untransduced primary T cells (x-axis) were used as responder cells in IFN-γ ELISPOT analysis. HLA-B*07:02-transduced T2 cells (T2-B*07:02) were generated. T2 or T2-B*07:02 cells pulsed with the MAGE-A1$_{289-297}$ or HIV nef$_{128-137}$ peptide (control) were used as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{**}P < 0.01$.

[0084] FIG. 14A is a graphical representation illustrating that primary T cells transduced with B*07:02/MAGE-A1$_{289-297}$ TCR genes recognize tumor cells. Primary T cells transduced with B*07:02/MAGE-A1$_{289-297}$ TCR genes or untransduced primary T cells were employed as responder cells in IFN-γ ELISPOT analysis. Me275, SL-MEL-37, and SK-MEL-21 cells that were either untransduced or transduced with HLA-B*07:02 or MAGE-A1, as indicated (FIG. 14B), were employed as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{*}P < 0.05$, $^{**}P < 0.01$.

[0085] FIGs. 15A-15D are graphical representations of the expression of MAGE-A1 derived from endogenous or transduced full-length gene. The expression of MAGE-A1 derived from endogenous or transduced full-length gene in target cells was analyzed via intracellular flow cytometry following staining with anti-MAGE-A1 mAb (open curve) and an isotype control (filled curve).

[0086] FIGs. 16A-16D are graphical representations of the expression of ΔNGFR in target cells transduced with the full-length HLA-B*07:02 gene tagged with ΔNGFR (FIGs. 16B and 16D). Surface expression of ΔNGFR in target cells transduced with the full-length HLA-B*07:02 gene tagged with ΔNGFR was analyzed by flow cytometry following staining with an anti-NGFR mAb (open curve) and an isotype control (filled curve). ΔNGFR alone was used as a control (FIGs. 16A and 16C).

[0087] FIG. 17 is a bar graph illustrating the number of B*18:01/MART1 T cells in melanoma TILs. The TILs were used as responder cells in IFN-γ ELISPOT analysis. B*18:01-artificial APCs pulsed with overlapping peptides to cover the whole protein of MART1 were employed as stimulator cells. When stimulated with B*18:01-artificial APCs pulsed with MART1-derived overlapping peptides, the TILs showed positive responses to two adjacent peptides with the shared sequence $_{21}$YTTAEEAAGIGILTV$_{35}$ (*see also* Table 5). Experiments were carried out in triplicate, and error bars depict SD. *$P < 0.05$, ***$P < 0.001$.

[0088] FIGs. 18A-18C are graphical representations of B*18:01/MART1$_{25\text{-}33}$ multimer staining of melanoma TILs. FIG. 18B shows staining of the TILs with B*18:01/MART1$_{25\text{-}33}$ multimer. B*18:01/HIV gag$_{161\text{-}170}$ (FIG. 18C) and B*18:01/unexchanged (FIG. 18A) multimers were used as negative controls. The percentage of multimer$^+$ cells in CD8$^+$ T cells is shown.

[0089] FIG. 19 is a bar graph illustrating the functional assessment of B*18:01/MART1$_{25\text{-}33}$ multimer-positive melanoma TILs. IFN-γ production by the TILs in a B*18:01/MART1$_{25\text{-}33}$-specific manner. The TILs were employed as responder cells in IFN-γ ELISPOT analysis. B*18:01-artificial APCs pulsed with the indicated peptides were used as stimulator cells. The HIV gag$_{161\text{-}170}$ peptide was employed as a control. Experiments were carried out in triplicate, and error bars depict standard deviation (SD). ***$P < 0.001$.

[0090] FIGs. 20A-20I are graphical representations of positive staining of Jurkat 76/CD8 cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes with a cognate multimer. Jurkat 76/CD8 cells transduced with the B*18:01/MART1$_{25\text{-}33}$ TCR (FIGs. 20B, 20E, and 20H) were stained with the B*18:01/MART1$_{25\text{-}33}$ multimer (FIG. 20B). The B*18:01/MAGE-A3$_{167\text{-}176}$ multimer (FIGs. 20D, 20E, and 20F), B*18:01/MAGE-A3$_{167\text{-}176}$ TCR (FIGs. 20C, 20F, and 20I), and B*18:01/unexchanged multimer (FIGs. 20G, 20H, and 20I) were employed as controls, as well as Jurkat 76/CD8 not transduced with a TCR (FIGs. 20A, 20D, and 20G). The percentage of multimer$^+$ CD8$^+$ cells is shown.

[0091] FIGs. 21A-21D are graphical representations of positive staining of human primary T cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes (FIGs. 21B and 21D) with a cognate multimer. Primary T cells transduced with the B*18:01/MART1$_{25\text{-}33}$ TCR were stained with the B*18:01/MART1$_{25\text{-}33}$ (FIG. 21B) or B*18:01/HIV gag$_{161\text{-}170}$ control multimer (FIG. 21D). Untransduced primary T cells were employed as negative controls (FIGs. 21A and 21C). The percentage of multimer$^+$ CD8$^+$ T cells is shown.

[0092] FIG. 22 is a bar graph illustrating that human primary T cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes react strongly with the cognate peptide presented by the target class I molecule. Primary T cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes or untransduced primary T cells (x-axis) were used as responder cells in IFN-γ ELISPOT analysis. HLA-B*18:01-transduced T2 cells (T2-B*18:01) were generated. T2 or T2-B*18:01 cells pulsed with the MART1$_{25\text{-}33}$ or HIV gag$_{161\text{-}170}$ peptide (control) were used as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{**}P < 0.01$.

[0093] FIGs. 23A is a graphical representation of illustrating that primary T cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes recognize tumor cells. Primary T cells transduced with B*18:01/MART1$_{25\text{-}33}$ TCR genes or untransduced primary T cells were employed as responder cells in IFN-γ ELISPOT analysis. Malme-3M, SL-MEL-28, and A375 cells that were either untransduced or transduced with HLA-B*18:01 or MART1, as indicated (FIG. 23B), were employed as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{*}P < 0.05$, $^{**}P < 0.01$.

[0094] FIGs. 24A-24E are graphical representations of the expression of MART1 derived from endogenous or transduced full-length gene. The expression of MART1 derived from endogenous or transduced full-length gene in target cells was analyzed via intracellular flow cytometry following staining with anti-MART1 mAb (open curve) and an isotype control (filled curve).

[0095] FIGs. 25A-25F are graphical representations of the expression of ΔNGFR in target cells transduced with the full-length HLA-B*18:01 gene tagged with ΔNGFR (FIGs. 25B, 25D, and 25F). Surface expression of ΔNGFR in target cells transduced with the full-length HLA-B*18:01 gene tagged with ΔNGFR was analyzed by flow cytometry following staining with an anti-NGFR mAb (open curve) and an isotype control (filled curve). ΔNGFR alone was used as a control (FIGs. 25A, 25C, and 25E).

[0096] FIGs. 26A-26C are graphical representations of B*18:01/MAGE-A3$_{167\text{-}176}$ multimer staining of melanoma TILs. The TILs were stimulated once with B*18:01-artificial APCs pulsed with the MAGE-A3$_{167\text{-}176}$ peptide. Data on B*18:01/MAGE-A3$_{167\text{-}176}$ (FIGs. 26A-26B) or control B18:01/HIV gag$_{161\text{-}170}$ multimer (FIG. 26C) staining before stimulation (day 0; FIG. 26A) and 14 days after stimulation (day 14; FIGs. 26B-26C) are shown. The percentage of multimer^{+} cells in CD8^{+} T cells is shown.

[0097] FIG. 27 is a bar graph illustrating the functional assessment of B*18:01/MAGE-A3$_{167-176}$ multimer-positive melanoma TILs. IFN-γ production by B*18:01-positive TILs in an HLA-B*18:01-restricted peptide-specific manner. The TILs stimulated with B*18:01-artificial APCs pulsed with the MAGE-A3$_{167-176}$ peptide were employed as responder cells in IFN-γ ELISPOT analysis. HLA-B*18:01 transduced T2 cells (T2-B*18:01) were generated. T2 or T2-B*18:01 cells pulsed with the indicated peptide were used as stimulator cells. The HIV gag$_{161-170}$ peptide was employed as a control. Experiments were carried out in triplicate, and error bars depict standard deviation (SD). **$P < 0.01$, ***$P < 0.001$.

[0098] FIGs. 28A-28I are graphical representations of positive staining of Jurkat 76/CD8 cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes with a cognate multimer. Jurkat 76/CD8 cells transduced with the B*18:01/MAGE-A3$_{167-176}$ TCR (FIGs. 28B, 28E, and 28H) were stained with the B*18:01/MAGE-A3$_{167-176}$ multimer (FIG. 28B). The B*18:01/MART1$_{25-33}$ multimer (FIGs. 28D, 28E, and 28F), B*18:01/unexchanged multimer (FIGs. 28G, 28H, and 28I), and B*18:01/MART1$_{25-33}$ TCR (FIGs. 28C, 28F, and 28I) were employed as controls, as well as Jurkat 76/CD8 not transduced with a TCR (FIGs. 28A, 28D, and 28G). The percentage of multimer$^+$ CD8$^+$ cells is shown.

[0099] FIGs. 29A-29D are graphical representations of positive staining of human primary T cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes (FIGs. 29B and 29D) with a cognate multimer. Primary T cells transduced with the B*18:01/MAGE-A3$_{167-176}$ TCR were stained with the B*18:01/MAGE-A3$_{167-176}$ (FIG. 29B) or B18:01/HIV gag$_{161-170}$ control multimer (FIG. 29D). Untransduced primary T cells were employed as negative controls (FIGs. 29A and 29C). The percentage of multimer$^+$ CD8$^+$ T cells is shown.

[0100] FIG. 30 is a bar graph illustrating that human primary T cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes react strongly with the cognate peptide presented by the target class I molecule. Primary T cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes or untransduced primary T cells (x-axis) were used as responder cells in IFN-γ ELISPOT analysis. T2 cells pulsed with the MAGE-A3$_{167-176}$ or HIV gag$_{161-170}$ peptide (control) were used as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. **$P < 0.01$.

[0101] FIG. 31A is a graphical representation illustrating that primary T cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes recognize tumor cells. Primary T cells transduced with B*18:01/MAGE-A3$_{167-176}$ TCR genes or untransduced primary T cells were employed as responder cells in IFN-γ ELISPOT analysis. SK-MEL-28 and HEK293T cells that were either untransduced or transduced with HLA-B*07:02 and/or MAGE-A1, as indicated (FIG. 31B), were employed as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $*P < 0.05$, $***P < 0.001$.

[0102] FIG. 32 is a graphical representation of the expression of MAGE-A3 derived from endogenous or transduced full-length gene. The expression of MAGE-A3 derived from endogenous or transduced full-length gene in target cells was evaluated by Western blot analysis with an anti-MAGE-A3 pAb. β-actin expression was employed as a positive control.

[0103] FIGs. 33A-33D are graphical representations of the expression of ΔNGFR in target cells transduced with the full-length HLA-B*18:01 gene tagged with ΔNGFR (FIGs. 33B and 33D). Surface expression of ΔNGFR in target cells transduced with the full-length HLA-B*18:01 gene tagged with ΔNGFR was analyzed by flow cytometry following staining with an anti-NGFR mAb (open curve) and an isotype control (filled curve). ΔNGFR alone was used as a control (FIGs. 33A and 33C).

[0104] FIGs. 34A-34B are graphical representations of A*02:01/SSX2$_{41-49}$ multimer staining of melanoma TILs. FIG. 34A shows staining of the TILs with A*02:01/SSX2$_{41-49}$ multimer. A*02:01/HTLV-1 tax$_{11-19}$ (FIG. 34B) multimer was used as a negative control. The percentage of multimer$^+$ cells in CD8$^+$ T cells is shown.

[0105] FIG. 35 is a bar graph illustrating the functional assessment of A*02:01/SSX2$_{41-49}$ multimer-positive melanoma TILs. IFN-γ production by the TILs in an A*02:01/SSX2$_{41-49}$-specific manner. The TILs were employed as responder cells in IFN-γ ELISPOT analysis. T2 cells pulsed with the indicated peptides were used as stimulator cells. The HTLV-1 tax$_{11-19}$ peptide was employed as a control. Experiments were carried out in triplicate, and error bars depict standard deviation (SD). $**P < 0.01$.

[0106] FIGs. 36A-36I are graphical representations of positive staining of Jurkat 76/CD8 cells transduced with A*02:01/SSX2$_{41-49}$ TCR genes with a cognate multimer. Jurkat 76/CD8 cells transduced with the A*02:01/SSX2$_{41-49}$ TCR (FIGs. 36B, 36E, and 36H) were stained with the A*02:01/SSX2$_{41-49}$ multimer (FIG. 36B). The A*02:01/NY-ESO-1$_{157-165}$ multimer (FIGs. 36D, 36E, and 36F), A*02:01/unexchanged multimer (FIGs. 36G, 36H, and 36I), and A*02:01/NY-ESO-1$_{157-165}$ TCR (clone 1G4LY; FIGs. 36C, 36F, and 36I) were employed as controls, as well as Jurkat 76/CD8 not transduced with a TCR (FIGs. 36A, 36D, and 36G). The percentage of multimer$^+$ CD8$^+$ cells is shown.

[0107] FIGs. 37A-37D are graphical representations of positive staining of human primary T cells transduced with A*02:01/SSX2$_{41\text{-}49}$ TCR genes with a cognate multimer. Primary T cells transduced with the A*02:01/SSX2$_{41\text{-}49}$ TCR (FIGs. 37B and 37D) were stained with the A*02:01/SSX2$_{41\text{-}49}$ (FIG. 37B) or A*02:01/HTLV-1 tax$_{11\text{-}19}$ control multimer (FIG. 37D). Untransduced primary T cells were employed as negative controls (FIGs. 37A and 37C). The percentage of multimer$^+$ CD8$^+$ T cells is shown.

[0108] FIG. 38 is a bar graph illustrating that human primary T cells transduced with A*02:01/SSX2$_{41\text{-}49}$ TCR genes react strongly with the cognate peptide presented by the target class I molecule. Primary T cells transduced with A*02:01/SSX2$_{41\text{-}49}$ TCR genes or untransduced primary T cells (x-axis) were used as responder cells in IFN-γ ELISPOT analysis. T2 cells pulsed with the SSX2$_{41\text{-}49}$ or HTLV-1 tax$_{11\text{-}19}$ peptide (control) were used as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{**}P < 0.01$.

[0109] FIG. 39A is a graphical representation illustrating that primary T cells transduced with A*02:01/SSX2$_{41\text{-}49}$ TCR genes recognize tumor cells. Primary T cells transduced with A*02:01/SSX2$_{41\text{-}49}$ TCR genes or untransduced primary T cells were employed as responder cells in IFN-γ ELISPOT analysis. SK-MEL-21, SL-MEL-37, and SK-MEL-28 cells that were either untransduced or transduced with HLA-A*02:01 and/or SSX2, as indicated (FIG. 39B), were employed as stimulator cells. Experiments were carried out in triplicate, and error bars depict SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

[0110] FIG. 40 is a graphical representation of the expression of SSX2 derived from endogenous or transduced full-length gene. The expression of SSX2 derived from endogenous or transduced full-length gene in target cells was evaluated by Western blot analysis with an anti-SSX2 pAb. β-actin expression was employed as a positive control.

[0111] FIGs. 41A-41D are graphical representations of the expression of HLA-A2 derived from endogenous or transduced full-length HLA-A*02:01 gene in target cells. Surface expression of HLA-A2 derived from endogenous or transduced full-length HLA-A*02:01 in target cells was analyzed via flow cytometry following staining with an anti-HLA-A2 mAb (open curve) and an isotype control (filled curve).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0112] The present disclosure is directed to TCRs or antigen binding portions thereof that specifically bind to an epitope on a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2, nucleic acid molecules that encode the same, and cells that comprise the TCR or the nucleic acid molecule. Some aspects of the present disclosure are directed to methods of treating a caner in a subject in need thereof, comprising administering to the subject the cell. Other aspects of the present disclosure are directed to HLA class I molecules complexed to a peptide comprising the tyrosinase, MAGE-A1, MART1, MAGE-A3, or SSX2 epitope.

I. Terms

[0113] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0114] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0115] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0116] The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 10 percent, up or down (higher or lower).

[0117] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0118] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0119] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0120] "Administering" refers to the physical introduction of an agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. In some embodiments, the formulation is administered via a non-parenteral route, *e.g.*, orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0121] The term "T cell receptor" (TCR), as used herein, refers to a heteromeric cell-surface receptor capable of specifically interacting with a target antigen. As used herein, "TCR" includes but is not limited to naturally occurring and non-naturally occurring TCRs; full-length TCRs and antigen binding portions thereof; chimeric TCRs; TCR fusion constructs; and synthetic TCRs. In human, TCRs are expressed on the surface of T cells, and they are responsible for T cell recognition and targeting of antigen presenting cells. Antigen presenting cells (APCs) display fragments of foreign proteins (antigens) complexed with the major histocompatibility complex (MHC; also referred to herein as complexed with an HLA molecule, *e.g.*, an HLA class 1 molecule). A TCR recognizes and binds to the antigen:HLA complex and recruits CD3 (expressed by T cells), activating the TCR. The activated TCR initiates downstream signaling and an immune response, including the destruction of the EPC.

[0122] In general, a TCR can comprise two chains, an alpha chain and a beta chain (or less commonly a gamma chain and a delta chain), interconnected by disulfide bonds. Each chain comprises a variable domain (alpha chain variable domain and beta chain variable domain) and a constant region (alpha chain constant region and beta chain constant region). The variable domain is located distal to the cell membrane, and the variable domain interacts with an antigen. The constant region is located proximal to the cell membrane. A TCR can further comprises a transmembrane region and a short cytoplasmic tail. As used herein, the term "constant region" encompasses the transmembrane region and the cytoplasmic tail, when present, as well as the traditional "constant region."

[0123] The variable domains can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each alpha chain variable domain and beta chain variable domain comprises three CDRs and four FRs: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Each variable domain contains a binding domain that interacts with an antigen. Though all three CDRs on each chain are involved in antigen binding, CDR3 is believed to be the primary antigen binding region. CDR1 is also interacts with the antigen, while CD2 is believed to primarily recognize the HLA complex.

[0124] Where not expressly stated, and unless the context indicates otherwise, the term "TCR" also includes an antigen-binding fragment or an antigen-binding portion of any TCR disclosed herein, and includes a monovalent and a divalent fragment or portion, and a single chain TCR. The term "TCR" is not limited to naturally occurring TCRs bound to the surface of a T cell. As used herein, the term "TCR" further refers to a TCR described herein that is expressed on the surface of a cell other than a T cell (*e.g.*, a cell that naturally expresses or that is modified to express CD3, as described herein), or a TCR described herein that is free from a cell membrane (*e.g.*, an isolated TCR or a soluble TCR).

[0125] An "antigen binding molecule," "portion of a TCR," or "TCR fragment" refers to any portion of an TCR less than the whole. An antigen binding molecule can include the antigenic complementarity determining regions (CDRs).

[0126] An "antigen" refers to any molecule, *e.g.*, a peptide, that provokes an immune response or is capable of being bound by a TCR. An "epitope," as used herein, refers to a portion of a polypeptide that provokes an immune response or is capable of being bound by a TCR. The immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. A person of skill in the art would readily understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. An antigen and/or an epitope can be endogenously expressed, *i.e.* expressed by genomic DNA, or can be recombinantly expressed. An antigen and/or an epitope can be specific to a certain tissue, such as a cancer cell, or it can be broadly expressed. In addition, fragments of larger molecules can act as antigens. In one embodiment, antigens are tumor antigens. An epitope can be present in a longer polypeptide (*e.g.*, in a protein), or an epitope can be present as a fragment of a longer polypeptide. In some embodiments, an epitope is complexed with a major histocompatibility complex (MHC; also referred to herein as complexed with an HLA molecule, *e.g.*, an HLA class 1 molecule).

[0127] "Tyrosinase" or "TYR" (UniProtKB - P14679), as used herein, refers to a copper-containing oxidase that functions in the formation of pigments such as melanins and other polyphenolic compounds. Tyrosinase catalyzes the initial and rate limiting step in the cascade of reactions leading to melanin production from tyrosine. In addition to hydroxylating tyrosine to DOPA (3,4-dihydroxyphenylalanine), tyrosinase also catalyzes the oxidation of DOPA to DOPA-quinone, and possibly the oxidation of DHI (5,6-dihydroxyindole) to indole-5,6 quinone. Tyrosinase is expressed in the retina, skin, heart, aorta, mouth, and various other organs in the human body. The canonical tyrosinase amino acid sequence (SEQ ID NO: 89) is shown in Table 1.

[0128] "Melanoma-associated antigen 1" or "MAGE-A1" (UniProtKB - P43355), as used herein, refers to a tumor antigen with expression in numerous cancer types, including melanoma, head and neck squamous cell carcinoma, lung carcinoma, and bread carcinoma. MAGE-A1 is not expressed in normal tissues other than the testes. MAGE-A1 is believed to be involved in transcriptional regulation through interaction with SNW1 and recruiting histone deactelyase HDAC1. MAGE-A1 is believed to also inhibit notch intracellular domain (NICD) transactivation and to potentially play a role in embryonal development and tumor transformation or aspects of tumor progression. The MAGE-A1 amino acid sequence (SEQ ID NO: 90) is shown in Table 1.

[0129] "MART1," "MART-1," or "Melanoma antigen recognized by T-cells 1" (UniProtKB - Q16655), as used herein, refers to an antigen involved in melanosome biogenesis by ensuring the stability of GPR143. MART1 plays a vital role in the expression, stability, trafficking, and processing of melanocyte protein PMEL, which is critical to the formation of stage II melanosomes. MART1 is expressed in melanoma cells, malanocytes, and in the retina. The MART1 amino acid sequence (SEQ ID NO: 91) is shown in Table 1.

[0130] "MAGE-A3" or "Melanoma-associated antigen 3" (UniProtKB - P43357), as used herein, refers to an antigen believed to enhance ubiquitin ligase activity of RING-type zinc finger-containing E3 ubiquitin-protein ligases. MAGE-A3 may also act to enhance ubiquitin ligase activity of TRIM28 and stimulate p53/TP53 ubiquitination by TRIM28. MAGE-A3 is also believed to act through recruitment and/or stabilization of the Ubl-conjugating enzyme (E2) at the E3: substrate complex. MAGE-A3 may also play a role in embryonal development and tumor transformation or aspects of tumor progression. *In vitro* expression of MAGE-A3 promotes cell viability in melanoma cell lines. MAGE-A3 is expressed in numerous cancer types, including melanoma, head and neck squamous cell carcinoma, lung carcinoma, and bread carcinoma. MAGE-A3 is not expressed in normal tissues other than the testes and the placenta. The MAGE-A3 amino acid sequence (SEQ ID NO: 92) is shown in Table 1.

[0131] "SSX2" or "protein SSX2" (UniProtKB - Q16385), as used herein, is an antigen that is expressed in rhabdomyosarcoma and fibrosarcoma cell lines. SSX2 is also expressed at high levels in the testis and at low levels in the thyroid. The function of SSX2 is not clear, though it is speculated that SSX2 may act as a modulator of transcription. The SSX2 amino acid sequence (SEQ ID NO: 93) is shown in Table 1.

Table 1. Target Protein Amino Acid Sequences

Target Protein	Amino Acid Sequence
Tyrosinase	MLLAVLYCLLWSFQTSAGHFPRACVSSKNLMEKECCPPWSGDRSPCGQLSGRGSCQNILLS NAPLGPQFPFTGVDDRESWPSVFYNRTCQCSGNFMGFNCGNCKFGFWGPNCTERRLLVRR NIFDLSAPEKDKFFAYLTLAKHTISSDYVIPIGTYGQMKNGSTPMFNDINIYDLFVWMHYYV SMDALLGGSEIWRDIDFAHEAPAFLPWHRLFLLRWEQEIQKLTGDENFTIPYWDWRDAEK CDICTDEYMGGQHPTNPNLLSPASFFSSWQIVCSRLEEYNSHQSLCNGTPEGPLRRNPGNHD KSRTPRLPSSADVEFCLSLTQYESGSMDKAANFSFRNTLEGFASPLTGIADASQSSMHNALH

	IYMNGTMSQVQGSANDPIFLLHHAFVDSIFEQWLRRHRPLQEVYPEANAPIGHNRESYMVPFIPLYRNGDFFISSKDLGYDYSYLQDSDPDSFQDYIKSYLEQASRIWSWLLGAAMVGAVLTALLAGLVSLLCRHKRKQLPEEKQPLLMEKEDYHSLYQSHL **(SEQ ID NO: 89)**
MAGE-A1	MSLEQRSLHCKPEEALEAQQEALGLVCVQAATSSSSPLVLGTLEEVPTAGSTDPPQSPQGASAFPTTINFTRQRQPSEGSSSREEEGPSTSCILESLFRAVITKKVADLVGFLLLKYRAREPVTKAEMLESVIKNYKHCFPEIFGKASESLQLVFGIDVKEADPTGHSYVLVTCLGLSYDGLLGDNQIMPKTGFLIIVLVMIAMEGGHAPEEEIWEELSVMEVYDGREHSAYGEPRKLLTQDLVQEKYLEYRQVPDSDPARYEFLWGPRALAETSYVKVLEYVIKVSARVRFFFPSLREAALREEEEGV **(SEQ ID NO: 90)**
MART1	MPREDAHFIYGYPKKGHGHSYTTAEEAAGIGILTVILGVLLLIGCWYCRRRNGYRALMDKSLHVGTQCALTRRCPQEGFDHRDSKVSLQEKNCEPVVPNAPPAYEKLSAEQSPPPYSP **(SEQ ID NO: 91)**
MAGE-A3	MPLEQRSQHCKPEEGLEARGEALGLVGAQAPATEEQEAASSSSTLVEVTLGEVPAAESPDPPQSPQGASSLPTTMNYPLWSQSYEDSSNQEEEGPSTFPDLESEFQAALSRKVAELVHFLLLKYRAREPVTKAEMLGSVVGNWQYFFPVIFSKASSSLQLVFGIELMEVDPIGHLYIFATCLGLSYDGLLGDNQIMPKAGLLIIVLAIIAREGDCAPEEKIWEELSVLEVFEGREDSILGDPKKLLTQHFVQENYLEYRQVPGSDPACYEFLWGPRALVETSYVKVLHHMVKISGGPHISYPPLHEWVLREGEE **(SEQ ID NO: 92)**
SSX2	MNGDDAFARRPTVGAQIPEKIQKAFDDIAKYFSKEEWEKMKASEKIFYVYMKRKYEAMTKLGFKATLPPFMCNKRAEDFQGNDLDNDPNRGNQVERPQMTFGRLQGISPKIMPKKPAEEGNDSEEVPEASGPQNDGKELCPPGKPTTSEKIHERSGPKRGEHAWTHRLRERKQLVIYEEISDPEEDDE **(SEQ ID NO: 93)**

[0132] The term "HLA," as used herein, refers to the human leukocyte antigen. HLA genes encode the major histocompatibility complex (MHC) proteins in humans. MHC proteins are expressed on the surface of cells, and are involved in activation of the immune response. HLA class I genes encode MHC class I molecules, which are expressed on the surface of cells in complex with peptide fragments (antigens) of self or non-self proteins. T cells expressing TCR and CD3 recognize the antigen:MHC class I complex and initiate an immune response to target and destroy antigen presenting cells displaying non-self proteins.

[0133] As used herein, an "HLA class I molecule" or "HLA class I molecule" refers to a protein product of a wild-type or variant HLA class I gene encoding an MHC class I molecule. Accordingly, "HLA class I molecule" and "MHC class I molecule" are used interchangeably herein.

[0134] The MHC Class I molecule comprises two protein chains: the alpha chain and the β2-microglobulin (β2m) chain. Human β2m is encoded by the B2M gene. The amino acid sequence of β2m is set forth in SEQ ID NO: 56 (Table 2). The alpha chain of the MHC Class I molecule is encoded by the HLA gene complex. The HLA complex is located within the 6p21.3 region on the short arm of human chromosome 6 and contains more than 220 genes of diverse function. The HLA gene are highly variant, with over 20,000 HLA alleles and related alleles, including over 15,000 HLA Class I alleles, known in the art, encoding thousands of HLA proteins, including over 10,000 HLA Class I proteins (*see,* *e.g.*, hla.alleles.org, last visited February 27, 2019). There are at least three genes in the HLA complex that encode an MHC Class I alpha chain protein: HLA-A, HLA-B, and HLA-C. In addition, HLA-E, HLA-F, and HLA-G encode proteins that associate with the MHC Class I molecule.

Table 2. Amino Acid Sequence of Human β2m

SEQ ID NO:	**Sequence**
56	MSRSVALAVLALLSLSGLEAIQRTPKIQVYSRHPAENGKSNFLNCYVSGFHPSDIEVDLLK NGERIEKVEHSDLSFSKDWSFYLLYYTEFTPTEKDEYACRVNHVTLSQPKIVKWDRDM

[0135] The term "autologous" refers to any material derived from the same individual to which it is later to be re-introduced. For example, an autologous T cell therapy comprises administering to a subject a T cell that was isolated from the same subject. The term "allogeneic" refers to any material derived from one individual which is then introduced to another individual of the same species. For example, an allogeneic T cell transplantation comprises administering to a subject a T cell that was obtained from a donor other than the subject.

[0136] A "cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor. Examples of cancers that can be treated by the methods of the present invention include, but are not limited to, cancers of the immune system including lymphoma, leukemia, and other leukocyte malignancies. In some embodiments, the methods of the present invention can be used to reduce the tumor size of a tumor derived from, for example, bone cancer, renal cancer, prostate cancer, breast cancer, colon cancer, lung cancer, cutaneous or intraocular malignant melanoma, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, 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 (AML), 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. The particular cancer can be responsive to chemo- or radiation therapy or the cancer can be refractory. A refractory cancer refers to a cancer that is not amendable to surgical intervention, and the cancer is either initially unresponsive to chemo- or radiation therapy or the cancer becomes unresponsive over time.

[0137] An "anti-tumor effect" as used herein, refers to a biological effect that can present as a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or amelioration of various physiological symptoms associated with the tumor. An anti-tumor effect can also refer to the prevention of the occurrence of a tumor, *e.g.*, a vaccine.

[0138] The term "progression-free survival," which can be abbreviated as PFS, as used herein refers to the time from the treatment date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma or death from any cause.

[0139] "Disease progression" or "progressive disease," which can be abbreviated as PD, as used herein, refers to a worsening of one or more symptom associated with a particular disease. For example, disease progression for a subject afflicted with a cancer can include an increase in the number or size of one or more malignant lesions, tumor metastasis, and death.

[0140] The "duration of response," which can be abbreviated as DOR, as used herein refers to the period of time between a subject's first objective response to the date of confirmed disease progression, per the revised IWG Response Criteria for Malignant Lymphoma, or death.

[0141] The term "overall survival," which can be abbreviated as OS, is defined as the time from the date of treatment to the date of death.

[0142] A "cytokine," as used herein, refers to a non-antibody protein that is released by one cell in response to contact with a specific antigen, wherein the cytokine interacts with a second cell to mediate a response in the second cell. A cytokine can be endogenously expressed by a cell or administered to a subject. Cytokines may be released by immune cells, including macrophages, B cells, T cells, and mast cells to propagate an immune response. Cytokines can induce various responses in the recipient cell. Cytokines can include homeostatic cytokines, chemokines, pro-inflammatory cytokines, effectors, and acute-phase proteins. For example, homeostatic cytokines, including interleukin (IL) 7 and IL-15, promote immune cell survival and proliferation, and pro-inflammatory cytokines can promote an inflammatory response. Examples of homeostatic cytokines include, but are not limited to, IL-2, IL-4, IL-5, IL-7, IL-10, IL-12p40, IL-12p70, IL-15, and interferon (IFN) gamma. Examples of pro-inflammatory cytokines include, but are not limited to, IL-1a, IL-1b, IL-6, IL-13, IL-17a, tumor necrosis factor (TNF)-alpha, TNF-beta, fibroblast growth factor (FGF) 2, granulocyte macrophage colony-stimulating factor (GM-CSF), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM-1), vascular endothelial growth factor (VEGF), VEGF-C, VEGF-D, and placental growth factor (PLGF). Examples of effectors include, but are not limited to, granzyme A, granzyme B, soluble Fas ligand (sFasL), and perforin. Examples of acute phase-proteins include, but are not limited to, C-reactive protein (CRP) and serum amyloid A (SAA).

[0143] "Chemokines" are a type of cytokine that mediates cell chemotaxis, or directional movement. Examples of chemokines include, but are not limited to, IL-8, IL-16, eotaxin, eotaxin-3, macrophage-derived chemokine (MDC or CCL22), monocyte chemotactic protein 1 (MCP-1 or CCL2), MCP-4, macrophage inflammatory protein 1α (MIP-1α, MIP-1a), MIP-1β (MIP-1b), gamma-induced protein 10 (IP-10), and thymus and activation regulated chemokine (TARC or CCL17).

[0144] Other examples of analytes and cytokines of the present invention include, but are not limited to chemokine (C-C motif) ligand (CCL) 1, CCL5, monocyte-specific chemokine 3 (MCP3 or CCL7), monocyte chemoattractant protein 2 (MCP-2 or CCL8), CCL13, IL-1, IL-3, IL-9, IL-11, IL-12, IL-14, IL-17, IL-20, IL-21, granulocyte colony-stimulating factor (G-CSF), leukemia inhibitory factor (LIF), oncostatin M (OSM), CD154, lymphotoxin (LT) beta, 4-1BB ligand (4-1BBL), a proliferation-inducing ligand (APRIL), CD70, CD153, CD178, glucocorticoid-induced TNFR-related ligand (GITRL), tumor necrosis factor superfamily member 14 (TNFSF14), OX40L, TNF- and ApoL-related leukocyte-expressed ligand 1 (TALL-1), or TNF-related apoptosis-inducing ligand (TRAIL).

[0145] A "therapeutically effective amount," "effective dose," "effective amount," or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0146] The term "lymphocyte" as used herein includes natural killer (NK) cells, T cells, or B cells. NK cells are a type of cytotoxic (cell toxic) lymphocyte that represent a major component of the inherent immune system. NK cells reject tumors and cells infected by viruses. It works through the process of apoptosis or programmed cell death. They were termed “natural killers” because they do not require activation in order to kill cells. T-cells play a major role in cell-mediated-immunity (no antibody involvement). T-cell receptors (TCR) differentiate T cells from other lymphocyte types. The thymus, a specialized organ of the immune system, is primarily responsible for the T cell’s maturation. There are six types of T-cells, namely: Helper T-cells (*e.g.,* CD4+ cells), Cytotoxic T-cells (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8+ T-cells or killer T cell), Memory T-cells ((i) stem memory T_{SCM} cells, like naive cells, are CD45RO−, CCR7+, CD45RA+, CD62L+ (L-selectin), CD27+, CD28+ and IL-7Rα+, but they also express large amounts of CD95, IL-2Rβ, CXCR3, and LFA-1, and show numerous functional attributes distinctive of memory cells); (ii) central memory T_{CM} cells express L-selectin and the CCR7, they secrete IL-2, but not IFNγ or IL-4, and (iii) effector memory T_{EM} cells, however, do not express L-selectin or CCR7 but produce effector cytokines like IFNγ and IL-4), Regulatory T-cells (Tregs, suppressor T cells, or CD4+CD25+ regulatory T cells), Natural Killer T-cells (NKT) and Gamma Delta T-cells. B-cells, on the other hand, play a principal role in humoral immunity (with antibody involvement). A B cell makes antibodies and antigens and performs the role of antigen-presenting cells (APCs) and turns into memory B-cells after activation by antigen interaction. In mammals, immature B-cells are formed in the bone marrow, where its name is derived from.

[0147] The term "genetically engineered" or "engineered" refers to a method of modifying the genome of a cell, including, but not limited to, deleting a coding or non-coding region or a portion thereof or inserting a coding region or a portion thereof. In some embodiments, the cell that is modified is a lymphocyte, *e.g.*, a T cell or a modified cell that expresses CD3, which can either be obtained from a patient or a donor. The cell can be modified to express an exogenous construct, such as, *e.g.*, a T cell receptor (TCR) disclosed herein, which is incorporated into the cell's genome. In some embodiments, the cell is modified to express CD3.

[0148] An "immune response" refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including Abs, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[0149] The term "immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response. Examples of immunotherapy include, but are not limited to, T cell therapies. T cell therapy can include adoptive T cell therapy, tumor-infiltrating lymphocyte (TIL) immunotherapy, autologous cell therapy, engineered autologous cell therapy (eACT), and allogeneic T cell transplantation.

[0150] Cells used in an immunotherapy described herein can come from any source known in the art. For example, T cells can be differentiated *in vitro* from a hematopoietic stem cell population, or T cells can be obtained from a subject. T cells can be obtained from, *e.g.*, peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In addition, the T cells can be derived from one or more T cell lines available in the art. T cells can also be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as FICOLL™ separation and/or apheresis. Additional methods of isolating T cells for a T cell therapy are disclosed in U.S. Patent Publication No. 2013/0287748, which is herein incorporated by references in its entirety. An immunotherapy can also comprise administering a modified cell to a subject, wherein the modified cell expresses CD3 and a TCR disclosed herein. In some embodiments, the modified cell is not a T cell.

[0151] A "patient" as used herein includes any human who is afflicted with a cancer (*e.g.*, a lymphoma or a leukemia). The terms "subject" and "patient" are used interchangeably herein.

[0152] The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[0153] "Stimulation," as used herein, refers to a primary response induced by binding of a stimulatory molecule with its cognate ligand, wherein the binding mediates a signal transduction event. A "stimulatory molecule" is a molecule on a T cell, *e.g.*, the T cell receptor (TCR)/CD3 complex, that specifically binds with a cognate stimulatory ligand present on an antigen present cell. A "stimulatory ligand" is a ligand that when present on an antigen presenting cell (*e.g.*, an aAPC, a dendritic cell, a B-cell, and the like) can specifically bind with a stimulatory molecule on a T cell, thereby mediating a primary response by the T cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands include, but are not limited to, an MHC Class I molecule loaded with a peptide, an anti-CD3 antibody, a superagonist anti-CD28 antibody, and a superagonist anti-CD2 antibody.

[0154] The terms "conditioning" and "pre-conditioning" are used interchangeably herein and indicate preparing a patient in need of a T cell therapy for a suitable condition. Conditioning as used herein includes, but is not limited to, reducing the number of endogenous lymphocytes, removing a cytokine sink, increasing a serum level of one or more homeostatic cytokines or pro-inflammatory factors, enhancing an effector function of T cells administered after the conditioning, enhancing antigen presenting cell activation and/or availability, or any combination thereof prior to a T cell therapy. In one embodiment, "conditioning" comprises increasing a serum level of one or more cytokines, *e.g.*, interleukin 7 (IL-7), interleukin 15 (IL-15), interleukin 10 (IL-10), interleukin 5 (IL-5), gamma-induced protein 10 (IP-10), interleukin 8 (IL-8), monocyte chemotactic protein 1 (MCP-1), placental growth factor (PLGF), C-reactive protein (CRP), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM-1), or any combination thereof. In another embodiment, "conditioning" comprises increasing a serum level of IL-7, IL-15, IP-10, MCP-1, PLGF, CRP, or any combination thereof.

[0155] "Treatment" or "treating" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease. In one embodiment, "treatment" or "treating" includes a partial remission. In another embodiment, "treatment" or "treating" includes a complete remission.

[0156] The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component.

[0157] The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 10% (*i.e.*, ±10%). For example, about 3mg can include any number between 2.7 mg and 3.3 mg (for 10%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0158] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0159] Various aspects of the invention are described in further detail in the following subsections.

II. Compositions of the Disclosure

[0160] The present disclosure is directed to T Cell Receptors (TCRs) or antigen binding portions thereof that specifically bind to an epitope on a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2, nucleic acid molecules that encode the same, and cells that comprise the TCR or the nucleic acid molecule. Some aspects of the present disclosure are directed to methods of treating a caner in a subject in need thereof, comprising administering to the subject a cell comprising the TCRs described herein. Other aspects of the present disclosure are directed to an epitope of tyrosinase, MAGE-A1, MART1, MAGE-A3, or SSX2that the TCRs bind to and HLA class I molecules complexed to a peptide comprising the epitope of tyrosinase, MAGE-A1, MART1, MAGE-A3, or SSX2.

[0161] The T-cell receptor, or TCR, is a molecule found on the surface of T cells, or T lymphocytes, that is responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex (MHC) molecules. The binding between TCR and antigen peptides is of relatively low affinity and is degenerate: that is, many TCRs recognize the same antigen peptide and many antigen peptides are recognized by the same TCR.

[0162] The TCR is composed of two different protein chains (that is, it is a heterodimer). In humans, in 95% of T cells the TCR consists of an alpha (α) chain and a beta (β) chain (encoded by TRA and TRB, respectively), whereas in 5% of T cells, the TCR consists of gamma and delta (γ/δ) chains (encoded by TRG and TRD, respectively). This ratio changes during ontogeny and in diseased states (such as leukemia). It also differs between species. Orthologues of the 4 loci have been mapped in various species. Each locus can produce a variety of polypeptides with constant and variable regions.

[0163] When the TCR engages with antigenic peptide and MHC (peptide/MHC), the T lymphocyte is activated through signal transduction, that is, a series of biochemical events mediated by associated enzymes, co-receptors, specialized adaptor molecules, and activated or released transcription factors.

II.A. Nucleic Acid Molecules

[0164] Certain aspects of the present disclosure are directed to nucleic acid molecules comprising (i) a first nucleotide sequence encoding a recombinant TCR or an antigen binding portion thereof that specifically binds a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2 ("epitope-specific TCR"); 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. In some embodiments, the second nucleotide sequence is a non-naturally occurring sequence. In other embodiments, the second nucleotide sequence is synthetic. In yet other embodiments, the second nucleotide sequence comprises a sequence that targets a nucleotide sequence encoding the endogenous TCR. In some embodiments, the epitope-specific TCR cross competes for binding to the target human protein with a reference TCR. In some embodiments, the TCR binds the same epitope or an overlapping epitope of the target human protein as a reference TCR.

[0165] In some embodiments, the reference TCR comprises an alpha chain and a beta chain; wherein the alpha chain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3; wherein the beta chain comprises a CDR1, a CDR2, and a CDR3; and wherein the reference TCR comprises an alpha chain CDR3 amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs: 7, 17, 27, 37, and 47; and a beta chain CDR3 amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs: 10, 20, 30, 40, and 50. In some embodiments, the alpha chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 7, and the beta chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 10. In some embodiments, the alpha chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 17, and the beta chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 20. In some embodiments, the alpha chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 27, and the beta chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 30. In some embodiments, the alpha chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 37, and the beta chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 40. In some embodiments, the alpha chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 47, and the beta chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 50.

[0166] In some embodiments, the reference TCR comprises the alpha chain CDR1, CDR2, and CDR3 sequences present in amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs: 1, 11, 21, 31, and 41, and the reference TCR comprises the beta chain CDR1, CDR2, and CDR3 sequences present in an amino acid sequence selected from the amino acid sequences set forth in SEQ ID NO: 2, 12, 22, 32, and 42. In some embodiments, the reference 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, 11, 21, 31, or 41; and the beta chain comprises an amino acid sequence as set forth in SEQ ID NO: 2, 12, 22, 32, or 42.

Table 3A. Tyrosinase Alpha Chain and Beta Chain TCR Sequences

SEQ ID NO:	TCR Chain	Sequence
1	Alpha Chain (amino acid)	MRQVARVIVFLTLSTLSLAKTTQPISMDSYEGQEVNITCSHNNIATNDYITWYQQFPSQGPRFIIQGYKTKVTNEVASLFIPADRKSSTLSLPRVSLSDTAVYYCLVGDVEGSQGNLIFGKGTKLSVKPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLMTLRLWSSZ
3	Alpha Chain (nucleotide)	ATGAGGCAAGTGGCGAGAGTGATCGTGTTCCTGACCCTGAGTACTTTGAGCCTTGCTAAGACCACCCAGCCCATCTCCATGGACTCATATGAAGGACAAGAAGTGAACATAACCTGTAGCCACAACAACATTGCTACAAATGATTATATCACGTGGTACCAACAGTTTCCCAGCCAAGGACCACGATTTATTATTCAAGGATACAAGACAAAAGTTACAAACGAAGTGGCCTCCCTGTTTATCCCTGCCGACAGAAAGTCCAGCACTCTGAGCCTGCCCCGGGTTTCCCTGAGCGACACTGCTGTGTACTACTGCCTCGTGGGTGACGTAGAAGGAAGCCAAGGAAATCTCATCTTTGGAAAAGGCACTAAACTCTCTGTTAAACCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGAAAGTTCCTGTGATGTCAAGCTGGTCGAGAAAAGCTTTGAAACAGATACGAACCTAAACTTTCAAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGCTGA
2	Beta Chain (amino acid)	MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASSHHSGGIYNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA

		TLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRGZ
4	Beta Chain (nucleotide)	ATGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGGTCCAGTGAATGCTGGTGTCACTCAGACCCCAAAATTCCAGGTCCTGAAGACAGGACAGAGCATGACACTGCAGTGTGCCCAGGATATGAACCATGAATACATGTCCTGGTATCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCATTACTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATCAACCACAGAGGATTTCCCGCTCAGGCTGCTGTCGGCTGCTCCCTCCCAGACATCTGTGTACTTCTGTGCCAGCAGTCACCATTCGGGGGGGATCTACAATGAGCAGTTCTTCGGGCCAGGGACACGGCTCACCGTGCTAGAGGACCTGAAAAACGTGTTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACACCCAAAAGGCCACACTGGTATGCCTGGCCACAGGCTTCTACCCCGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACAGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGCAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGGACCCAGGATAGGGCCAAACCTGTCACCCAGATCGTCAGCGCCGAGGCCTGGGGTAGAGCAGACTGTGGCTTCACCTCCGAGTCTTACCAGCAAGGGGTCCTGTCTGCCACCATCCTCTATGAGATCTTGCTAGGGAAGGCCACCTTGTATGCCGTGCTGGTCAGTGCCCTCGTGCTGATGGCCATGGTCAAGAGAAAGGATTCCAGAGGCTAG

Table 3B. MAGE-A1 Alpha Chain and Beta Chain TCR Sequences

SEQ ID NO:	TCR Chain	Sequence
11	Alpha Chain (amino acid)	MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDVTLDCVYETRDTTYYLFWYKQPPSGELVFLIRRNSFDEQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALSESYSGAGSYQLTFGKGTKLSVIPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLMTLRLWSSZ
13	Alpha Chain (nucleotide)	ATGCTGACTGCCAGCCTGTTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAGGTAACTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCCTTATTCGTCGGAACTCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACTTCCAGAAATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCTGTGCTCTGAGTGAGTCATACTCTGGGGCTGGGAGTTACCAACTCACTTTCGGGAAGGGGACCAAACTCTCGGTCATACCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGAAAGTTCCTGTGATGTCAAGCTGGTCGAGAAAAGCTTTGAAACAGATACGAACCTAAACTTTCAAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGCTGA
12	Beta Chain (amino acid)	MGTSLLCWMALCLLGADHADTGVSQNPRHKITKRGQNVTFRCDPISEHNRLYWYRQTLGQGPEFLTYFQNEAQLEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYLCASSLASGSNQPQHFGDGTRLSILEDLNKVFPPEVAVFEPSEAEISHTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVS

		ATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSVSYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDFZ
14	Beta Chain (nucleotide)	ATGGGCACCAGCCTCCTCTGCTGGATGGCCCTGTGTCTCCTGGGGGCAGATCACGCAGATACTGGAGTCTCCCAGAACCCCAGACACAAGATCACAAAGAGGGGACAGAATGTAACTTTCAGGTGTGATCCAATTTCTGAACACAACCGCCTTTATTGGTACCGACAGACCCTGGGGCAGGGCCCAGAGTTTCTGACTTACTTCCAGAATGAAGCTCAACTAGAAAAATCAAGGCTGCTCAGTGATCGGTTCTCTGCAGAGAGGCCTAAGGGATCTTTCTCCACCTTGGAGATCCAGCGCACAGAGCAGGGGGACTCGGCCATGTATCTCTGTGCCAGCAGCTTAGCTTCGGGCAGCAATCAGCCCCAGCATTTTGGTGATGGGACTCGACTCTCCATCCTAGAGGACCTGAACAAGGTGTTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCTTCTTCCCCGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACGGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGCAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGGACCCAGGATAGGGCCAAACCCGTCACCCAGATCGTCAGCGCCGAGGCCTGGGGTAGAGCAGACTGTGGCTTTACCTCGGTGTCCTACCAGCAAGGGGTCCTGTCTGCCACCATCCTCTATGAGATCCTGCTAGGGAAGGCCACCCTGTATGCTGTGCTGGTCAGCGCCCTTGTGTTGATGGCCATGGTCAAGAGAAAGGATTTCTGA

Table 3C. MART1 Alpha Chain and Beta Chain TCR Sequences

SEQ ID NO:	TCR Chain	Sequence
21	Alpha Chain (amino acid)	MWGVFLLYVSMKMGGTTGQNIDQPTEMTATEGAIVQINCTYQTSGFNGLFWYQQHAGEAPTFLSYNVLDGLEEKGRFSSFLSRSKGYSYLLLKELQMKDSASYLCAVYGGATNKLIFGTGTLLAVQPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLMTLRLWSSZ
23	Alpha Chain (nucleotide)	ATGTGGGGAGTTTTCCTTCTTTATGTTTCCATGAAGATGGGAGGCACTACAGGACAAAACATTGACCAGCCCACTGAGATGACAGCTACGGAAGGTGCCATTGTCCAGATCAACTGCACGTACCAGACATCTGGGTTCAACGGGCTGTTCTGGTACCAGCAACATGCTGGCGAAGCACCCACATTTCTGTCTTACAATGTTCTGGATGGTTTGGAGGAGAAAGGTCGTTTTTCTTCATTCCTTAGTCGGTCTAAAGGGTACAGTTACCTCCTTTTGAAGGAGCTCCAGATGAAAGACTCTGCCTCTTACCTCTGTGCTGTGTATGGTGGTGCTACAAACAAGCTCATCTTTGGAACTGGCACTCTGCTTGCTGTCCAGCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGAAAGTTCCTGTGATGTCAAGCTGGTCGAGAAAAGCTTTGAAACAGATACGAACCTAAACTTTCAAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGCTGA
22	Beta Chain (amino acid)	MDTRVLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPMKGHSHVYWYRQLPEEGLKFMVYLQKENIIDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYFCASSPHAGGVDEKLFFGSGTQLSVLEDLNKVFPPEVAVFEPSEAEISHTQKATLVCLATGFFPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSVSYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDFZ
24	Beta Chain	ATGGACACCAGAGTACTCTGCTGTGCGGTCATCTGTCTTCTGGGGGCAGGTC

	(nucleotide)	TCTCAAATGCCGGCGTCATGCAGAACCCAAGACACCTGGTCAGGAGGAGGGGACAGGAGGCAAGACTGAGATGCAGCCCAATGAAAGGACACAGTCATGTTTACTGGTATCGGCAGCTCCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAGAAAATATCATAGATGAGTCAGGAATGCCAAAGGAACGATTTTCTGCTGAATTTCCCAAAGAGGGCCCCAGCATCCTGAGGATCCAGCAGGTAGTGCGAGGAGATTCGGCAGCTTATTTCTGTGCCAGCTCACCACACGCGGGGGGAGTTGATGAAAAACTGTTTTTTGGCAGTGGAACCCAGCTCTCTGTCTTGGAGGACCTGAACAAGGTGTTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCTTCTTCCCTGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACGGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGCAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGGACCCAGGATAGGGCCAAACCCGTCACCCAGATCGTCAGCGCCGAGGCCTGGGGTAGAGCAGACTGTGGCTTTACCTCGGTGTCCTACCAGCAAGGGGTCCTGTCTGCCACCATCCTCTATGAGATCCTGCTAGGGAAGGCCACCCTGTATGCTGTGCTGGTCAGCGCCCTTGTGTTGATGGCCATGGTCAAGAGAAAGGATTTCTGA

Table 3D. MAGE-A3 Alpha Chain and Beta Chain TCR Sequences

SEQ ID NO:	TCR Chain	Sequence
31	Alpha Chain (amino acid)	MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDVTLDCVYETRDTTYYLFWYKQPPSGELVFLIRRNSFDEQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALEVRSSASKIIFGSGTRLSIRPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLMTLRLWSSZ
33	Alpha Chain (nucleotide)	ATGCTGACTGCCAGCCTGTTGAGGGCAGTCATAGCCTCCATCTGTGTTGTATCCAGCATGGCTCAGAAGGTAACTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAGGATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATTCTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCCTTATTCGTCGGAACTCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACTTCCAGAAATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCAGCAGTATACTTCTGTGCTCTGGAAGTGAGAAGCAGTGCTTCCAAGATAATCTTTGGATCAGGGACCAGACTCAGCATCCGGCCAAATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGAAAGTTCCTGTGATGTCAAGCTGGTCGAGAAAAGCTTTGAAACAGATACGAACCTAAACTTTCAAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGCTGA
32	Beta Chain (amino acid)	MLLLLLLLGPGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYICSANPRTTLYEQYFGPGTRLTVTEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRGZ
34	Beta Chain (nucleotide)	ATGCTGCTGCTTCTGCTGCTTCTGGGGCCAGGCTCCGGGCTTGGTGCTGTCGTCTCTCAACATCCGAGCTGGGTTATCTGTAAGAGTGGAACCTCTGTGAAGATCGAGTGCCGTTCCCTGGACTTTCAGGCCACAACTATGTTTTGGTATCGTCAGTTCCCGAAACAGAGTCTCATGCTGATGGCAACTTCCAATGAGGGCTCCAAGGCCACATACGAGCAAGGCGTCGAGAAGGACAAGTTTCTCATCAACCATGCAAGC

		CTGACCTTGTCCACTCTGACAGTGACCAGTGCCCATCCTGAAGACAGCAGCTTCTACATCTGCAGTGCAAACCCCCGGACTACCCTCTACGAGCAGTACTTCGGGCCGGGCACCAGGCTCACGGTCACAGAGGACCTGAAAAACGTGTTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCTTCTACCCCGACCACGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACAGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGCAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGGACCCAGGATAGGGCCAAACCTGTCACCCAGATCGTCAGCGCCGAGGCCTGGGGTAGAGCAGACTGTGGCTTCACCTCCGAGTCTTACCAGCAAGGGGTCCTGTCTGCCACCATCCTCTATGAGATCTTGCTAGGGAAGGCCACCTTGTATGCCGTGCTGGTCAGTGCCCTTGTGCTGATGGCCATGGTCAAGAGAAAGGATTCCAGAGGCTAG

Table 3E. SSX2 Alpha Chain and Beta Chain TCR Sequences

SEQ ID NO:	TCR Chain	Sequence
41	Alpha Chain (amino acid)	METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFTDSAIYNLQWFRQDPGKGLTSLLLIQSSQREQTSGRLNASLDKSSGRSTLYIAASQPGDSATYLCAVEPMEYGNKLVFGAGTILRVKSYIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLMTLRLWSSZ
43	Alpha Chain (nucleotide)	ATGGAGACCCTCTTGGGCCTGCTTATCCTTTGGCTGCAGCTGCAATGGGTGAGCAGCAAACAGGAGGTGACACAGATTCCTGCAGCTCTGAGTGTCCCAGAAGGAGAAAACTTGGTTCTCAACTGCAGTTTCACTGATAGCGCTATTTACAACCTCCAGTGGTTTAGGCAGGACCCTGGGAAAGGTCTCACATCTCTGTTGCTTATTCAGTCAAGTCAGAGAGAGCAAACAAGTGGAAGACTTAATGCCTCGCTGGATAAATCATCAGGACGTAGTACTTTATACATTGCAGCTTCTCAGCCTGGTGACTCAGCCACCTACCTCTGTGCTGTGGAACCCATGGAATATGGAAACAAACTGGTCTTTGGCGCAGGAACCATTCTGAGAGTCAAGTCCTATATCCAGAACCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGTCTGTCTGCCTATTCACCGATTTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGTGTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTGGCCTGGAGCAACAAATCTGACTTTGCATGTGCAAACGCCTTCAACAACAGCATTATTCCAGAAGACACCTTCTTCCCCAGCCCAGAAAGTTCCTGTGATGTCAAGCTGGTCGAGAAAAGCTTTGAAACAGATACGAACCTAAACTTTCAAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGCTGA
42	Beta Chain (amino acid)	MSNQVLCCVVLCLLGANTVDGGITQSPKYLFRKEGQNVTLSCEQNLNHDAMYWYRQDPGQGLRLIYYSQIVNDFQKGDIAEGYSVSREKKESFPLTVTSAQKNPTAFYLCASSALFSGANVLTFGAGSRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRGZ
44	Beta Chain (nucleotide)	ATGAGCAACCAGGTGCTCTGCTGTGTGGTCCTTTGTCTCCTGGGAGCAAACACCGTGGATGGTGGAATCACTCAGTCCCCAAAGTACCTGTTCAGAAAGGAAGGACAGAATGTGACCCTGAGTTGTGAACAGAATTTGAACCACGATGCCATGTACTGGTACCGACAGGACCCAGGGCAAGGGCTGAGATTGATCTACTACTCACAGATAGTAAATGACTTTCAGAAAGGAGATATAGCTGAAGGGTACAGCGTCTCTCGGGAGAAGAAGGAATCCTTTCCTCTCACTGTGACATCGGCCCAAAAGAACCCGACAGCTTTCTATCTCTGTGCCAGTAGTGCGTTATTCTCTGGGGCCAACGTCCTGACTTTCGGGGCCGGCAGCAGGCTGACCGTGCTGGAGGACCTGAAAAACGTGTTCCCACCCGAGGTCGCTGTGTTTGAGCCATCAGAAGCAGAGATCTCCCACACCCAAAAGGCCACACTGGTGTGCCTGGCCACAGGCTTCTACCCCGACCA

		CGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGGTCAGCACAGACCCGCAGCCCCTCAAGGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCCTGAGGGTCTCGGCCACCTTCTGGCAGAACCCCCGCAACCACTTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATGACGAGTGGACCCAGGATAGGGCCAAACCTGTCACCCAGATCGTCAGCGCCGAGGCCTGGGGTAGAGCAGACTGTGGCTTCACCTCCGAGTCTTACCAGCAAGGGGTCCTGTCTGCCACCATCCTCTATGAGATCTTGCTAGGGAAGGCCACCTTGTATGCCGTGCTGGTCAGTGCCCTCGTGCTGATGGCCATGGTCAAGAGAAAGGATTCCAGAGGCTGA

II.A.1. Epitope-Specific TCRs

[0167] Certain aspects of the present disclosure are directed to an epitope-specific TCR. In some embodiments, the epitope-specific TCR is encoded by a first nucleotide sequence described herein. In some embodiments, the epitope-specific TCR, *e.g.*, encoded by the first nucleotide sequence, specifically binds an epitope of a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2. In some embodiments, the epitope-specific TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a variable domain comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; and wherein the beta chain comprises a variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3.

II.A.1.a. Anti-Tyrosinase TCRs

[0168] In some embodiments, the epitope-specific TCR, *e.g.*, the epitope-specific TCR encoded by the first nucleotide sequence, specifically binds an epitope on human tyrosinase ("anti-tyrosinase TCR"), and the anti-tyrosinase TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 7 (CLVGDVEGSQGNLIF). In some embodiments, the anti-tyrosinase TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 10 (CASSHHSGGIYNEQFF). In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1, wherein the alpha chain CDR1 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 5 (NIATNDY). In some embodiments, the anti-tyrosinase TCR, *e.g.*, the epitope-specific TCR encoded by the first nucleotide sequence, comprises a beta chain CDR1, wherein the beta chain CDR1 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 8 (MNHEY).

[0169] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR2, wherein the alpha chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 6 (GYKTK). In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR2, wherein the beta chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 9 (SVGAGI).

[0170] In certain embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 5; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 6; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 7; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 8; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 9; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 10.

[0171] In some embodiments, the non-CDR regions in the alpha chain and/or the beta chain of the epitope-specific TCR, *e.g.*, the anti-tyrosinase TCR, are further modified, *e.g.*, substitution or mutation of one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, or six amino acids, thereby the alpha chain and/or the beta chain are not naturally occurring. In some embodiments, the substitutions or mutations can improve the TCRs described herein in various ways, *e.g.*, binding affinity, binding specificity, stability, viscosity, or any combination thereof.

[0172] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, 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 with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 1, wherein the anti-tyrosinase TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 7. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain present in the alpha chain amino acid sequence set forth in SEQ ID NO: 1.

[0173] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, 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 with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 2, wherein the anti-tyrosinase TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 10. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain present in the amino acid sequence set forth in SEQ ID NO: 2.

[0174] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, further comprises an alpha chain constant region, a beta chain constant region, or both an alpha chain constant region and a beta chain constant region. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, 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 with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 1, wherein the anti-tyrosinase TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 7. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region present in the alpha chain amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, further comprises an alpha constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the alpha chain. In some embodiments, 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 the amino acid sequence of the constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 1.

[0175] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, 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 with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 2, wherein the anti-tyrosinase TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 10. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region present in the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, further comprises a beta constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the beta chain. In some embodiments, 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 the amino acid sequence of the constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 2.

[0176] In certain embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 1, wherein the anti-tyrosinase TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 7. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 1.

[0177] In certain embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 2, wherein the anti-tyrosinase TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 10. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 2.

[0178] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region, a beta chain constant region, or both; 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. In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a constant region, and wherein the beta chain comprises a constant region; wherein (i) the alpha chain constant region comprises an amino acid sequence having at least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 1; and (ii) the beta chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 2.

[0179] In some embodiments, the anti-tyrosinase TCR, *e.g.*, encoded by the first nucleotide sequence, cross competes for binding to human tyrosinase with a reference TCR. In some embodiments, the anti-tyrosinase TCR binds the same epitope or an overlapping epitope of human tyrosinase as a reference TCR. In some embodiments, the reference TCR comprises an alpha chain and a beta chain, and the alpha chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 1. In some embodiments, the beta chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 2.

II.A.1.b. Anti-MAGE-A1 TCRs

[0180] In some embodiments, the epitope-specific TCR, *e.g.*, the epitope specific TCR encoded by the first nucleotide sequence, specifically binds an epitope on human MAGE-A1 ("anti-MAGE-A1 TCR"), and the anti-MAGE-A1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 17 (CALSESYSGAGSYQLTF). In some embodiments, the anti-MAGE-A1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 20 (CASSLASGSNQPQHF).

[0181] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1, wherein the alpha chain CDR1 of the anti-MAGE-A1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 15 (TRDTTYYL). In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR1, wherein the beta chain CDR1 of the anti-MAGE-A1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 18 (SEHNR).

[0182] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR2, wherein the alpha chain CDR2 of the anti-MAGE-A1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 16 (RNSFDEQN). In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR2, wherein the beta chain CDR2 of the anti-MAGE-A1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 19 (FQNEAQ).

[0183] In certain embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 15; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 16; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 18; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 19; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 20.

[0184] In some embodiments, the non-CDR regions in the alpha chain and/or the beta chain of the epitope-specific TCR, *e.g.*, the anti-MAGE-A1 TCR, are further modified, *e.g.*, substitution or mutation of one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, or six amino acids, thereby the alpha chain and/or the beta chain are not naturally occurring. In some embodiments, the substitutions or mutations can improve the TCRs described herein in various ways, *e.g.*, binding affinity, binding specificity, stability, viscosity, or any combination thereof.

[0185] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, 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 with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 11, wherein the anti-MAGE-A1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 17. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain present in the alpha chain amino acid sequence set forth in SEQ ID NO: 11.

[0186] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, 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 with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 12, wherein the anti-MAGE-A1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 20. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain present in the amino acid sequence set forth in SEQ ID NO: 12.

[0187] In some embodiments, the anti-MAGE-A1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha chain constant region, a beta chain constant region, or both an alpha chain constant region and a beta chain constant region. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, 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 with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 11, wherein the anti-MAGE-A1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 17. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region present in the alpha chain amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the anti-MAGE-A1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the alpha chain. In some embodiments, 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 the amino acid sequence of the constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 11.

[0188] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, 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 with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 12, wherein the anti-MAGE-A1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 20. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region present in the amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the anti-MAGE-A1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises a beta constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the beta chain. In some embodiments, 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 the amino acid sequence of the constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 12.

[0189] In certain embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 11. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 11, wherein the anti-MAGE-A1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 17. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 11.

[0190] In certain embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 12. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 12, wherein the anti-MAGE-A1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 10. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 12.

[0191] In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, 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. In some embodiments, the anti-MAGE-A1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a constant region, and wherein the beta chain comprises a constant region; wherein (i) the alpha chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 11; and (ii) the beta chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 12.

[0192] In some embodiments, the anti-MAGE-A1 TCR cross competes for binding to human MAGE-A1 with a reference TCR. In some embodiments, the anti-MAGE-A1 TCR binds the same epitope or an overlapping epitope of human MAGE-A1 as a reference TCR. In some embodiments, the reference TCR comprises an alpha chain and a beta chain, and the alpha chain of the reference TCR comprises an amino acid sequence as set forth in SEQ

ID NO: 11. In some embodiments, the beta chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 12.

II.A.1.c. Anti-MART1 TCRs

[0193] In some embodiments, the epitope-specific TCR, *e.g.*, the epitope specific TCR encoded by the first nucleotide sequence, specifically binds an epitope on human MART1 ("anti-MART1 TCR"), and the anti-MART1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 27 (CAVYGGATNKLIF). In some embodiments, the anti-MART1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 30 (CASSPHAGGVDEKLFF).

[0194] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1, wherein the alpha chain CDR1 of the anti- anti-MART1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 25 (TSGFNG). In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR1, wherein the beta chain CDR1 of the anti-MART1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 28 (KGHSH).

[0195] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR2, wherein the alpha chain CDR2 of the anti-MART1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 26 (NVLDGL). In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR2, wherein the beta chain CDR2 of the anti-MART1 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 29 (LQKENI).

[0196] In certain embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 25; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 26; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 27; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30.

[0197] In some embodiments, the non-CDR regions in the alpha chain and/or the beta chain of the epitope-specific TCR, *e.g.*, the anti-MART1 TCR, are further modified, *e.g.*, substitution or mutation of one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, or six amino acids, thereby the alpha chain and/or the beta chain are not naturally occurring. In some embodiments, the substitutions or mutations can improve the TCRs described herein in various ways, *e.g.*, binding affinity, binding specificity, stability, viscosity, or any combination thereof.

[0198] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, 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 with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 21, wherein the anti-MART1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 27. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain present in the alpha chain amino acid sequence set forth in SEQ ID NO: 21.

[0199] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, 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 with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 22, wherein the anti-MART1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 30. In some embodiments, the anti-

MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain present in the amino acid sequence set forth in SEQ ID NO: 22.

[0200] In some embodiments, the anti-MART1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha chain constant region, a beta chain constant region, or both an alpha chain constant region and a beta chain constant region. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, 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 with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 21, wherein the anti-MART1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 27. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region present in the alpha chain amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the anti-MART1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the alpha chain. In some embodiments, 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 the amino acid sequence of the constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 21.

[0201] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, 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 with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 22, wherein the anti-MART1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 30. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region present in the amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the anti-MART1 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises a beta constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the beta chain. In some embodiments, 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 the amino acid sequence of the constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 22.

[0202] In certain embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 21. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 21, wherein the anti-MART1 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 27. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 21.

[0203] In certain embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 22. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 22, wherein the anti-MART1 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 30. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 22.

[0204] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, 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. In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a constant region, and wherein the beta chain comprises a constant region; wherein (i) the alpha chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 21; and (ii) the beta chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 22.

[0205] In some embodiments, the anti-MART1 TCR, *e.g.*, encoded by the first nucleotide sequence, cross competes for binding to human MART1 with a reference TCR. In some embodiments, the anti-MART1 TCR binds the same epitope or an overlapping epitope of human MART1 as a reference TCR. In some embodiments, the reference TCR comprises an alpha chain and a beta chain, and the alpha chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 21. In some embodiments, the beta chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 22.

II.A.1.d. Anti-MAGE-A3 TCRs

[0206] In some embodiments, the epitope-specific TCR, *e.g.*, the epitope specific TCR encoded by the first nucleotide sequence, specifically binds an epitope on human MAGE-A3 ("anti-MAGE-A3 TCR"), and the anti-MAGE-A3 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 37 (CALEVRSSASKIIF).

In some embodiments, the anti-MAGE-A3 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 40 (CSANPRTTLYEQYF).

[0207] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1, wherein the alpha chain CDR1 of the anti-MAGE-A3 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 35 (TRDTTYY). In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR1, wherein the beta chain CDR1 of the anti-MAGE-A3 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 38 (DFQATT).

[0208] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR2, wherein the alpha chain CDR2 of the anti-MAGE-A3 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 36 (RNSFDEQN). In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR2, wherein the beta chain CDR2 of the anti-MAGE-A3 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 39 (SNEGSKA).

[0209] In certain embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 35; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 36; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 37; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 38; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 39; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 40

[0210] In some embodiments, the non-CDR regions in the alpha chain and/or the beta chain of the epitope-specific TCR, *e.g.*, the anti-MAGE-A3 TCR, are further modified, *e.g.*, substitution or mutation of one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, or six amino acids, thereby the alpha chain and/or the beta chain are not naturally occurring. In some embodiments, the substitutions or mutations can improve the TCRs described herein in various ways, *e.g.*, binding affinity, binding specificity, stability, viscosity, or any combination thereof.

[0211] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 31. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, 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 with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 31, wherein the anti-MAGE-A3 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 37. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain present in the alpha chain amino acid sequence set forth in SEQ ID NO: 31.

[0212] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 32. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, 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 with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 32, wherein the anti-MAGE-A3 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 40. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain present in the amino acid sequence set forth in SEQ ID NO: 32.

[0213] In some embodiments, the anti-MAGE-A3 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha chain constant region, a beta chain constant region, or both an alpha chain constant region and a beta chain constant region. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 31. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, 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 with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 31, wherein the anti-MAGE-A3 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 37. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region present in the alpha chain amino acid sequence set forth in SEQ ID NO: 31. In some embodiments, the anti-MAGE-A3 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the alpha chain. In some embodiments, 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 the amino acid sequence of the constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 31.

[0214] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 32. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, 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 with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 32, wherein the anti-MAGE-A3 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 40. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region present in the amino acid sequence set forth in SEQ ID NO: 32. In some embodiments, the anti-MAGE-A3 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises a beta constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the beta chain. In some embodiments, 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 the amino acid sequence of the constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 32.

[0215] In certain embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 31. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 31, wherein the anti-MAGE-A3 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 37. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 31.

[0216] In certain embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 32. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 32, wherein the anti-MAGE-A3 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 40. In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 32.

[0217] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, 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.

[0218] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a constant region, and wherein the beta chain comprises a constant region; wherein (i) the alpha chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 31; and (ii) the beta chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 32.

[0219] In some embodiments, the anti-MAGE-A3 TCR, *e.g.*, encoded by the first nucleotide sequence, cross competes for binding to human MAGE-A3 with a reference TCR. In some embodiments, the anti-MAGE-A3 TCR binds the same epitope or an overlapping epitope of human MAGE-A3 as a reference TCR. In some embodiments, the reference TCR comprises an alpha chain and a beta chain, and the alpha chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 31. In some embodiments, the beta chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 32.

II.A.1.e. Anti-SSX2 TCRs

[0220] In some embodiments, the epitope-specific TCR, *e.g.*, the epitope specific TCR encoded by the first nucleotide sequence, specifically binds an epitope on human SSX2 ("anti-SSX2 TCR"), and the anti-SSX2 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 47 (CAVEPMEYGNKLVF). In some embodiments, the anti-SSX2 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 50 (CASSALFSGANVLTF).

[0221] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1, wherein the alpha chain CDR1 of the anti-SSX2 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 45 (DSAIYN). In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR1, wherein the beta chain CDR1 of the anti-SSX2 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 48 (LNHDA).

[0222] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR2, wherein the alpha chain CDR2 of the anti-SSX2 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 46 (IQSSQRE). In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain CDR2, wherein the beta chain CDR2 of the anti-SSX2 TCR comprises an amino acid sequence as set forth in SEQ ID NO: 49 (SQIVND).

[0223] In certain embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 45; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 46; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 47; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 48; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 49; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 50.

[0224] In some embodiments, the non-CDR regions in the alpha chain and/or the beta chain of the epitope-specific TCR, *e.g.*, the anti-SSX2 TCR, are further modified, *e.g.*, substitution or mutation of one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, or six amino acids, thereby the alpha chain and/or the beta chain are not naturally occurring. In some embodiments, the substitutions or mutations can improve the TCRs described herein in various ways, *e.g.*, binding affinity, binding specificity, stability, viscosity, or any combination thereof.

[0225] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 41. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain having at least about 80%, 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 with a variable domain of the alpha chain amino acid sequence set forth in SEQ ID NO: 41, wherein the anti-SSX2 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 47. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain variable domain present in the alpha chain amino acid sequence set forth in SEQ ID NO: 41.

[0226] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 42. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain having at least about 80%, 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 with a variable domain of the beta chain amino acid sequence set forth in SEQ ID NO: 42, wherein the anti-SSX2 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 50. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain variable domain present in the amino acid sequence set forth in SEQ ID NO: 42.

[0227] In some embodiments, the anti-SSX2 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha chain constant region, a beta chain constant region, or both an alpha chain constant region and a beta chain constant region. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 41. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region having at least about 80%, 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 with a constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 41, wherein the anti-SSX2 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 7. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain constant region present in the alpha chain amino acid sequence set forth in SEQ ID NO: 41. In some embodiments, the anti-SSX2 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises an alpha constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the alpha chain. In some embodiments, 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 the amino acid sequence of the constant region of the alpha chain amino acid sequence set forth in SEQ ID NO: 41.

[0228] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 42. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region having at least about 80%, 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 with a constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 42, wherein the anti-SSX2 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 50. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain constant region present in the amino acid sequence set forth in SEQ ID NO: 42. In some embodiments, the anti-SSX2 TCR, *e.g*, encoded by the first nucleotide sequence, further comprises a beta constant region that is different from endogenous, *e.g.*, naturally occurring, constant regions of the beta chain. In some embodiments, 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 the amino acid sequence of the constant region of the beta chain amino acid sequence set forth in SEQ ID NO: 42.

[0229] In certain embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 41. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the alpha chain amino acid sequence set forth in SEQ ID NO: 41, wherein the anti-SSX2 TCR comprises an alpha chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 47. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 41.

[0230] In certain embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 42. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97% at least about 98%, at least about 99%, or about 100% sequence identity with the beta chain amino acid sequence set forth in SEQ ID NO: 42, wherein the anti-SSX2 TCR comprises a beta chain CDR3 comprising an amino acid sequence as set forth in SEQ ID NO: 50. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 42.

[0231] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, 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. In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, comprises an alpha chain and a beta chain, wherein the alpha chain comprises a constant region, and wherein the beta chain comprises a constant region; wherein (i) the alpha chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of an alpha chain comprising the amino acid sequence set forth in SEQ ID NO: 41; and (ii) the beta chain constant region comprises an amino acid sequence having a least 1, at least 2, at least 3, at least 4, or at least 5 amino acid substitutions relative to the constant region of a beta chain comprising the amino acid sequence set forth in SEQ ID NO: 42.

[0232] In some embodiments, the anti-SSX2 TCR, *e.g.*, encoded by the first nucleotide sequence, cross competes for binding to human SSX2 with a reference TCR. In some embodiments, the anti-SSX2 TCR binds the same epitope or an overlapping epitope of human SSX2 as a reference TCR. In some embodiments, the reference TCR comprises an alpha chain and a beta chain, and the alpha chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 41. In some embodiments, the beta chain of the reference TCR comprises an amino acid sequence as set forth in SEQ ID NO: 42.

II.A.2 The Second Nucleotide Sequence

[0233] The second nucleotide sequence of the nucleic acid molecule disclosed herein can be any sequence or can encode for any polypeptide that is capable of inhibiting the expression of an endogenous TCR. In some embodiments, the second nucleotide sequence is one or more siRNAs. In some embodiments, the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of an endogenous TCR. In certain embodiments, the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of wild-type, human TCR. In some embodiments, the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the alpha chain of wild-type TCR. In some embodiments, the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the beta chain of wild-type TCR. In some embodiments, the one or more siRNAs comprise (i) one or more siRNA's that are complementary to a target sequence within a nucleotide sequence encoding a constant region of the alpha chain of wild-type TCR and (ii) one or more siRNA's that are complementary to a target sequence within a nucleotide sequence encoding a constant region of the beta chain of wild-type TCR.

[0234] In some embodiments, the one or more siRNAs comprise a nucleotide sequence selected from the group consisting of SEQ ID NOs: 57-60 (Table 4). In some embodiments, the second nucleotide sequence of the nucleic acid molecule encodes one or more siRNAs, wherein the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the alpha chain of wild-type TCR, and wherein the one or more siRNAs comprise the nucleic acid sequences set forth in SEQ ID NOs: 57 and 58.

Table 4. siRNA Sequences

SEQ ID NO:	siRNA	Sequence (Nucleotides 1-19 are ribonucleotides; nucleotides 20-21 are deoxyribonucleotides)
57	siRNA-TCRa-1	GUAAGGAUUCUGAUGUGUATT
58	siRNA-TCRa-2	UACACAUCAGAAUCCUUACTT
59	siRNA-TCRb-1	CCACCAUCCUCUAUGAGAUTT
60	siRNA-TCRb-2	AUCUCAUAGAGGAUGGUGGTT

[0235] In some embodiments, the second nucleotide sequence of the nucleic acid molecule encodes one or more siRNAs, wherein the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the beta chain of wild-type TCR, and wherein the one or more siRNAs comprise the nucleic acid sequences set forth in SEQ ID NOs: 59 and 60. In some embodiments, the second nucleotide sequence of the nucleic acid molecule encodes one or more siRNAs, wherein the one or more siRNAs comprise (i) one or more siRNAs that are complementary to a target sequence within a nucleotide sequence encoding a constant region of the alpha chain of wild-type TCR, wherein the one or more siRNAs comprise the nucleic acid sequences set forth in SEQ ID NOs: 57 and 58; and (ii) one or more siRNAs that are complementary to a target sequence within a nucleotide sequence encoding a constant region of the beta chain of wild-type TCR, wherein the one or more siRNAs comprise the nucleic acid sequences set forth in SEQ ID NOs: 59 and 60.

[0236] In some embodiments, the second nucleotide sequence of the nucleic acid molecule comprises SEQ ID NOs: 57-60. In some embodiments, the second nucleotide sequence comprises SEQ ID NOs: 57-60, wherein one or more of SEQ ID NOs: 57-60 is separated by one or more nucleic acids that do not encode an siRNA. In certain embodiments, the one or more siRNAs are selected from the siRNAs disclosed in U.S. Publication No. 2010/0273213 A1, which is incorporated by reference herein in its entirety.

[0237] In some embodiments, the second nucleotide sequence of the nucleic acid molecule encodes a protein, wherein the protein is capable of inhibiting the expression of an endogenous, *e.g.*, wild-type, TCR. In some embodiments, the second nucleotide sequence encodes Cas9.

II.A.3 Vectors

[0238] Certain aspects of the present disclosure are directed to vectors comprising a nucleic acid molecule disclosed herein. In some embodiments, the vector is a viral vector.

In some embodiments, the vector is a viral particle or a virus. In some embodiments, the vector is a mammalian vector. In some embodiments, the vector is a bacterial vector.

[0239] In certain embodiments, the vector is a retroviral vector. In some embodiments, the vector is selected from the group consisting of an adenoviral vector, a lentivirus, a Sendai virus, a baculoviral vector, an Epstein Barr viral vector, a papovaviral vector, a vaccinia viral vector, a herpes simplex viral vector, and an adeno associated virus (AAV) vector. In particular embodiments, the vector is an AAV vector. In some embodiments, the vector is a lentivirus. In particular embodiments, the vector is an AAV vector. In some embodiments, the vector is a Sendai virus. In some embodiments, the vector is a hybrid vector. Examples of hybrid vectors that can be used in the present disclosure can be found in Huang and Kamihira, *Biotechnol. Adv. 31(2)*:208-23 (2103), which is incorporated by reference herein in its entirety.

II.B. Recombinant T Cell Receptors (TCRs)

[0240] Certain aspects of the present disclosure are directed to recombinant T cell receptors (TCRs) or an antigen binding portion thereof that specifically bind a target human protein selected from the group consisting of tyrosinase, MAGE-A1, MART1, MAGE-A3, and SSX2. In some embodiments, the antigen-specific TCR is encoded by a nucleic acid molecule disclosed herein.

[0241] The epitope-specific TCR can be selected from (i) any epitope-specific TCR disclosed herein, *e.g.*, a TCR disclosed in sections IIA.1.a. to II.A.1.e., above, and (ii) any TCR that cross-competes for binding to the target human protein with a reference antibody, wherein the reference antibody is selected from any epitope-specific TCR disclosed herein, *e.g.*, a TCR disclosed in sections IIA.1.a. to II.A.1.e., above.

[0242] In certain embodiments, the epitope-specific TCR is an anti-tyrosinase TCR disclosed herein. In certain embodiments, the anti-tyrosinase TCR comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 5; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 6; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 7; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 8; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 9; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 10.

[0243] In certain embodiments, the epitope-specific TCR is an anti-MAGE-A1 TCR disclosed herein. In certain embodiments, the anti-MAGE-A1 TCR comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 15; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 16; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 18; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 19; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 20.

[0244] In certain embodiments, the epitope-specific TCR is an anti-MART1 TCR disclosed herein. In certain embodiments, the anti-MART1 TCR comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 25; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 26; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 27; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 29; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 30.

[0245] In certain embodiments, the epitope-specific TCR is an anti-MAGE-A3 TCR disclosed herein. In certain embodiments, the anti-MAGE-A3 TCR comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 35; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 36; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 37; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 38; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 39; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 40.

[0246] In certain embodiments, the epitope-specific TCR is an anti-SSX2 TCR disclosed herein. In certain embodiments, the anti-SSX2 TCR comprises an alpha chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 45; an alpha chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 46; an alpha chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 47; a beta chain CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 48; a beta chain CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 49; and a beta chain CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 50.

II.B.3. Bispecific T Cell Receptors (TCRs)

[0247] Certain aspects of the present disclosure are directed to a bispecific TCR comprising a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen-binding domain comprises a TCR or an antigen-binding portion thereof disclosed herein. In some embodiments, the bispecific TCR comprises a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen binding domain comprises an anti-tyrosinase TCR disclosed herein or an antigen-binding portion thereof. In some embodiments, the bispecific TCR comprises a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen binding domain comprises an anti-MAGE-A1 TCR disclosed herein or an antigen-binding portion thereof. In some embodiments, the bispecific TCR comprises a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen binding domain comprises an anti-MART1 TCR disclosed herein or an antigen-binding portion thereof. In some embodiments, the bispecific TCR comprises a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen binding domain comprises an anti-MAGE-A3 TCR disclosed herein or an antigen-binding portion thereof. In some embodiments, the bispecific TCR comprises a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen binding domain comprises an anti-SSX2 TCR disclosed herein or an antigen-binding portion thereof. In some embodiments, the first antigen-binding domain comprises a single chain variable fragment ("scFv").

[0248] In some embodiments, the second antigen-binding domain binds specifically to a protein expressed on the surface of a T cell. Any protein expressed on the surface of a T cell can be targeted by the bispecific antibody disclosed herein. In certain embodiments, the protein expressed on the surface of a T cell is not expressed by other cells. In some embodiments, the protein expressed on the surface of a T cell is expressed on the surface of one or more other human immune cells. In some embodiments, the protein expressed on the surface of a T cell is expressed on the surface of one or more other human immune cells, but it is not expressed on the surface of a human non-immune cell. In some embodiments, the second antigen-binding domain binds specifically to a protein expressed on the surface of a T cell selected from CD3, CD2, CD5, CD6, CD8, CD11a (LFA-1α), CD43, CD45, and CD53. In certain embodiments, the second antigen-binding domain binds specifically to CD3. In some embodiments, the second antigen-binding domain comprises an scFv.

[0249] In some embodiments, the first antigen-binding domain and the second antigen-binding domain are linked or associated by a covalent bond. In some embodiments, the first antigen-binding domain and the second antigen-binding domain are linked by a peptide bond.

II.C. Epitopes

[0250] In some embodiments, the antigen-specific TCR binds the same epitope as a reference TCR. In some embodiments, the antigen-specific TCR specifically binds to human tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR binds to an epitope of tyrosinase comprising the amino acid sequence set forth in SEQ ID NO: 51 (FQDYIKSYL). In some embodiments, the anti-tyrosinase TCR binds to an epitope of tyrosinase consisting of an amino acid sequence as set forth in SEQ ID NO: 51. In some embodiments, the epitope comprises amino acid residues 460-468 of tyrosinase (SEQ ID NO: 89), *e.g.*, "tyrosinase$_{460-468}$." In some embodiments, the epitope consists of amino acid residues 460-468 of tyrosinase (SEQ ID NO: 89), *e.g.*, "tyrosinase$_{460-468}$."

[0251] In some embodiments, the antigen-specific TCR specifically binds to human MAGE-A1 ("anti-MAGE-A1 TCR"), wherein the anti-MAGE-A1 TCR binds to an epitope of MAGE-A1 comprising the amino acid sequence set forth in SEQ ID NO: 52 (RVRFFFPSL). In some embodiments, 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. In some embodiments, the epitope comprises amino acid residues 289-297 of MAGE-A1 (SEQ ID NO: 90), *e.g.*, "MAGE-A1$_{289-297}$." In some embodiments, the epitope consists of amino acid residues 289-297 of MAGE-A1 (SEQ ID NO: 90), *e.g.*, "MAGE-A1$_{289-297}$."

[0252] In some embodiments, the antigen-specific TCR specifically binds to human MART1 ("anti-MART1 TCR"), wherein the anti-MART1 TCR binds to an epitope of MART1 comprising the amino acid sequence set forth in SEQ ID NO: 53 (EEAAGIGIL). In some embodiments, the anti-MART1 TCR binds to an epitope of MART1 consisting of an amino acid sequence as set forth in SEQ ID NO: 53. In some embodiments, the epitope comprises amino acid residues 25-33 of MART1 (SEQ ID NO: 91), *e.g.*, "MART1$_{25-33}$." In some embodiments, the epitope consists of amino acid residues 25-33 of MART1 (SEQ ID NO: 91), *e.g.*, "MART1$_{25-33}$."

[0253] In some embodiments, the antigen-specific TCR specifically binds to human MAGE-A3 ("anti-MAGE-A3 TCR"), wherein the anti-MAGE-A3 TCR binds to an epitope of MAGE-A3 comprising the amino acid sequence set forth in SEQ ID NO: 54 (MEVDPIGHLY). In some embodiments, 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. In some embodiments, the epitope comprises amino acid residues 167-176 of MAGE-A3 (SEQ ID NO: 92), *e.g.*, "MAGE-A3$_{167\text{-}176}$." In some embodiments, the epitope consists of amino acid residues 167-176 of MAGE-A3 (SEQ ID NO: 92), *e.g.*, "MAGE-A3$_{167\text{-}176}$."

[0254] In some embodiments, the antigen-specific TCR specifically binds to human SSX2 ("anti-SSX2 TCR"), wherein the anti-SSX2 TCR binds to an epitope of SSX2 comprising the amino acid sequence set forth in SEQ ID NO: 55 (KASEKIFYV). In some embodiments, the anti-SSX2 TCR binds to an epitope of SSX2 consisting of an amino acid sequence as set forth in SEQ ID NO: 55. In some embodiments, the epitope comprises amino acid residues 41-49 of SSX2 (SEQ ID NO: 93), *e.g.*, "SSX2$_{41\text{-}49}$." In some embodiments, the epitope consists of amino acid residues 41-49 of SSX2 (SEQ ID NO: 93), *e.g.*, " SSX2$_{41\text{-}49}$."

II.D. HLA Class I Molecules

[0255] Certain aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope disclosed herein. The HLA class I molecule can be any HLA class I molecule known in the art. In some embodiments, the HLA class I molecule is selected from an HLA-A, HLA-B, and HLA-C allele. In some embodiments, the HLA class I molecule is selected from an HLA-E, HLA-F, and HLA-G allele. In certain embodiments, the HLA class I molecule is an HLA-A allele. In certain embodiments, the HLA class I molecule is an HLA-B allele. In certain embodiments, the HLA class I molecule is an HLA-C allele.

[0256] Many HLA-A, HLA-B, and HLA-C alleles are known in the art, and any of the known alleles can be used in the present disclosure. An updated list of HLA alleles is available at hla.alleles.org/ (last visited on February 27, 2019).

II.D.1. HLA-A Alleles and Complexes Thereof

[0257] Certain aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope, wherein the HLA class I molecule is an HLA-A allele, and wherein the epitope is an SSX2 epitope disclosed herein. In certain embodiments, the SSX2 epitope comprises, consists of, or consists essentially of SEQ ID NO: 55.

[0258] In some embodiments, the HLA-A allele is selected from an HLA-A*01, an HLA-A*02, an HLA-A*03, an HLA-A*11, an HLA-A*23, an HLA-A*24, an HLA-A*25, an HLA-A*26, an HLA-A*29, an HLA-A*30, an HLA-A*31, an HLA-A*32, an HLA-A*33, an HLA-A*34, an HLA-A*36, an HLA-A*43, an HLA-A*66, an HLA-A*68, an HLA-A*69, an HLA-A*74, and an HLA-A*80. In certain embodiments, the HLA-A allele is an HLA-A*02 allele.

[0259] In certain embodiments, the complex comprises an HLA-A*02 allele and an SSX2 epitope disclosed herein, *e.g.*, an epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 55. In certain embodiments, the HLA-A allele is an HLA-A*02:01 allele. In particular embodiments, the complex comprises an HLA-A*02:01 allele and an SSX2 epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 55.

[0260] In certain embodiments, the HLA-A allele is selected from the group consisting of HLA-A*02:01:01:01, HLA-A*02:01:01:02L, HLA-A*02:01:01:03, HLA-A*02:01:01:04, HLA-A*02:01:01:05, HLA-A*02:01:01:06, HLA-A*02:01:01:07, HLA-A*02:01:01:08, HLA-A*02:01:01:09, HLA-A*02:01:01:10, HLA-A*02:01:01:11, HLA-A*02:01:01:12, HLA-A*02:01:01:13, HLA-A*02:01:01:14, HLA-A*02:01:01:15, HLA-A*02:01:01:16, HLA-A*02:01:01:17, HLA-A*02:01:01:18, HLA-A*02:01:01:19, HLA-A*02:01:01:20, HLA-A*02:01:01:21, HLA-A*02:01:01:22, HLA-A*02:01:01:23, HLA-A*02:01:01:24, HLA-A*02:01:01:25, HLA-A*02:01:01:26, HLA-A*02:01:01:27, HLA-A*02:01:01:28, HLA-A*02:01:01:29, HLA-A*02:01:01:30, HLA-A*02:01:01:31, HLA-A*02:01:01:32, HLA-A*02:01:01:33, HLA-A*02:01:01:34, HLA-A*02:01:01:35, HLA-A*02:01:01:36, HLA-A*02:01:01:37, HLA-A*02:01:01:38, HLA-A*02:01:01:39, HLA-A*02:01:01:40, HLA-A*02:01:01:41, HLA-A*02:01:01:42, HLA-A*02:01:01:43, HLA-A*02:01:01:44, HLA-A*02:01:01:45, HLA-A*02:01:01:46, HLA-A*02:01:01:47, HLA-A*02:01:01:48, HLA-A*02:01:01:49, HLA-A*02:01:01:50, HLA-A*02:01:01:51, HLA-A*02:01:01:52, HLA-A*02:01:01:53, HLA-A*02:01:01:54, HLA-A*02:01:01:55, HLA-A*02:01:02, HLA-A*02:01:03, HLA-A*02:01:04, HLA-A*02:01:05, HLA-A*02:01:06, HLA-A*02:01:07, HLA-A*02:01:08, HLA-A*02:01:09, HLA-A*02:01:10, HLA-A*02:01:100, HLA-A*02:01:101, HLA-A*02:01:102, HLA-A*02:01:103, HLA-A*02:01:104, HLA-A*02:01:105, HLA-A*02:01:106, HLA-A*02:01:107, HLA-A*02:01:108, HLA-A*02:01:109, HLA-A*02:01:11, HLA-A*02:01:110, HLA-A*02:01:111, HLA-A*02:01:112, HLA-A*02:01:113, HLA-A*02:01:114, HLA-A*02:01:115, HLA-

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II.D.2. HLA-B Alleles and Complexes Thereof

[0261] Certain aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope, wherein the HLA class I molecule is an HLA-B allele, and wherein the epitope is a MAGE-A1 epitope disclosed herein. In certain embodiments, the MAGE-A1 epitope comprises, consists of, or consists essentially of SEQ ID NO: 52.

[0262] Other aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope, wherein the HLA class I molecule is an HLA-B allele, and wherein the epitope is a MART1 epitope disclosed herein. In certain embodiments, the MART1 epitope comprises, consists of, or consists essentially of SEQ ID NO: 53.

[0263] Other aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope, wherein the HLA class I molecule is an HLA-B allele, and wherein the epitope is a MAGE-A3 epitope disclosed herein. In certain embodiments, the MAGE-A3 epitope comprises, consists of, or consists essentially of SEQ ID NO: 54.

[0264] In some embodiments, the HLA-B allele is selected from selected from an HLA-B*07, an HLA-B*08, an HLA-B*13, an HLA-B*14, an HLA-B*15, an HLA-B*18, an HLA-B*27, an HLA-B*35, an HLA-B*37, an HLA-B*38, an HLA-B*39, an HLA-B*40, an HLA-B*41, an HLA-B*42, an HLA-B*44, an HLA-B*45, an HLA-B*46, an HLA-B*47, an HLA-B*48, an HLA-B*49, an HLA-B*50, an HLA-B*51, an HLA-B*52, an HLA-B*53, an HLA-B*54, an HLA-B*55, an HLA-B*56, an HLA-B*57, an HLA-B*58, an HLA-B*59, an HLA-B*67, an HLA-B*73, an HLA-B*78, an HLA-B*79, an HLA-B*81, an HLA-B*82, and an HLA-B*83.

II.D.2.a. HLA-B*07 Alleles and Complexes Thereof

[0265] In some embodiments, the HLA-B allele is an HLA-B*07 allele. In certain embodiments, the complex comprises an HLA-B*07 allele and a MAGE-A1 epitope disclosed herein, *e.g.*, an epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 52. In certain embodiments, the HLA-B allele is an HLA-B*07:02 allele. In certain embodiments, the HLA-B allele is an HLA-B*07:03 allele. In certain embodiments, the HLA-B allele is an HLA-B*07:04 allele. In certain embodiments, the HLA-B allele is an HLA-B*07:05 allele. In certain embodiments, the HLA-B allele is an HLA-B*07:06 allele. In particular embodiments, the complex comprises an HLA-B*07:02 allele and a MAGE-A1 epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 52.

[0266] In certain embodiments, the HLA-B allele is selected from the group consisting of HLA-B*07:02:01:01, HLA-B*07:02:01:02, HLA-B*07:02:01:03, HLA-B*07:02:01:04, HLA-B*07:02:01:05, HLA-B*07:02:01:06, HLA-B*07:02:01:07, HLA-B*07:02:01:08, HLA-B*07:02:01:09, HLA-B*07:02:01:10, HLA-B*07:02:01:11, HLA-B*07:02:01:12, HLA-B*07:02:01:13, HLA-B*07:02:01:14, HLA-B*07:02:02, HLA-B*07:02:03, HLA-B*07:02:04, HLA-B*07:02:05, HLA-B*07:02:06, HLA-B*07:02:07, HLA-B*07:02:08, HLA-B*07:02:09, HLA-B*07:02:10, HLA-B*07:02:11, HLA-B*07:02:12, HLA-B*07:02:13, HLA-B*07:02:14, HLA-B*07:02:15, HLA-B*07:02:16, HLA-B*07:02:17, HLA-B*07:02:18, HLA-B*07:02:19, HLA-B*07:02:20, HLA-B*07:02:21, HLA-

B*07:02:22, HLA-B*07:02:23, HLA-B*07:02:24, HLA-B*07:02:25, HLA-B*07:02:26, HLA-B*07:02:27, HLA-B*07:02:28, HLA-B*07:02:29, HLA-B*07:02:30, HLA-B*07:02:31, HLA-B*07:02:32, HLA-B*07:02:33, HLA-B*07:02:34, HLA-B*07:02:35, HLA-B*07:02:36, HLA-B*07:02:37, HLA-B*07:02:38, HLA-B*07:02:39, HLA-B*07:02:40, HLA-B*07:02:41, HLA-B*07:02:42, HLA-B*07:02:43, HLA-B*07:02:44, HLA-B*07:02:45, HLA-B*07:02:46, HLA-B*07:02:47, HLA-B*07:02:48, HLA-B*07:02:49, HLA-B*07:02:50, HLA-B*07:02:51, HLA-B*07:02:52, HLA-B*07:02:53, HLA-B*07:02:54, HLA-B*07:02:55, HLA-B*07:02:56, HLA-B*07:02:57, HLA-B*07:02:58, HLA-B*07:02:59, HLA-B*07:02:60, HLA-B*07:02:61, HLA-B*07:02:62, HLA-B*07:02:63, HLA-B*07:02:64, HLA-B*07:02:65, HLA-B*07:02:66, HLA-B*07:02:67, HLA-B*07:02:68, HLA-B*07:02:69, HLA-B*07:02:70, HLA-B*07:02:71, HLA-B*07:02:72, HLA-B*07:02:73, HLA-B*07:03, HLA-B*07:04:01, HLA-B*07:04:02, HLA-B*07:05:01:01, HLA-B*07:05:01:02, HLA-B*07:05:01:03, HLA-B*07:05:01:04, HLA-B*07:05:02, HLA-B*07:05:03, HLA-B*07:05:04, HLA-B*07:05:05, HLA-B*07:05:06, HLA-B*07:05:07, HLA-B*07:05:08, HLA-B*07:05:09, HLA-B*07:06:01, HLA-B*07:06:02, HLA-B*07:06:03, HLA-B*07:07:01, HLA-B*07:07:02, HLA-B*07:08:01, HLA-B*07:08:02, HLA-B*07:09:01, HLA-B*07:09:02, HLA-B*07:10, HLA-B*07:100, HLA-B*07:101, HLA-B*07:102, HLA-B*07:103, HLA-B*07:104, HLA-B*07:105, HLA-B*07:106, HLA-B*07:107, HLA-B*07:108, HLA-B*07:109, HLA-B*07:11, HLA-B*07:110, HLA-B*07:111, HLA-B*07:112, HLA-B*07:113, HLA-B*07:114, HLA-B*07:115, HLA-B*07:116, HLA-B*07:117, HLA-B*07:118, HLA-B*07:119, HLA-B*07:12, HLA-B*07:120, HLA-B*07:121, HLA-B*07:122, HLA-B*07:123, HLA-B*07:124, HLA-B*07:125, HLA-B*07:126, HLA-B*07:127, HLA-B*07:128, HLA-B*07:129, HLA-B*07:13, HLA-B*07:130, HLA-B*07:131, HLA-B*07:132, HLA-B*07:133, HLA-B*07:134, HLA-B*07:135, HLA-B*07:136:01, HLA-B*07:136:02, HLA-B*07:137, HLA-B*07:138, HLA-B*07:139:01, HLA-B*07:139:02, HLA-B*07:14, HLA-B*07:140, HLA-B*07:141, HLA-B*07:142, HLA-B*07:143, HLA-B*07:144, HLA-B*07:145, HLA-B*07:146, HLA-B*07:147, HLA-B*07:148, HLA-B*07:149, HLA-B*07:15, HLA-B*07:150, HLA-B*07:151:01, HLA-B*07:151:02, HLA-B*07:152, HLA-B*07:153, HLA-B*07:154, HLA-B*07:155, HLA-B*07:156, HLA-B*07:157, HLA-B*07:158, HLA-B*07:159, HLA-B*07:16, HLA-B*07:160, HLA-B*07:161, HLA-B*07:162, HLA-B*07:163, HLA-B*07:164, HLA-B*07:165, HLA-B*07:166, HLA-B*07:167, HLA-B*07:168, HLA-B*07:169, HLA-B*07:17, HLA-

B*07:170, HLA-B*07:171, HLA-B*07:172, HLA-B*07:173, HLA-B*07:174, HLA-B*07:175, HLA-B*07:176, HLA-B*07:177, HLA-B*07:178, HLA-B*07:179, HLA-B*07:180, HLA-B*07:181, HLA-B*07:182, HLA-B*07:183, HLA-B*07:184, HLA-B*07:185, HLA-B*07:186, HLA-B*07:187, HLA-B*07:188, HLA-B*07:189, HLA-B*07:18:01, HLA-B*07:18:02, HLA-B*07:19, HLA-B*07:190, HLA-B*07:191, HLA-B*07:192, HLA-B*07:193, HLA-B*07:194, HLA-B*07:195, HLA-B*07:196, HLA-B*07:197, HLA-B*07:198, HLA-B*07:199, HLA-B*07:20, HLA-B*07:200, HLA-B*07:201, HLA-B*07:202, HLA-B*07:203, HLA-B*07:204, HLA-B*07:205, HLA-B*07:206, HLA-B*07:207, HLA-B*07:208, HLA-B*07:209, HLA-B*07:21, HLA-B*07:210, HLA-B*07:211, HLA-B*07:212, HLA-B*07:213, HLA-B*07:214, HLA-B*07:215, HLA-B*07:216, HLA-B*07:217, HLA-B*07:218, HLA-B*07:219, HLA-B*07:220, HLA-B*07:221, HLA-B*07:222, HLA-B*07:223, HLA-B*07:224, HLA-B*07:225, HLA-B*07:226, HLA-B*07:227, HLA-B*07:228:01, HLA-B*07:228:02, HLA-B*07:229, HLA-B*07:22:01, HLA-B*07:22:02, HLA-B*07:23, HLA-B*07:230, HLA-B*07:231, HLA-B*07:232, HLA-B*07:233, HLA-B*07:234, HLA-B*07:235, HLA-B*07:236, HLA-B*07:237, HLA-B*07:238, HLA-B*07:239, HLA-B*07:24, HLA-B*07:240, HLA-B*07:241, HLA-B*07:242, HLA-B*07:243, HLA-B*07:244, HLA-B*07:245, HLA-B*07:246, HLA-B*07:247, HLA-B*07:248, HLA-B*07:249, HLA-B*07:25, HLA-B*07:250, HLA-B*07:251, HLA-B*07:252, HLA-B*07:253, HLA-B*07:254, HLA-B*07:255, HLA-B*07:256, HLA-B*07:257, HLA-B*07:258, HLA-B*07:259, HLA-B*07:26, HLA-B*07:260, HLA-B*07:261, HLA-B*07:262, HLA-B*07:263, HLA-B*07:264, HLA-B*07:265, HLA-B*07:266, HLA-B*07:267, HLA-B*07:268, HLA-B*07:269, HLA-B*07:27, HLA-B*07:270, HLA-B*07:271, HLA-B*07:272, HLA-B*07:273, HLA-B*07:274, HLA-B*07:275, HLA-B*07:276:01, HLA-B*07:276:02, HLA-B*07:277, HLA-B*07:278, HLA-B*07:279, HLA-B*07:28, HLA-B*07:280, HLA-B*07:281, HLA-B*07:282, HLA-B*07:283, HLA-B*07:284, HLA-B*07:285, HLA-B*07:286, HLA-B*07:287, HLA-B*07:288, HLA-B*07:289, HLA-B*07:29, HLA-B*07:290, HLA-B*07:291, HLA-B*07:292, HLA-B*07:293, HLA-B*07:294, HLA-B*07:295, HLA-B*07:296, HLA-B*07:297, HLA-B*07:298, HLA-B*07:299, HLA-B*07:30, HLA-B*07:300, HLA-B*07:301, HLA-B*07:302, HLA-B*07:303:01, HLA-B*07:303:02, HLA-B*07:304, HLA-B*07:305, HLA-B*07:306, HLA-B*07:307, HLA-B*07:308, HLA-B*07:309, HLA-B*07:31, HLA-B*07:310, HLA-B*07:311, HLA-B*07:312, HLA-B*07:313, HLA-B*07:314, HLA-B*07:315, HLA-

B*07:316, HLA-B*07:317, HLA-B*07:318, HLA-B*07:319, HLA-B*07:32, HLA-B*07:320, HLA-B*07:321, HLA-B*07:322, HLA-B*07:323, HLA-B*07:324, HLA-B*07:325, HLA-B*07:326, HLA-B*07:327, HLA-B*07:328, HLA-B*07:329, HLA-B*07:330, HLA-B*07:331, HLA-B*07:332, HLA-B*07:333, HLA-B*07:334, HLA-B*07:335, HLA-B*07:336, HLA-B*07:337, HLA-B*07:338, HLA-B*07:339, HLA-B*07:33:01, HLA-B*07:33:02, HLA-B*07:33:03, HLA-B*07:34, HLA-B*07:340, HLA-B*07:341, HLA-B*07:342, HLA-B*07:343, HLA-B*07:344, HLA-B*07:345, HLA-B*07:346, HLA-B*07:347, HLA-B*07:348, HLA-B*07:349, HLA-B*07:35, HLA-B*07:350, HLA-B*07:351, HLA-B*07:352, HLA-B*07:353, HLA-B*07:354, HLA-B*07:355, HLA-B*07:356, HLA-B*07:357, HLA-B*07:358, HLA-B*07:36, HLA-B*07:37:01, HLA-B*07:37:02, HLA-B*07:38, HLA-B*07:39, HLA-B*07:40, HLA-B*07:41, HLA-B*07:42, HLA-B*07:43, HLA-B*07:44, HLA-B*07:45, HLA-B*07:46, HLA-B*07:47, HLA-B*07:48, HLA-B*07:49, HLA-B*07:50, HLA-B*07:51, HLA-B*07:52, HLA-B*07:53, HLA-B*07:54, HLA-B*07:55, HLA-B*07:56:01, HLA-B*07:56:02, HLA-B*07:57, HLA-B*07:58, HLA-B*07:59, HLA-B*07:60, HLA-B*07:61, HLA-B*07:62, HLA-B*07:63, HLA-B*07:64, HLA-B*07:65, HLA-B*07:66, HLA-B*07:67, HLA-B*07:68:01, HLA-B*07:68:02, HLA-B*07:68:03, HLA-B*07:69, HLA-B*07:70, HLA-B*07:71, HLA-B*07:72, HLA-B*07:73, HLA-B*07:74, HLA-B*07:75:01:01, HLA-B*07:75:01:02, HLA-B*07:76, HLA-B*07:77, HLA-B*07:78, HLA-B*07:79, HLA-B*07:80, HLA-B*07:81, HLA-B*07:82, HLA-B*07:83, HLA-B*07:84, HLA-B*07:85:01, HLA-B*07:85:02, HLA-B*07:86, HLA-B*07:87, HLA-B*07:88, HLA-B*07:89, HLA-B*07:90, HLA-B*07:91, HLA-B*07:92, HLA-B*07:93, HLA-B*07:94, HLA-B*07:95, HLA-B*07:96:01, HLA-B*07:96:02, HLA-B*07:97, HLA-B*07:98, and HLA-B*07:99.

II.D.2.b. HLA-B*18 Alleles and Complexes Thereof

[0267] In some embodiments, the HLA-B allele is an HLA-B*18 allele. In certain embodiments, the complex comprises an HLA-B*18 allele and a MART1 epitope disclosed herein, *e.g.*, an epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 53. In certain embodiments, the HLA-B allele is an HLA-B*18:01 allele. In particular embodiments, the complex comprises an HLA-B*18:01 allele and a MART1 epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 53.

[0268] In some embodiments, the HLA-B allele is an HLA-B*18 allele. In certain embodiments, the complex comprises an HLA-B*18 allele and a MAGE-A3 epitope disclosed herein, *e.g.*, an epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 54. In certain embodiments, the HLA-B allele is an HLA-B*18:01 allele. In particular embodiments, the complex comprises an HLA-B*18:01 allele and a MAGE-A3 epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 54.

[0269] In certain embodiments, the HLA-B allele is selected from the group consisting of HLA-B*18:01:01:01, HLA-B*18:01:01:02, HLA-B*18:01:01:03, HLA-B*18:01:01:04, HLA-B*18:01:01:05, HLA-B*18:01:01:06, HLA-B*18:01:01:07, HLA-B*18:01:01:08, HLA-B*18:01:01:09, HLA-B*18:01:01:10, HLA-B*18:01:01:11, HLA-B*18:01:01:12, HLA-B*18:01:01:13, HLA-B*18:01:01:14, HLA-B*18:01:01:15, HLA-B*18:01:01:16, HLA-B*18:01:01:17, HLA-B*18:01:01:18, HLA-B*18:01:01:19, HLA-B*18:01:02, HLA-B*18:01:03, HLA-B*18:01:04, HLA-B*18:01:05, HLA-B*18:01:06, HLA-B*18:01:07, HLA-B*18:01:08, HLA-B*18:01:09, HLA-B*18:01:10, HLA-B*18:01:11, HLA-B*18:01:12, HLA-B*18:01:13, HLA-B*18:01:14, HLA-B*18:01:15, HLA-B*18:01:16, HLA-B*18:01:17, HLA-B*18:01:18, HLA-B*18:01:19, HLA-B*18:01:20, HLA-B*18:01:21, HLA-B*18:01:22, HLA-B*18:01:23, HLA-B*18:01:24, HLA-B*18:01:25, HLA-B*18:01:26, HLA-B*18:01:27, HLA-B*18:01:28, HLA-B*18:01:29, HLA-B*18:01:30, HLA-B*18:01:31, and HLA-B*18:01:32.

[0270] In certain embodiments, the HLA-B allele is selected from the group consisting of HLA-B*18:02, HLA-B*18:03:01, HLA-B*18:03:02, HLA-B*18:04:01, HLA-B*18:04:02, HLA-B*18:05:01:01, HLA-B*18:05:01:02, HLA-B*18:06, HLA-B*18:07:01, HLA-B*18:07:02, HLA-B*18:08, HLA-B*18:09, HLA-B*18:10, HLA-B*18:100, HLA-B*18:101, HLA-B*18:102, HLA-B*18:103, HLA-B*18:104, HLA-B*18:105, HLA-B*18:106, HLA-B*18:107, HLA-B*18:108, HLA-B*18:109, HLA-B*18:11, HLA-B*18:110, HLA-B*18:111, HLA-B*18:112, HLA-B*18:113, HLA-B*18:114, HLA-B*18:115, HLA-B*18:116, HLA-B*18:117, HLA-B*18:118, HLA-B*18:119, HLA-B*18:120, HLA-B*18:121, HLA-B*18:122, HLA-B*18:123, HLA-B*18:124, HLA-B*18:125, HLA-B*18:126, HLA-B*18:127, HLA-B*18:128, HLA-B*18:129, HLA-B*18:12:01, HLA-B*18:12:02, HLA-B*18:13, HLA-B*18:130, HLA-B*18:131:01:01, HLA-B*18:131:01:02, HLA-B*18:132, HLA-B*18:133, HLA-B*18:134, HLA-B*18:135, HLA-B*18:136, HLA-B*18:137, HLA-B*18:138N, HLA-B*18:139, HLA-B*18:14, HLA-B*18:140, HLA-B*18:141, HLA-B*18:142, HLA-B*18:143, HLA-B*18:144, HLA-B*18:145, HLA-B*18:146, HLA-B*18:147, HLA-B*18:148, HLA-B*18:149, HLA-B*18:15, HLA-B*18:150, HLA-B*18:151, HLA-B*18:152, HLA-B*18:153, HLA-

B*18:154N, HLA-B*18:155, HLA-B*18:156:01:01, HLA-B*18:156:01:02, HLA-B*18:157:01:01, HLA-B*18:157:01:02, HLA-B*18:158, HLA-B*18:159, HLA-B*18:160, HLA-B*18:161, HLA-B*18:17N, HLA-B*18:18:01:01, HLA-B*18:18:01:02, HLA-B*18:19, HLA-B*18:20, HLA-B*18:21, HLA-B*18:22, HLA-B*18:23N, HLA-B*18:24, HLA-B*18:25, HLA-B*18:26, HLA-B*18:27, HLA-B*18:28, HLA-B*18:29, HLA-B*18:30, HLA-B*18:31, HLA-B*18:32, HLA-B*18:33, HLA-B*18:34, HLA-B*18:35, HLA-B*18:36, HLA-B*18:37:01, HLA-B*18:37:02, HLA-B*18:38, HLA-B*18:39, HLA-B*18:40, HLA-B*18:41, HLA-B*18:42, HLA-B*18:43, HLA-B*18:44:01, HLA-B*18:44:02, HLA-B*18:45, HLA-B*18:46, HLA-B*18:47, HLA-B*18:48, HLA-B*18:49, HLA-B*18:50, HLA-B*18:51, HLA-B*18:52, HLA-B*18:53, HLA-B*18:54, HLA-B*18:55, HLA-B*18:56, HLA-B*18:57:01, HLA-B*18:57:02, HLA-B*18:58, HLA-B*18:59, HLA-B*18:60, HLA-B*18:61, HLA-B*18:62, HLA-B*18:63, HLA-B*18:64, HLA-B*18:65, HLA-B*18:66, HLA-B*18:67, HLA-B*18:68, HLA-B*18:69, HLA-B*18:70, HLA-B*18:71, HLA-B*18:72:01, HLA-B*18:72:02, HLA-B*18:72:03, HLA-B*18:73, HLA-B*18:74N, HLA-B*18:75, HLA-B*18:76, HLA-B*18:77, HLA-B*18:78, HLA-B*18:79, HLA-B*18:80, HLA-B*18:81, HLA-B*18:82, HLA-B*18:83, HLA-B*18:84, HLA-B*18:85, HLA-B*18:86, HLA-B*18:87, HLA-B*18:88, HLA-B*18:89, HLA-B*18:90, HLA-B*18:91, HLA-B*18:92, HLA-B*18:93, HLA-B*18:94N, HLA-B*18:95, HLA-B*18:96, HLA-B*18:97, HLA-B*18:98, and HLA-B*18:99.

II.D.3. HLA-C Alleles and Complexes Thereof

[0271] Certain aspects of the present disclosure are directed to a complex comprising an HLA class I molecule and an epitope, wherein the HLA class I molecule is an HLA-C allele, and wherein the epitope is a tyrosinase epitope disclosed herein. In certain embodiments, the tyrosinase epitope comprises, consists of, or consists essentially of SEQ ID NO: 51.

[0272] In some embodiments, the HLA-C allele 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. In certain embodiments, the HLA-C allele is an HLA-C*05:01 allele. In certain embodiments, the HLA-C allele is an HLA-C*05:03 allele. In certain embodiments, the HLA-C allele is an HLA-C*05:04 allele. In certain embodiments, the HLA-C allele is an HLA-C*05:05 allele. In certain embodiments, the HLA-C allele is an HLA-C*05:06 allele.

[0273] In certain embodiments, the complex comprises an HLA-C*05 allele and a tyrosinase epitope disclosed herein, *e.g.*, an epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 51. In certain embodiments, the HLA-C allele is an HLA-C*05:01 allele. In particular embodiments, the complex comprises an HLA-C*05:01 allele and a tyrosinase epitope compromising, consisting of, or consisting essentially of SEQ ID NO: 51.

[0274] In certain embodiments, the HLA-C allele is selected from the group consisting of HLA-C*05:01:01:01, HLA-C*05:01:01:02, HLA-C*05:01:01:03, HLA-C*05:01:01:04, HLA-C*05:01:01:05, HLA-C*05:01:01:06, HLA-C*05:01:01:07, HLA-C*05:01:01:08, HLA-C*05:01:01:09, HLA-C*05:01:01:10, HLA-C*05:01:01:11, HLA-C*05:01:01:12, HLA-C*05:01:01:13, HLA-C*05:01:01:14, HLA-C*05:01:01:15, HLA-C*05:01:01:16, HLA-C*05:01:02, HLA-C*05:01:03, HLA-C*05:01:04, HLA-C*05:01:05, HLA-C*05:01:06, HLA-C*05:01:07, HLA-C*05:01:08, HLA-C*05:01:09, HLA-C*05:01:10, HLA-C*05:01:11, HLA-C*05:01:12, HLA-C*05:01:13, HLA-C*05:01:14, HLA-C*05:01:15, HLA-C*05:01:16, HLA-C*05:01:17, HLA-C*05:01:18, HLA-C*05:01:19, HLA-C*05:01:20, HLA-C*05:01:21, HLA-C*05:01:22, HLA-C*05:01:23, HLA-C*05:01:24, HLA-C*05:01:25, HLA-C*05:01:26, HLA-C*05:01:27, HLA-C*05:01:28, HLA-C*05:01:29, HLA-C*05:01:30, HLA-C*05:01:31, HLA-C*05:01:32, HLA-C*05:01:33, HLA-C*05:01:34, HLA-C*05:01:35, HLA-C*05:01:36, HLA-C*05:01:37, HLA-C*05:01:38, HLA-C*05:01:39, HLA-C*05:01:40, HLA-C*05:01:41, HLA-C*05:01:42, HLA-C*05:01:43, HLA-C*05:01:44, HLA-C*05:01:45, HLA-C*05:03, HLA-C*05:04:01, HLA-C*05:04:02, HLA-C*05:05:01, HLA-C*05:05:02, HLA-C*05:06, HLA-C*05:07N, HLA-C*05:08, HLA-C*05:09:01, HLA-C*05:09:02, HLA-C*05:09:03, HLA-C*05:10, HLA-C*05:100, HLA-C*05:101, HLA-C*05:102, HLA-C*05:103:01, HLA-C*05:103:02, HLA-C*05:104, HLA-C*05:105, HLA-C*05:106:01, HLA-C*05:106:02, HLA-C*05:107, HLA-C*05:108, HLA-C*05:109, HLA-C*05:11, HLA-C*05:110, HLA-C*05:111, HLA-C*05:112, HLA-C*05:113N, HLA-C*05:114, HLA-C*05:115, HLA-C*05:116, HLA-C*05:117, HLA-C*05:118, HLA-C*05:119, HLA-C*05:12, HLA-C*05:120, HLA-C*05:121, HLA-C*05:122, HLA-C*05:123, HLA-C*05:124, HLA-C*05:125, HLA-C*05:126, HLA-C*05:127, HLA-C*05:128N, HLA-C*05:129, HLA-C*05:13, HLA-C*05:130, HLA-C*05:131, HLA-C*05:132, HLA-C*05:133, HLA-C*05:134, HLA-C*05:135, HLA-C*05:136, HLA-C*05:137, HLA-C*05:138, HLA-C*05:139, HLA-C*05:14, HLA-C*05:140, HLA-C*05:141, HLA-C*05:142, HLA-

C*05:143, HLA-C*05:144, HLA-C*05:145, HLA-C*05:146, HLA-C*05:147, HLA-C*05:148, HLA-C*05:149, HLA-C*05:15, HLA-C*05:150, HLA-C*05:151, HLA-C*05:152, HLA-C*05:153N, HLA-C*05:154N, HLA-C*05:155, HLA-C*05:156, HLA-C*05:157, HLA-C*05:158, HLA-C*05:159, HLA-C*05:16, HLA-C*05:160, HLA-C*05:161, HLA-C*05:162, HLA-C*05:163, HLA-C*05:164, HLA-C*05:165, HLA-C*05:166, HLA-C*05:167, HLA-C*05:168, HLA-C*05:169N, HLA-C*05:17, HLA-C*05:170, HLA-C*05:171:01:01, HLA-C*05:171:01:02, HLA-C*05:172, HLA-C*05:173, HLA-C*05:174, HLA-C*05:175N, HLA-C*05:176, HLA-C*05:177, HLA-C*05:178, HLA-C*05:179, HLA-C*05:180N, HLA-C*05:181, HLA-C*05:182, HLA-C*05:183, HLA-C*05:184, HLA-C*05:185, HLA-C*05:186, HLA-C*05:187, HLA-C*05:188, HLA-C*05:189, HLA-C*05:18:01, HLA-C*05:18:02, HLA-C*05:18:03, HLA-C*05:18:04, HLA-C*05:18:05, HLA-C*05:19, HLA-C*05:190, HLA-C*05:191, HLA-C*05:192, HLA-C*05:193, HLA-C*05:194, HLA-C*05:195, HLA-C*05:196, HLA-C*05:197, HLA-C*05:198, HLA-C*05:199, HLA-C*05:20, HLA-C*05:200, HLA-C*05:201, HLA-C*05:202Q, HLA-C*05:203, HLA-C*05:21, HLA-C*05:22:01, HLA-C*05:22:02, HLA-C*05:23, HLA-C*05:24, HLA-C*05:25, HLA-C*05:26, HLA-C*05:27, HLA-C*05:28, HLA-C*05:29:01, HLA-C*05:29:02, HLA-C*05:30, HLA-C*05:31, HLA-C*05:32, HLA-C*05:33, HLA-C*05:34, HLA-C*05:35, HLA-C*05:36, HLA-C*05:37, HLA-C*05:38, HLA-C*05:39, HLA-C*05:40, HLA-C*05:41, HLA-C*05:42, HLA-C*05:43, HLA-C*05:44:01, HLA-C*05:44:02, HLA-C*05:45, HLA-C*05:46, HLA-C*05:47, HLA-C*05:48N, HLA-C*05:49, HLA-C*05:50, HLA-C*05:51Q, HLA-C*05:52, HLA-C*05:53, HLA-C*05:54, HLA-C*05:55, HLA-C*05:56, HLA-C*05:57, HLA-C*05:58:01, HLA-C*05:58:02, HLA-C*05:58:03, HLA-C*05:58:04, HLA-C*05:59, HLA-C*05:60, HLA-C*05:61, HLA-C*05:62, HLA-C*05:63, HLA-C*05:64:01, HLA-C*05:64:02, HLA-C*05:65, HLA-C*05:66, HLA-C*05:67, HLA-C*05:68, HLA-C*05:69, HLA-C*05:70, HLA-C*05:71, HLA-C*05:72, HLA-C*05:73, HLA-C*05:74, HLA-C*05:75, HLA-C*05:76, HLA-C*05:77, HLA-C*05:78:01, HLA-C*05:78:02, HLA-C*05:79, HLA-C*05:80, HLA-C*05:81, HLA-C*05:82, HLA-C*05:83, HLA-C*05:84, HLA-C*05:85, HLA-C*05:86, HLA-C*05:87, HLA-C*05:88, HLA-C*05:89, HLA-C*05:90, HLA-C*05:91N, HLA-C*05:92N, HLA-C*05:93, HLA-C*05:94, HLA-C*05:95, HLA-C*05:96, HLA-C*05:97, HLA-C*05:98, and HLA-C*05:99N.

II.E. Cells Expressing TCRs

[0275] Certain aspects of the present disclosure are directed to cells comprising a nucleic acid molecule disclosed herein, a vector disclosed herein, a recombinant TCR disclosed herein, a bispecific TCR disclosed herein, or any combination thereof. Any cell can be used in the present disclosure.

[0276] In certain embodiments, the cell expresses CD3. CD3 expression can be naturally occurring, *e.g.*, the CD3 is expressed from a nucleic acid sequence that is endogenously expressed by the cell. For example, T cells and natural killer (NK) cells naturally express CD3. Thus, in some embodiments, the cell is a T cell or a natural killer cell. In certain embodiments, the cell is a T cell selected from a natural killer T (NKT) cell and an innate lymphoid cell (ILC).

[0277] In some embodiments, the T cell is isolated from a human subject. In some embodiments, the human subject is the same subject that will ultimately receive the T cell therapy. In other embodiments, the subject is a donor subject, wherein the donor subject is not the same subject that will receive the T cell therapy.

[0278] In some embodiments, the cell is a cell that does not naturally express CD3, wherein the cell has been modified to express CD3. In some embodiments, the cell comprises a transgene encoding CD3, wherein the transgene is expressed by the cell. In some embodiments, the cell comprises a transgene encoding a protein that activates expression of endogenous CD3 by the cell. In some embodiments, the cell comprises a transgene encoding a protein or siRNA that inhibits an inhibitor of CD3 expression in the cell. In some embodiments, the transgene is incorporated into the genome of the cell. In some embodiments, the transgene is not incorporated into the genome of the cell.

[0279] In some embodiments, the cell that is modified to express CD3 is isolated from a human subject. In some embodiments, the human subject is the same subject that will ultimately receive the cell therapy. In other embodiments, the subject is a donor subject, wherein the donor subject is not the same subject that will receive the cell therapy.

II.F. Vaccines

[0280] Certain aspects of the present disclosure a cancer vaccine comprising a peptide comprising an amino acid sequence as set forth in SEQ ID NO: 13. In some embodiments, the cancer vaccine comprises a peptide that consists of the amino acid sequence set forth in SEQ ID NO: 13. In some embodiments, the vaccine further comprises one or more excipient. In some embodiments, the vaccine further comprises one or more additional peptides. In some embodiments, the one or more additional peptides comprise one or more additional epitopes.

III. Methods of the Disclosure

[0281] Certain aspects of the present disclosure are directed to methods of treating a cancer in a subject in need thereof. Other aspects of the present disclosure are directed to methods of engineering an antigen-targeting cell. Other aspects of the present disclosure are directed to methods of enriching a target population of T cells obtained from a human subject.

III.A. Methods of Treating Cancer

[0282] Certain aspects of the present disclosure are directed to methods of treating a cancer in a subject in need thereof, comprising administering to the subject a nucleic acid molecule disclosed herein, a recombinant TCR disclosed herein, a bispecific TCR disclosed herein, an epitope disclosed herein, or an HLA class I molecule disclosed herein, or a vector or cell comprising any of the above.

[0283] In some embodiments, the cancer is selected from melanoma, bone cancer, renal cancer, prostate cancer, breast cancer, colon cancer, lung cancer, cutaneous or intraocular malignant melanoma, 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 (AML), 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. In some embodiments, the cancer melanoma.

[0284] In some embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is advanced. In some embodiments, the cancer is metastatic.

[0285] In some embodiments, the methods disclosed herein treat a cancer in a subject. In some embodiments, the methods disclosed herein reduce the severity of one or more symptom of the cancer. In some embodiments, the methods disclosed herein reduce the size or number of a tumor derived from the cancer. In some embodiments, the methods disclosed herein increase the overall survival of the subject, relative to a subject not provided the methods disclosed herein. In some embodiments, the methods disclosed herein increase the progressive-free survival of the subject, relative to a subject not provided the methods disclosed herein. In some embodiments, the methods disclosed herein lead to a partial response in the subject. In some embodiments, the methods disclosed herein lead to a complete response in the subject.

[0286] In some embodiments, the methods disclosed herein comprise treating a cancer in a subject in need thereof, comprising administering to the subject a cell described herein, wherein the cell comprises a nucleic acid molecule disclosed herein, a vector disclosed herein, a recombinant TCR disclosed herein, and/or a bispecific antibody disclosed herein. In some embodiments, the cell is a T cell. In some embodiments, the cell is a cell that is modified to express CD3.

[0287] In some embodiments, the cell, *e.g.*, a T cell, is obtained from the subject. In some embodiments, the cell, *e.g.*, a T cell, is obtained from a donor other than the subject.

[0288] In some embodiments, the subject is preconditioned prior to administering the cells. The preconditioning can comprise any substance that promotes T cell function and/or survival. In some embodiments, the preconditioning comprises administering to the subject a chemotherapy, a cytokine, a protein, a small molecule, or any combination thereof. In some embodiments, the preconditioning comprises administering an interleukin. In some embodiments, the preconditioning comprises administering IL-2, , IL-4, IL-7, IL-9, IL-15, IL-21, or any combination thereof. In some embodiments, the preconditioning comprises administering cyclophosphamide, fludarabine, or both. In some embodiments, the preconditioning comprises administering vitamin C, an AKT inhibitor, ATRA (vesanoid, tretinoin), rapamycin, or any combination thereof.

III.B. Methods of Engineering an Antigen-Targeting Cell

[0289] Certain aspects of the present disclosure are directed to methods of engineering an antigen-targeting cell. In some embodiments, the antigen is selected from the group consisting of a tyrosinase antigen, a MAGE-A1 antigen, a MART1 antigen, a MAGE-A3 antigen, an SSX antigen, and any combination thereof. In some embodiments, the method comprises transducing a cell with a nucleic acid molecule disclosed herein or a vector disclosed herein. The cell can be any cell described herein. In some embodiments, the cell is a T cell described herein. In some embodiments, the cell is a cell that is modified to express CD3, as described herein. In some embodiments, the cell, *e.g.*, the T cell, is obtained from a subject in need of a T cell therapy. In some embodiments, the cell is obtained from a donor other than the subject in need of the T cell therapy. In some embodiments, the cell is a T cell or a natural killer cell.

III.C. Methods of Enriching a Target Population of T Cells

[0290] Certain aspects of the present disclosure are directed to methods of enriching a target population of T cells obtained from a human subject. In some embodiments, the method comprises contacting the T cells with an HLA class I molecule disclosed herein. In some embodiments, the method comprises contacting the T cells with an APC disclosed herein. In some embodiments, 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.

[0291] In some embodiments, the method comprises contacting the T cells *in vitro* with a peptide, wherein the peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 51, 52, 53, 54, 55, and any combination thereof. In some embodiments, the method comprises 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. In some embodiments, 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.

[0292] Some aspects of the present disclosure are directed to a method of selecting a T cell capable of targeting a tumor cell. In some embodiments, the method comprises 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. In some embodiments, the T cells are obtained from a human subject.

[0293] The T cells obtained from the human subject can be any T cells disclosed herein. In some embodiments, the T cells obtained from the human subject are tumor infiltrating lymphocytes (TIL).

[0294] In some embodiments, the method further comprises administering to the human subject the enriched T cells. In some embodiments, the subject is preconditioned prior to receiving the T cells, as described herein.

[0295] All of the various aspects, embodiments, and options described herein can be combined in any and all variations.

[0296] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0297] Having generally described this disclosure, a further understanding can be obtained by reference to the examples provided herein. These examples are for purposes of illustration only and are not intended to be limiting.

EXAMPLES

Example 1 – Methods

[0298] ***Cell samples***

[0299] Peripheral blood samples were obtained from healthy donors. Mononuclear cells were obtained via density gradient centrifugation (Ficoll-Paque PLUS; GE Healthcare). K562 is an erythroleukemic cell line with defective HLA expression. T2 is an HLA-A*02:01$^+$ T cell leukemia/B-LCL hybrid cell line. Jurkat 76 is a T cell leukemic cell line lacking TCR and CD8 expression. The K562, T2, and Jurkat 76 cell lines were cultured in

RPMI 1640 supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen). TILs isolated from a metastatic melanoma patient were grown *in vitro*.

[0300] *Tyrosinase:* Me275 and MCF7 cell lines were grown in DMEM supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen). Melme-3M cell line was grown in IMDM supplemented with 20% FBS and 50 µg/ml gentamicin (Invitrogen).

[0301] *MAGE-A1:* Me275, SK-MEL-37, and SK-MEL-21 cell lines were grown in DMEM supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen).

[0302] *MART1:* A375 and SK-MEL-28 cell lines were grown in DMEM supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen). Malme-3M cell line was grown in IMDM supplemented with 20% FBS and 50 µg/ml gentamicin.

[0303] *MAGE-A3:* SK-MEL-28 and HEK293T cell lines were grown in DMEM supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen).

[0304] *SSX2:* SK-MEL-21, SK-MEL-37, and SK-MEL-28 cell lines were grown in DMEM supplemented with 10% FBS and 50 µg/ml gentamicin (Invitrogen).

[0305] ***Peptides***

[0306] Synthetic peptides were dissolved to 50 µg/ml in DMSO.

[0307] *Tyrosinase:* Peptides used were C*05:01-restricted tyrosinase$_{460\text{-}468}$ (FQDYIKSYL; SEQ ID NO: 51) and HIV rev$_{67\text{-}75}$ (SAEPVPLQL; SEQ ID NO: 82) peptides. The HIV rev$_{67\text{-}75}$ peptide was utilized as a negative control.

[0308] *MAGE-A1:* Peptides used were B*07:02-restricted MAGE-A1$_{289\text{-}297}$ (RVRFFFPSL; SEQ ID NO: 52), NY-ESO-1$_{60\text{-}72}$ (APRGPHGGAASGL; SEQ ID NO: 83), EBV EBNA3A$_{379\text{-}387}$ (RPPIFIRRL; SEQ ID NO: 84), and HIV nef$_{128\text{-}137}$ (TPGPGVRYPL; SEQ ID NO: 85) peptides. The NY-ESO-1$_{60\text{-}72}$, EBV EBNA3A$_{379\text{-}387}$, and HIV nef$_{128\text{-}137}$ peptides were utilized as negative controls.

[0309] *MART1:* Peptides used were 20-mer overlapping peptides to cover the whole protein of MART1 and B*18:01-restricted MART1$_{25\text{-}33}$ (EEAAGIGIL; SEQ ID NO: 53), MAGE-A3$_{167\text{-}176}$ (MEVDPIGHLY; SEQ ID NO: 54), and HIV gag$_{161\text{-}170}$ (FRDYVDRFYK; SEQ ID NO: 86) peptides. The MAGE-A3$_{167\text{-}176}$ and HIV gag$_{161\text{-}170}$ peptides were utilized as negative controls.

[0310] *MAGE-A3:* Peptides used were B*18:01-restricted MAGE-A3$_{167-176}$ (MEVDPIGHLY; SEQ ID NO: 54), MART1$_{25-33}$ (EEAAGIGIL; SEQ ID NO: 53) and HIV gag$_{161-170}$ (FRDYVDRFYK; SEQ ID NO: 86) peptides. The MART1$_{25-33}$ and HIV gag$_{161-170}$ peptide was utilized as negative controls.

[0311] *SSX2:* Peptides used were A*02:01-restricted SSX2$_{41-49}$ (KASEKIFYV; SEQ ID NO: 55), NY-ESO-1$_{157-165}$ (SLLMWITQV; SEQ ID NO: 87), and HTLV-1 tax$_{11-19}$ (LLFGYPVYV; SEQ ID NO: 88) peptides. The NY-ESO-1$_{157-165}$ and HTLV-1 tax$_{11-19}$ peptides were utilized as negative controls.

[0312] ***Genes***

[0313] Each of the HLA C*05:01, B*07:02, and B*18:01 genes, as applicable, was fused with a truncated version of the human nerve growth factor receptor (ΔNGFR) via the internal ribosome entry site. ΔNGFR-transduced cells were isolated using anti-NGFR mAb. The full-length tyrosinase gene was cloned from SK-MEL-28 cells via RT-PCR according to the published sequence. The full-length MART1 gene was cloned from Malme-3M cells via RT-PCR according to the published sequence. The full-length SSX2 gene was cloned from SK-MEL-37 cells via RT-PCR according to the published sequence. TCR genes were cloned by 5'-rapid amplification of cDNA ends (RACE) PCR using a SMARTer RACE cDNA amplification kit (Takara Bio). The 5'-RACE PCR products were cloned into a retrovirus vector and sequenced. All genes were cloned into the pMX retrovirus vector and transduced using the 293GPG cell-based retrovirus system.

[0314] ***Transfectants***

[0315] Jurkat 76/CD8 cells were transduced with individual TCRα and TCRβ genes. The Jurkat 76/CD8-derived TCR transfectants were purified (>95% purity) using CD3 Microbeads (Miltenyi Biotec). The K562-based artificial APCs individually expressing various HLA class I genes as a single HLA allele in conjunction with CD80 and CD83 have been reported previously (Butler and Hirano, *Immunol. Rev. 257*:191-209 (2014); Hirano et al., *Clin. Cancer Res. 12*:2967-75 (2006)). PG13-derived retrovirus supernatants were used to transduce TCR genes into human primary T cells. TransIT293 (Mirus Bio) was used to transfect TCR genes into the 293GPG cell line.

[0316] Tyrosinase^{-} MCF7 cells were retrovirally transduced with the full-length tyrosinase gene to generate MCF7/tyrosinase cells. The expression of transduced tyrosinase was evaluated by flow cytometry after staining with an anti-tyrosinase monoclonal antibody (mAb) (clone ERP10141; Abcam). HLA-C*05:01^{-} Malme-3M and Me275 cells were retrovirally transduced with HLA-C*05:01 to generate Malme-3M/C*05:01 and Me275/C*05:01 cells. HLA-C*05:01 gene were tagged with the ΔNGFR gene as described above, and the $\Delta NGFR^+$ cells were purified (>95% purity) and used in subsequent experiments. The ΔNGFR gene alone was retrovirally transduced as a control.

[0317] MAGE-A1$^-$ SK-MEL-21 cells were retrovirally transduced with the full-length MAGE-A1 gene to generate SK-MEK-21/MAGE-A1 cells. The expression of transduced MAGE-A1 was evaluated by flow cytometry after staining with an anti-MAGE-A1 mAb (clone MA454; LifeSpan Biosciences). HLA-B*07:02$^-$ Me275 and SK-MEL-37 cells were retrovirally transduced with HLA-B*07:02 to generate Me275/B*07:02 and SK-MEL-37/B*07:02 cells. HLA-B*07:02 gene were tagged with the ΔNGFR gene as described above, and the $\Delta NGFR^+$ cells were purified (>95% purity) and used in subsequent experiments. The ΔNGFR gene alone was retrovirally transduced as a control.

[0318] MART1$^-$ A375 cells were retrovirally transduced with the full-length MART1 gene to generate A375/MART1 cells. The expression of transduced MART1 was evaluated by flow cytometry after staining with an anti-MART1 mAb (clone A103; Santa Cruz Biotechnology). HLA-B*18:01$^-$ Malme-3M, SK-MEL-28, and A375 cells were retrovirally transduced with HLA-B*18:01 to generate Malme-3M/B*18:01, SK-MEL-28/B*18:01, and A375/B*18:01 cells. HLA-B*18:01 gene were tagged with the ΔNGFR gene as described above, and the $\Delta NGFR^+$ cells were purified (>95% purity) and used in subsequent experiments. The ΔNGFR gene alone was retrovirally transduced as a control.

[0319] MAGE-A3$^-$ HEK293T cells were retrovirally transduced with the full-length MAGE-A3 gene to generate HEK293T/MAGE-A3 cells. The expression of MAGE-A3 in the transduced cells was evaluated by Western blot analysis with an anti-MAGE-A3 polyclonal antibody (pAb) (LifeSpan Biosciences). HLA-B*18:01$^-$ SK-MEL-28 and HEK293T cells were retrovirally transduced with HLA-B*18:01 to generate SK-MEL-28/B*18:01 and HEK293T/B*18:01 cells. HLA-B*18:01 gene were tagged with the Δ NGFR gene as described above, and the $\Delta NGFR^+$ cells were purified (>95% purity) and used in subsequent experiments. The ΔNGFR gene alone was retrovirally transduced as a control.

[0320] SSX2$^-$ SK-MEL-21 and SK-MEL-28 cells were retrovirally transduced with the full-length SSX2 gene to generate SK-MEK-21/SSX2 and SK-MEL-28/SSX2 cells. The expression of SSX2 in the transduced cells was evaluated by Western blot analysis with an anti-SSX2 pAb (Thermo Fisher Scientific). HLA-A*02:01$^-$ SK-MEL-28 cells were retrovirally transduced with HLA-A*02:01 to generate SK-MEL-28/A*02:01 cells.

[0321] ***Flow cytometry and cell sorting***

[0322] Cell surface molecules were stained with a PC5-conjugated anti-CD8 mAb (clone B9.11; Beckman Coulter), FITC-conjugated anti-NGFR (clone ME20.4; Biolegend), and APC/Cy7-conjugated anti-CD3 (clone UCHT1; Biolegend). Dead cells were discriminated with the LIVE/DEAD Fixable Aqua Dead Cell Stain kit (Life Technologies). For intracellular staining, cells were fixed and permeabilized by using a Cytofix/Cytoperm kit (BD Biosciences). Stained cells were analyzed with flow cytometry (BD Biosciences), and data analysis was performed using FlowJo (Tree Star). Cell sorting was conducted using a FACS Aria II (BD Bioscience).

[0323] ***Cytokine ELISPOT analysis***

[0324] IFN-γ ELISPOT assays were conducted as described previously (*see, e.g.*, Kagoya et al., *Nat. Commun. 9*:1915 (2018); Anczurowski et al., *Sci. Rep. 8*:4804 (2018); and Yamashita et al., *Nat Commun. 8*:15244 (2017)). PVDF plates (Millipore, Bedford, MA) were coated with the capture mAb (1-D1K; MABTECH, Mariemont, OH), and T cells were incubated with 2 x 10^4 target cells per well in the presence or absence of a peptide for 20–24 hours at 37°C. The plates were subsequently washed and incubated with a biotin-conjugated detection mAb (7-B6-1; MABTECH). HRP-conjugated SA (Jackson ImmunoResearch) was then added, and IFN-γ spots were developed. The reaction was stopped by rinsing thoroughly with cold tap water. ELISPOT plates were scanned and counted using an ImmunoSpot plate reader and ImmunoSpot version 5.0 software (Cellular Technology Limited, Shaker Heights, OH).

[0325] ***Expansion of CD8$^+$ TILs in an HLA-restricted peptide-specific manner***

[0326] When applicable, *e.g.*, for the MAGE-A3 TCRs, CD8$^+$ TILs were purified through negative magnetic selection using a CD8$^+$ T Cell Isolation Kit (Miltenyi Biotec). B*18:01-artificial APCs were pulsed with 10 μg/mL class I- restricted peptides of interest for 6 hours. The artificial APCs were then irradiated at 200 Gy, washed, and added to the TILs at an effector to target (E:T) ratio of 20:1. Starting on the next day, 10 IU/ml IL-2 (Novartis), 10 ng/ml IL-15 (Peprotech), and 30 ng/ml IL-21 (Peprotech) were added to the cultures every three days.

[0327] ***Expansion of primary CD8$^+$ T cells transduced with the cloned TCR***

[0328] CD3$^+$ T cells were purified through negative magnetic selection using a Pan T Cell Isolation Kit (Miltenyi Biotec). Purified T cells were stimulated with artificial APC/mOKT3 irradiated with 200 Gy at an E:T ratio of 20:1. Starting on the next day, activated T cells were retrovirally transduced with the cloned TCR genes via centrifugation for 1 hour at 1,000 g at 32°C for 3 consecutive days. On the following day, 100 IU/ml IL-2 and 10 ng/ml IL-15 were added to the TCR-transduced T cells. The culture medium was replenished every 2-3 days.

[0329] ***Production of mammalian cell-based pHLA multimers***

[0330] The affinity-matured HLA class I gene was engineered to carry a Glu (E) residue in lieu of the Gln (Q) residue at position 115 of the α2 domain and a mouse K^b gene-derived α3 domain instead of the HLA class I α3 domain. By fusing the extracellular domain of the affinity-matured HLA class I gene with a Gly-Ser (GS) flexible linker followed by a 6x His tag, we generated the soluble HLA class I^{Q115E}-K^b gene. HEK293T cells were individually transduced with various soluble HLA class I^{Q115E}-K^b genes along with the β2m gene using the 293GPG cell-based retrovirus system. Stable HEK293T cells ectopically expressing soluble affinity-matured class I^{Q115E}-K^b were grown until confluent, and the medium was then changed. Forty-eight hours later, the conditioned medium was harvested and immediately used or frozen until use. The soluble HLA class I^{Q115E}-K^b-containing supernatant produced by the HEK293T transfectants was incubated with 100-1000 μg/ml of class I-restricted peptide of interest overnight at 37°C for *in vitro* peptide exchange. Soluble monomeric class I^{Q115E}-K^b loaded with the peptide was dimerized using an anti-His mAb (clone AD1.1.10; Abcam) conjugated to a fluorochrome such as phycoerythrin (PE) at a 2:1 molar ratio for 2 hours at room temperature or overnight at 4°C. The concentration of functional soluble HLA class I^{Q115E}-K^b molecules was measured by specific ELISA using an anti-pan class I mAb (clone W6/32, in-house) and an anti-His tag biotinylated mAb (clone AD1.1.10, R&D systems) as capture and detection Abs, respectively.

[0331] ***pHLA multimer staining***

[0332] T cells (1 x 10^5) were incubated for 30 minutes at 37°C in the presence of 50 nM dasatinib (LC laboratories). The cells were then washed and incubated with 5-10 μg/ml of multimer for 30 minutes at room temperature, and R-phycoerythrin-conjugated AffiniPure Fab fragment goat anti-mouse IgG1 (Jackson ImmunoResearch Laboratories) was added for 15 minutes at 4°C. Next, the cells were washed three times and co-stained with an anti-CD8 mAb for 15 minutes at 4°C. Dead cells were finally discriminated using the LIVE/DEAD Fixable Dead Cell Stain kit.

[0333] ***Statistical analysis***

[0334] Statistical analysis was performed using GraphPad Prism 5.0e. A Welch's t test (two-sided) analysis was conducted to determine whether two groups were significantly different for a given variable. *P* values < 0.05 were considered significant.

Example 2 – Tyrosinase-Specific TCR

[0335] Tumor infiltrating lymphocytes (TILs) were isolated from a metastatic melanoma patient, then polyclonally expanded *in vitro*, and their tyrosinase antigen specificity for HLA-C*05:01 allele was examined. The combination of structure-based analysis using peptide/HLA (pHLA) multimers and functional analysis has been used to measure antigen-specific T cell responses. The T cells were stained using pHLA multimer with tyrosinase$_{460-468}$ peptide (FIG. 1). The TILs showed positivity for C*05:01/tyrosinase$_{460-468}$ multimer. The multimer-positive T cells secreted detectable IFN-γ in an HLA-restricted peptide-specific manner according to ELISPOT analysis (FIG. 2).

[0336] The multimer-positive antitumor T cells were collected and their TCR genes were molecularly cloned (FIG. 3). The antigen specificity and functional reactivity of the cloned TCR were verified by multimer staining and ELISPOT assay of TCR-reconstituted T cells. When reconstituted on primary T cells, C*05:01/tyrosinase$_{460-468}$ TCR-transduced T cells were successfully stained with the cognate multimer (FIG. 4) and strongly reacted with the tyrosinase$_{460-468}$ peptide presented by surface C*05:01 molecules (FIG. 5). Importantly, these cells were able to recognize C*05:01-matched and peptide-unpulsed tumor cells naturally expressing the tyrosinase gene. Although Malme-3M and Me275 melanoma cell lines are negative for C*05:01, they express the tyrosinase gene endogenously. When C*05:01 molecules were ectopically expressed, both melanoma cell lines were successfully recognized by C*05:01/tyrosinase$_{460-468}$ TCR-transduced T cells. Moreover, MCF7 breast cancer cells, which lack endogenous expression of tyrosinase, became reactive to C*05:01/tyrosinase$_{460-468}$ TCR-transduced T cells when the full-length tyrosinase gene was transduced (FIGs. 6-8). These results clearly demonstrate that the C*05:01/tyrosinase$_{460-468}$ TCR-transduced T cells were sufficiently avid to recognize tumor cells and that the cloned C*05:01/tyrosinase$_{460-468}$ TCR was tumor-reactive.

Example 3 – MAGE-A1-Specific TCR

[0337] TILs were isolated from a metastatic melanoma patient, then polyclonally expanded *in vitro*, and their MAGE-A1 antigen specificity for HLA-B*07:02 allele was examined. The T cells were stained using pHLA multimer with MAGE-A1$_{289-297}$ peptide (FIG. 9). The TILs showed positivity for B*07:02/MAGE-A1$_{289-297}$ multimer. The multimer-positive T cells secreted detectable IFN-γ in an HLA-restricted peptide-specific manner according to ELISPOT analysis (FIG. 10).

[0338] The multimer-positive antitumor T cells were collected and their TCR genes were molecularly cloned (FIG. 11). The antigen specificity and functional reactivity of the cloned TCR were verified by multimer staining and ELISPOT assay of TCR-reconstituted T cells. When reconstituted on primary T cells, B*07:02/MAGE-A1$_{289-297}$ TCR-transduced T cells were successfully stained with the cognate multimer (FIG. 12) and strongly reacted with the MAGE-A1$_{289-297}$ peptide presented by surface B*07:02 molecules (FIG. 13). Importantly, these cells were able to recognize B*07:02-matched and peptide-unpulsed tumor cells naturally expressing the MAGE-A1 gene. Although both the Me275 and SK-MEL-37 melanoma cell lines are negative for B*07:02, they express the MAGE-A1 gene endogenously. When B*07:02 molecules were ectopically expressed, both melanoma cell lines were successfully recognized by B*07:02/MAGE-A1$_{289-297}$ TCR-transduced T cells. Moreover, SK-MEL-21 melanoma cells, which lack endogenous expression of MAGE-A1, became reactive to B*07:02/MAGE-A1$_{289-297}$ TCR-transduced T cells when the full-length MAGE-A1 gene was transduced (FIGs. 14-16). These results clearly demonstrate that the B*07:02/MAGE-A1$_{289-297}$ TCR-transduced T cells were sufficiently avid to recognize tumor cells and that the cloned B*07:02/MAGE-A1$_{289-297}$ TCR was tumor-reactive.

[0339] The use of the newly cloned tumor-reactive B*07:02-restricted MAGE-A1 TCR genes may widen the applicability of anti-MAGE-A1 TCR gene therapy.

Example 4 – MART1-Specific TCR

[0340] TILs were isolated from a metastatic melanoma patient, then polyclonally expanded *in vitro*, and their MART1 antigen specificity for HLA-B*18:01 allele was examined. Since pHLA multimer production requires the use of a peptide with a known exact sequence, it is not straightforward or practical to conduct high-throughput screening for new epitope peptides using a pHLA multimer-based strategy. In addition to structure-based analysis using pHLA multimers, functional analysis can be applied to determine the antigen specificity of T cells. We conducted functional assays using artificial antigen-presenting cells (APCs), which can take up and process longer peptides and present epitope peptides via class I molecules, as stimulator cells. HLA-B*18:01-artificial APCs were pulsed with overlapping peptides to cover the whole protein of MART1 (Table 5) and used as stimulators in cytokine ELISPOT assays. When stimulated with B*18:01-artificial APCs pulsed with MART1-derived overlapping peptides, B*18:01^{+} melanoma TILs showed positive responses to two adjacent peptides with the shared sequence $_{21}$YTTAEEAAGIGILTV$_{35}$ in the IFN-γ ELISPOT analysis (FIG. 17). Using a series of mutant deletion peptides, we determined the minimally required peptide epitope, $_{25}$EEAAGIGIL$_{33}$ presented by B*18:01 molecules. Importantly, the B*18:01/MART1$_{25\text{-}33}$ multimer successfully stained up to 9.2% of the polyclonally expanded TILs, suggesting that the B*18:01/MART1$_{25\text{-}33}$ T cells were a dominant population of the TILs (FIG. 18). The multimer-positive T cells secreted detectable IFN-γ in an HLA-restricted peptide-specific manner according to ELISPOT analysis (FIG. 19).

Table 5. MART1-derived overlapping peptides.

Position	Peptide Sequence	SEQ ID NO
1	MPREDAHFIYGYPKKGHGHS	61
6	AHFIYGYPKKGHGHSYTTAE	62
11	GYPKKGHGHSYTTAEEAAGI	63
16	GHGHSYTTAEEAAGIGILTV	64
21	YTTAEEAAGIGILTVILGVL	65
26	EAAGIGILTVILGVLLLIGC	66
31	GILTVILGVLLLIGCWYCRR	67
36	ILGVLLLIGCWYCRRRNGYR	68
41	LLIGCWYCRRRNGYRALMDK	69
46	WYCRRRNGYRALMDKSLHVG	70
51	RNGYRALMDKSLHVGTQCAL	71
56	ALMDKSLHVGTQCALTRRCP	72
61	SLHVGTQCALTRRCPQEGFD	73
66	TQCALTRRCPQEGFDHRDSK	74
71	TRRCPQEGFDHRDSKVSLQE	75
76	QEGFDHRDSKVSLQEKNCEP	76
81	HRDSKVSLQEKNCEPVVPNA	77

86	VSLQEKNCEPVVPNAPPAYE	78
91	KNCEPVVPNAPPAYEKLSAE	79
96	VVPNAPPAYEKLSAEQSPPP	80
99	NAPPAYEKLSAEQSPPPYSP	81

[0341] The multimer-positive antitumor T cells were collected and their TCR genes were molecularly cloned (FIG. 20). The antigen specificity and functional reactivity of the cloned TCR were verified by multimer staining and ELISPOT assay of TCR-reconstituted T cells. When reconstituted on primary T cells, B*18:01/MART1$_{25-33}$ TCR-transduced T cells were successfully stained with the cognate multimer (FIG. 21) and strongly reacted with the MART1$_{25-33}$ peptide presented by surface B*18:01 molecules (FIG. 22). Importantly, these cells were able to recognize B*18:01-matched and peptide-unpulsed tumor cells naturally expressing the MART1 gene. Although both the Malme-3M and SK-MEL-28 melanoma cell lines are negative for B*18:01, they express the MART1 gene endogenously. When B*18:01 molecules were ectopically expressed, both melanoma cell lines were successfully recognized by B*18:01/MART1$_{25-33}$ TCR-transduced T cells. Moreover, A375 melanoma cells, which lack endogenous expression of both B*18:01 and MART1, became reactive to B*18:01/MART1$_{25-33}$ TCR-transduced T cells only when both the B*18:01 and full-length MART1 genes (but not either of the single genes) were transduced (FIGs. 23-25). These results clearly demonstrate that the B*18:01/MART1$_{25-33}$ TCR-transduced T cells were sufficiently avid to recognize tumor cells and that the cloned B*18:01/MART1$_{25-33}$ TCR was tumor-reactive.

[0342] The use of the newly cloned tumor-reactive B*18:01-restricted MART1 TCR genes may widen the applicability of anti-MART1 TCR gene therapy beyond HLA-A*02:01-positive cancer patients.

Example 5 – MAGE-A3-Specific TCR

[0343] TILs were isolated from a metastatic melanoma patient, then polyclonally expanded *in vitro*, and their MAGE-A3 antigen specificity for HLA-B*18:01 allele was examined. The T cells were stained using pHLA multimer with MAGE-A3$_{167-176}$ peptide. The B*18:01/MAGE-A3$_{167-176}$ multimer positivity of polyclonally expanded TILs was only 0.04% prior to peptide-specific stimulation. However, when the TILs were weakly stimulated once with B*18:01-artificial APCs pulsed with the MAGE-A3$_{167-176}$ peptide, 5.5% of the TILs were stained with the cognate multimer and secreted IFN-γ in a B*18:01/MAGE-A3$_{167-176}$-specific manner (FIGs. 26-27).

[0344] The multimer-positive antitumor T cells were collected and their TCR genes were molecularly cloned (FIG. 28). The antigen specificity and functional reactivity of the cloned TCR were verified by multimer staining and ELISPOT assay of TCR-reconstituted T cells. When reconstituted on primary T cells, B*18:01/MAGE-A3$_{167-176}$ TCR-transduced T cells were successfully stained with the cognate multimer (FIG. 29) and strongly reacted with the MAGE-A3$_{167-176}$ peptide presented by surface B*18:01 molecules (FIG. 30). Importantly, these cells were able to recognize B*18:01-matched and peptide-unpulsed tumor cells naturally expressing the MAGE-A3 gene. Although the SK-MEL-28 melanoma cells are negative for B*18:01, they express the MAGE-A3 gene endogenously. When B*18:01 molecules were ectopically expressed, the melanoma cells were successfully recognized by B*18:01/MAGE-A3$_{167-176}$ TCR-transduced T cells. Moreover, HEK293T melanoma cells, which lack endogenous expression of both B*18:01 and MAGE-A3, became reactive to B*18:01/MAGE-A3$_{167-176}$ TCR-transduced T cells only when both the B*18:01 and full-length MAGE-A3 genes (but not either of the single genes) were transduced (FIGs. 31-33). These results clearly demonstrate that the B*18:01/MAGE-A3$_{167-176}$ TCR-transduced T cells were sufficiently avid to recognize tumor cells and that the cloned B*18:01/MAGE-A3$_{167-176}$ TCR was tumor-reactive.

[0345] The use of the newly cloned tumor-reactive B*18:01/MAGE-A3 TCR genes may widen the applicability of anti-MAGE-A3 TCR gene therapy beyond HLA-A*02:01-positive cancer patients.

Example 6 – SSX2-Specific TCR

[0346] TILs were isolated from a metastatic melanoma patient, then polyclonally expanded *in vitro*, and their SSX2 antigen specificity for HLA-A*02:01 allele was examined. The T cells were stained using pHLA multimer with SSX2$_{41-49}$ peptide (FIG. 34). The TILs showed positivity for A*02:01/SSX2$_{41-49}$ multimer. The multimer-positive T cells secreted detectable IFN-γ in an HLA-restricted peptide-specific manner according to ELISPOT analysis (FIG. 35).

[0347] The multimer-positive antitumor T cells were collected and their TCR genes were molecularly cloned (FIG. 36). The antigen specificity and functional reactivity of the cloned TCR were verified by multimer staining and ELISPOT assay of TCR-reconstituted

T cells. When reconstituted on primary T cells, A*02:01/SSX2$_{41-49}$ TCR-transduced T cells were successfully stained with the cognate multimer (FIG. 37) and strongly reacted with the SSX2$_{41-49}$ peptide presented by surface A*02:01 molecules (FIG. 38). Importantly, these cells were able to recognize A*02:01-matched and peptide-unpulsed tumor cells naturally expressing the SSX2 gene. Although the SK-MEL-21 melanoma cells are positive for A*02:01, they do not express the SSX2 gene endogenously. When the SSX2 gene was ectopically expressed, the melanoma cells were successfully recognized by A*02:01/SSX2$_{41-49}$ TCR-transduced T cells. Moreover, SK-MEL-28 melanoma cells, which lack endogenous expression of both A*02:01 and SSX2, became reactive to A*02:01/SSX2$_{41-49}$ TCR-transduced T cells only when both the A*02:01 and full-length SSX2 genes (but not either of the single genes) were transduced (FIG. 39-41). These results clearly demonstrate that the A*02:01/SSX2$_{41-49}$ TCR-transduced T cells were sufficiently avid to recognize tumor cells and that the cloned A*02:01/SSX2$_{41-49}$ TCR was tumor-reactive.

[0348] The use of the newly cloned tumor-reactive A*02:01-restricted SSX2 TCR genes may widen the applicability of anti-SSX2 TCR gene therapy.

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 $\alpha1$ domain, an $\alpha2$ domain, an $\alpha3$ domain and a $\beta2m$, 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).

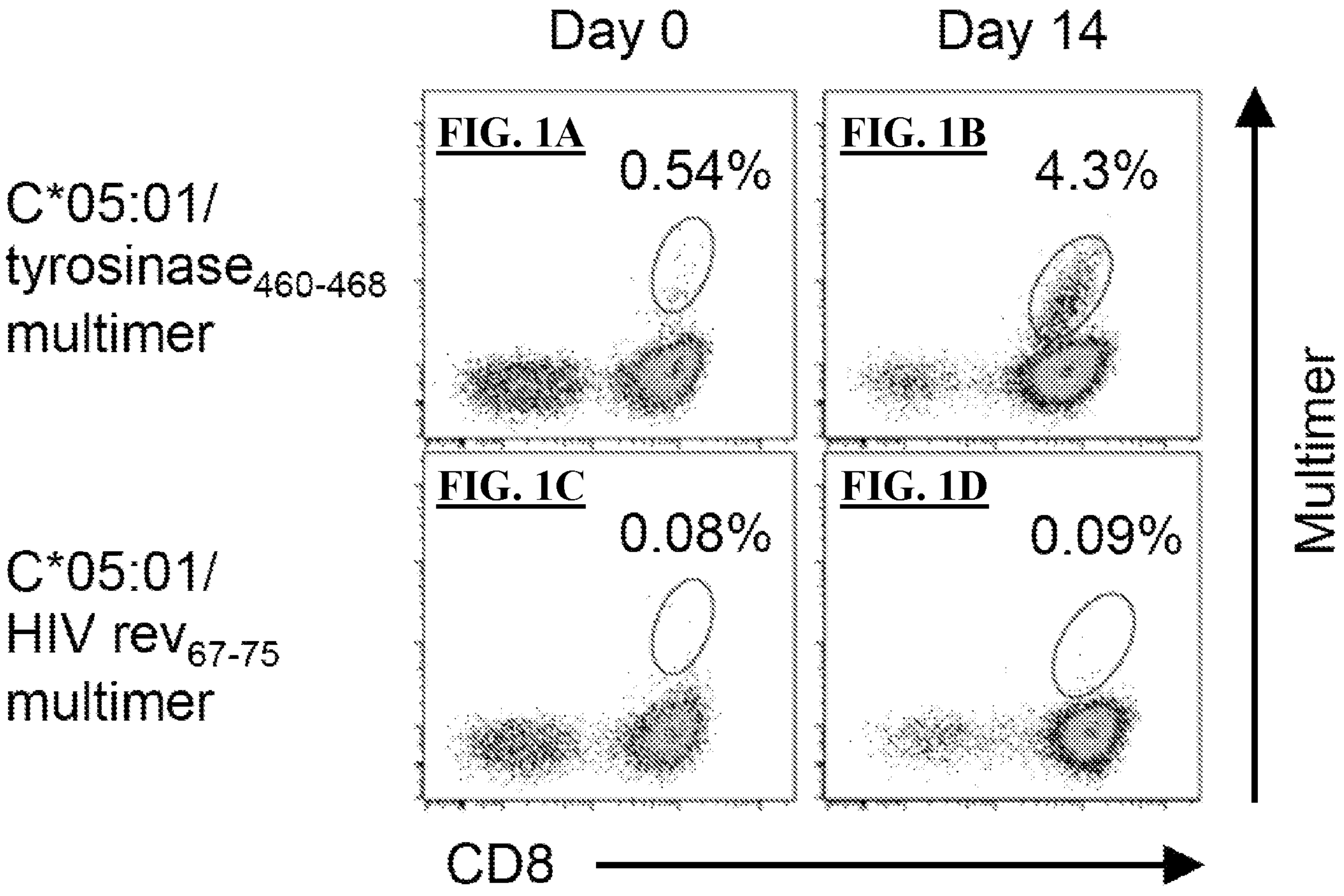


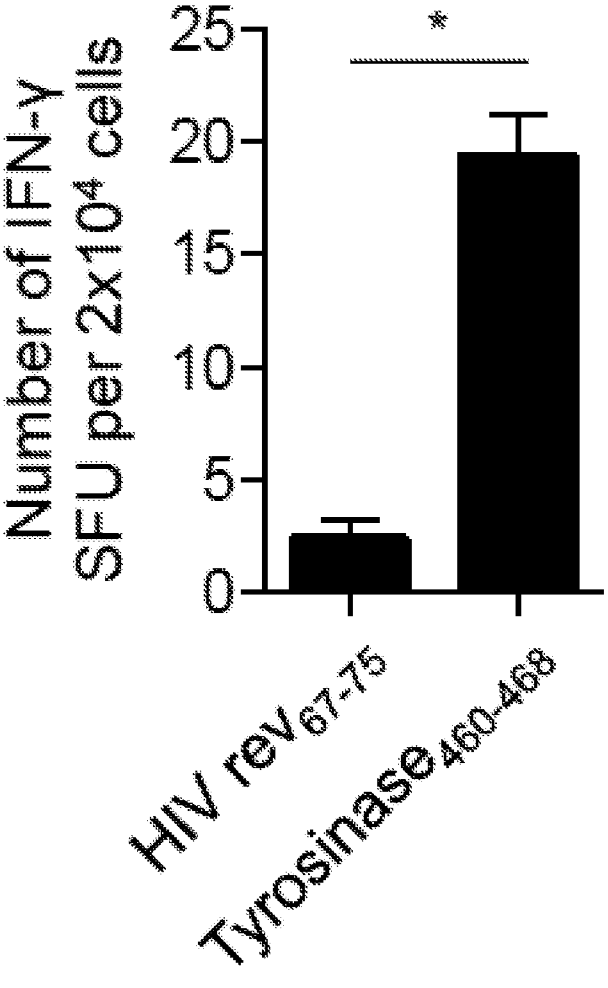
FIG. 1A

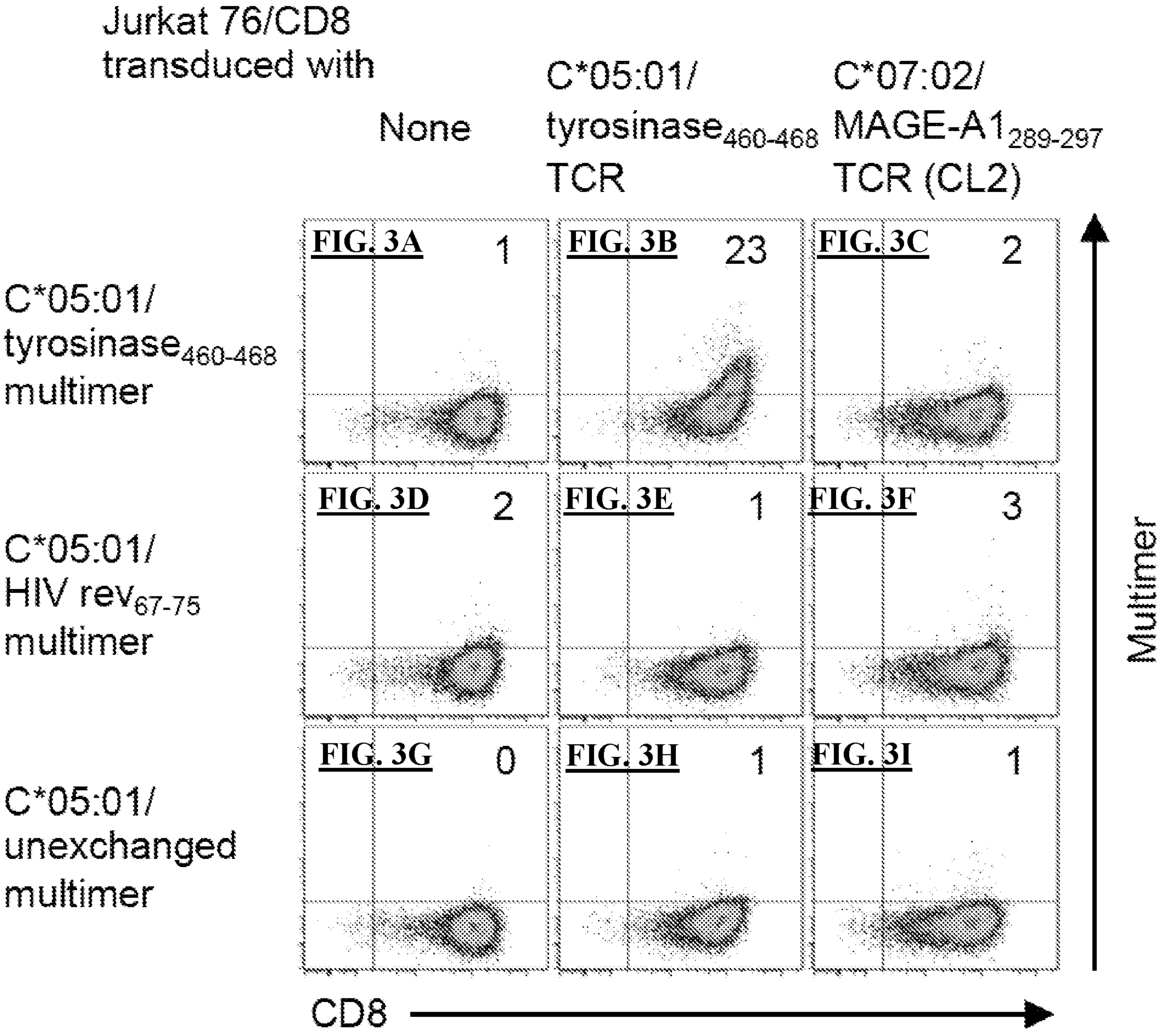
FIG. 1B

FIG. 1C

FIG. 1D

FIG. 2


Number of IFN-γ SFU per 2X10⁴ cells
25
20
15
10
5
0
*
HIV rev67-75
Tyrosinase460-468


Jurkat 76/CD8
transduced with
None
C*05:01/
tyrosinase$_{460-468}$
TCR
C*07:02/
MAGE-A1$_{289-297}$
TCR (CL2)
C*05:01/
tyrosinase$_{460-468}$
multimer
C*05:01/
HIV rev$_{67-75}$
multimer
C*05:01/
unexchanged
multimer
FIG. 3A
1
FIG. 3B
23
FIG. 3C
2
FIG. 3D
2
FIG. 3E
1
FIG. 3F
3
FIG. 3G
0
FIG. 3H
1
FIG. 3I
1
Multimer
CD8

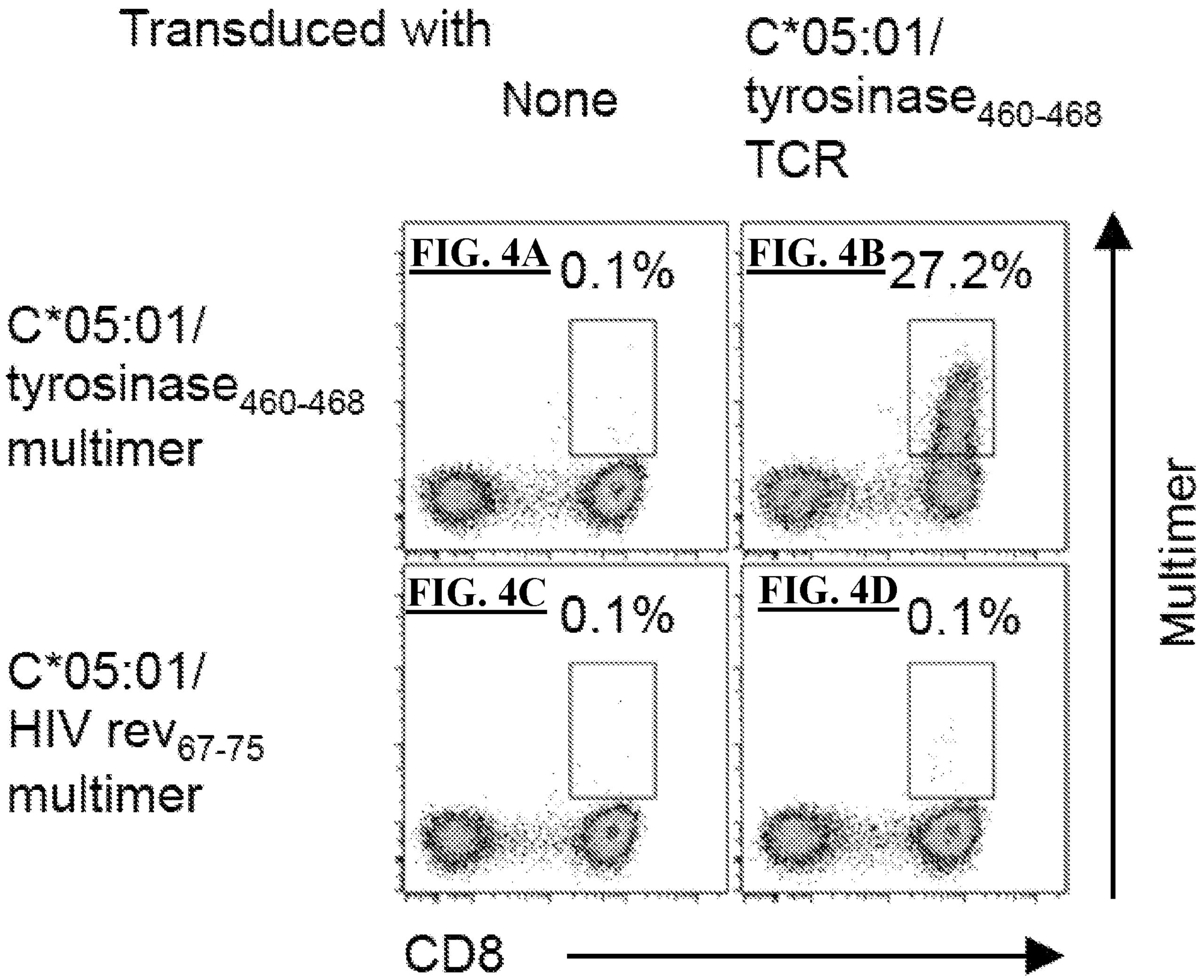


FIG. 4A **FIG. 4B** **FIG. 4C** **FIG. 4D**

FIG. 5

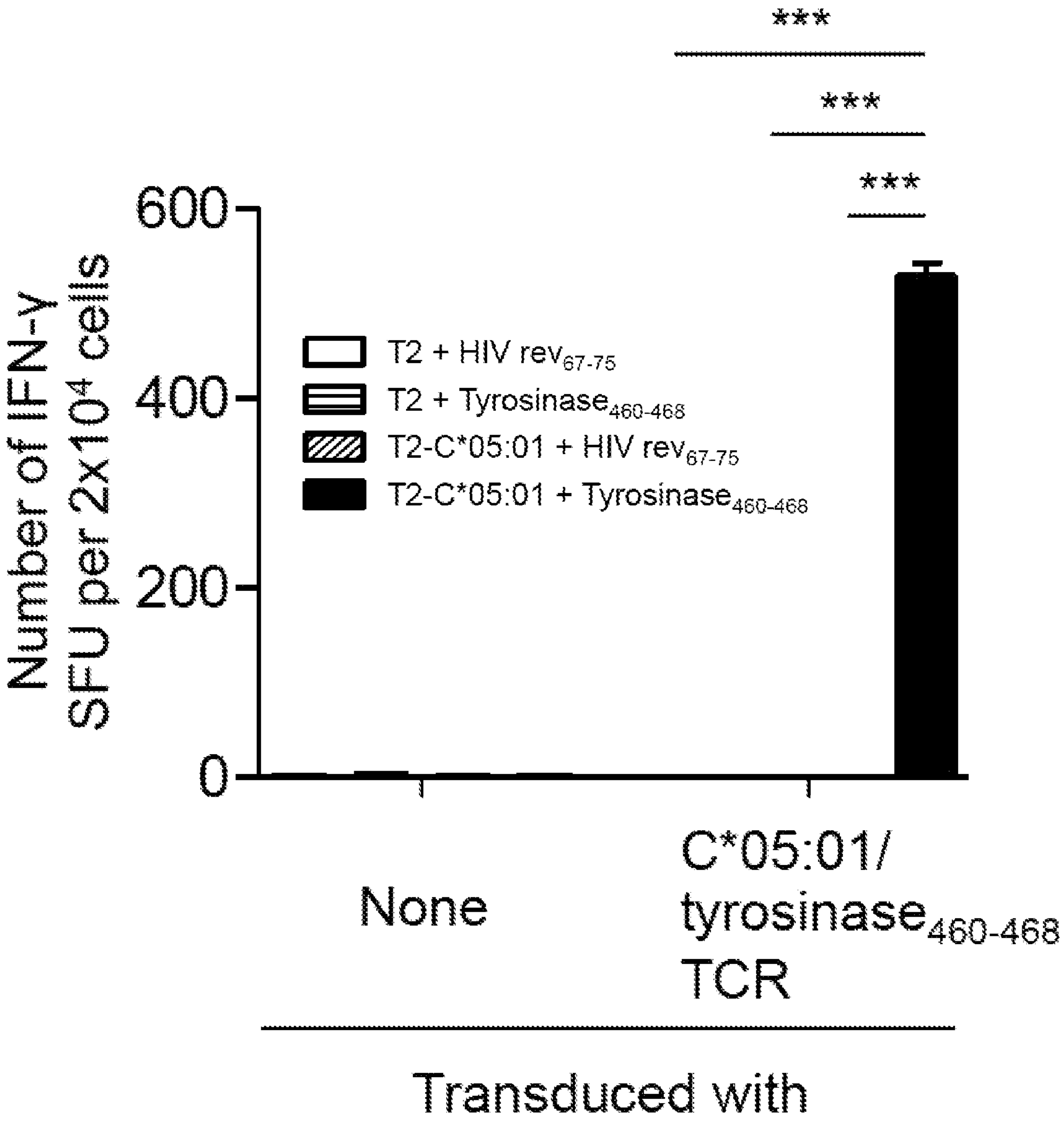

***
***
***
600
400
200
0
Number of IFN-γ SFU per 2x10⁴ cells
T2 + HIV rev67-75
T2 + Tyrosinase460-468
T2-C*05:01 + HIV rev67-75
T2-C*05:01 + Tyrosinase460-468
None
C*05:01/ tyrosinase460-468 TCR
Transduced with

FIG. 6A

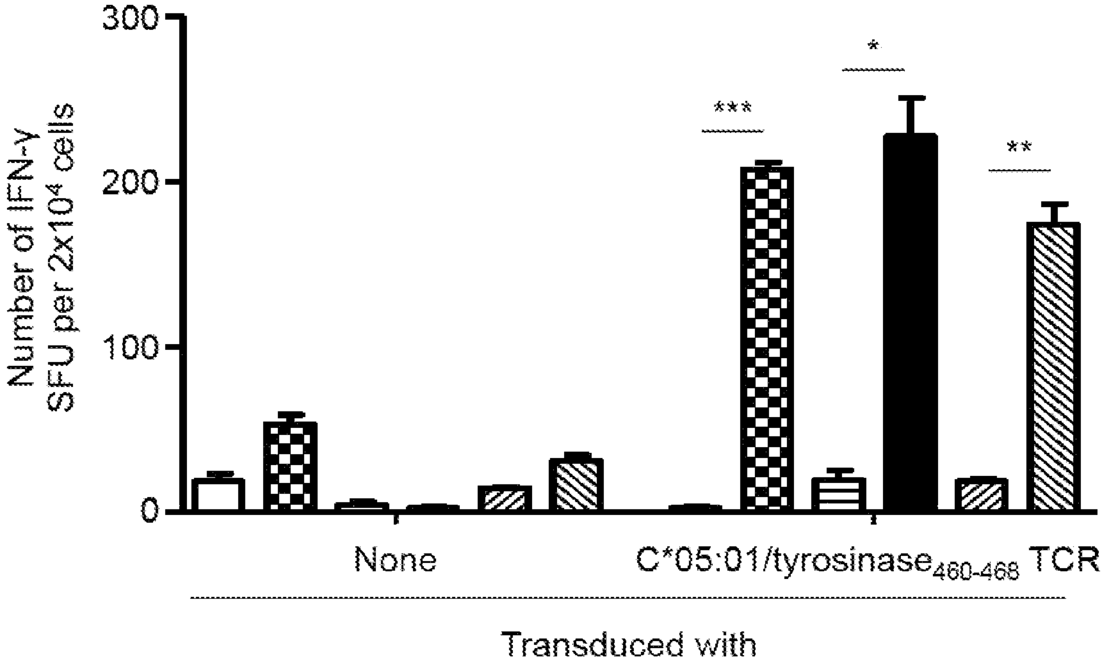


FIG. 6B

		C*05:01	Tyrosinase
□	Malme-3M	-	+
▩	Malme-3M/C*05:01	+	+
☰	Me275	-	+
■	Me275/C*05:01	+	+
▨	MCF7	+	-
▧	MCF7/tyrosinase	+	+

FIG. 7A

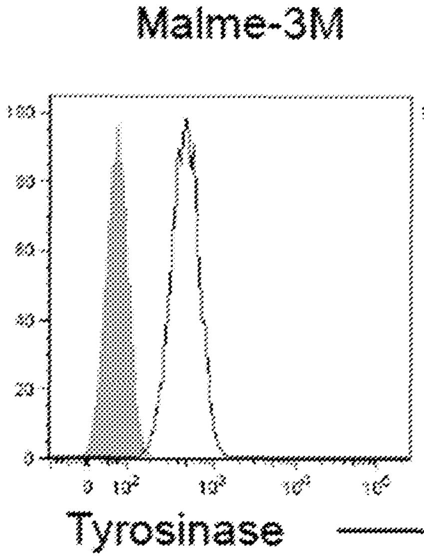


FIG. 7B

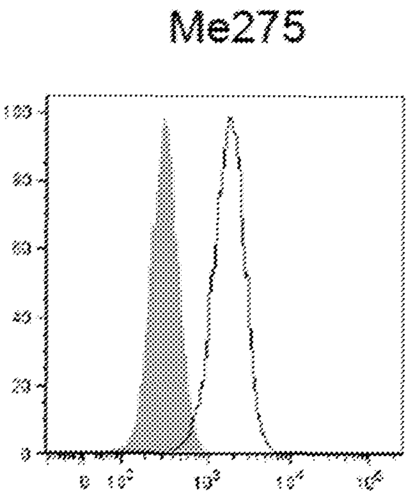


FIG. 7C

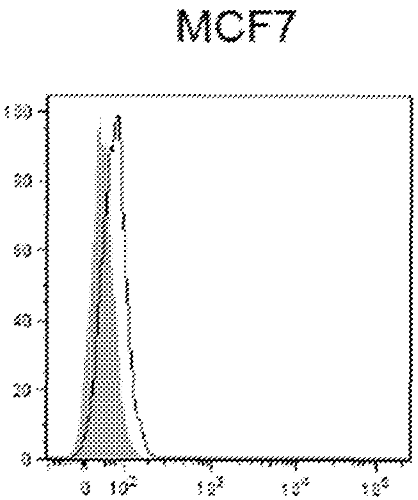


FIG. 7D

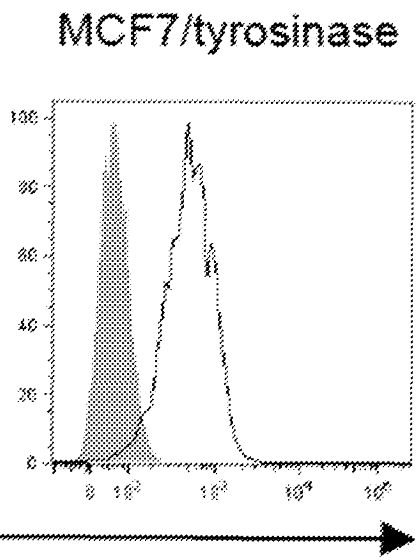


FIG. 8A

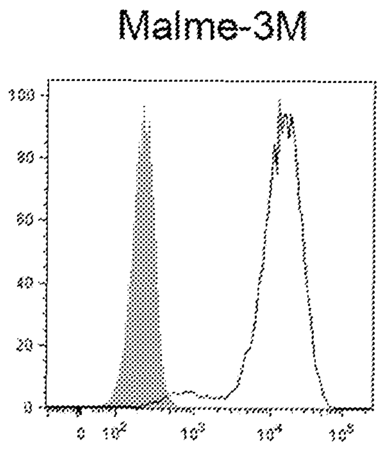


FIG. 8B

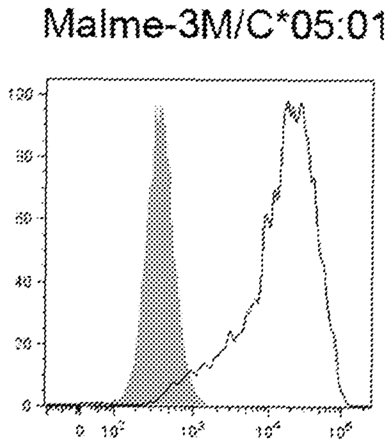


FIG. 8C

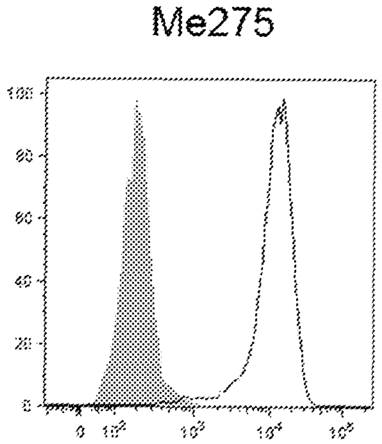
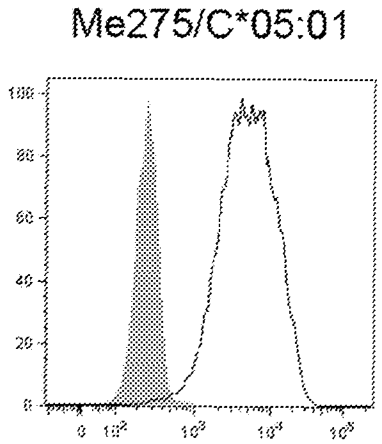


FIG. 8D



ΔNGFR

FIG. 9A

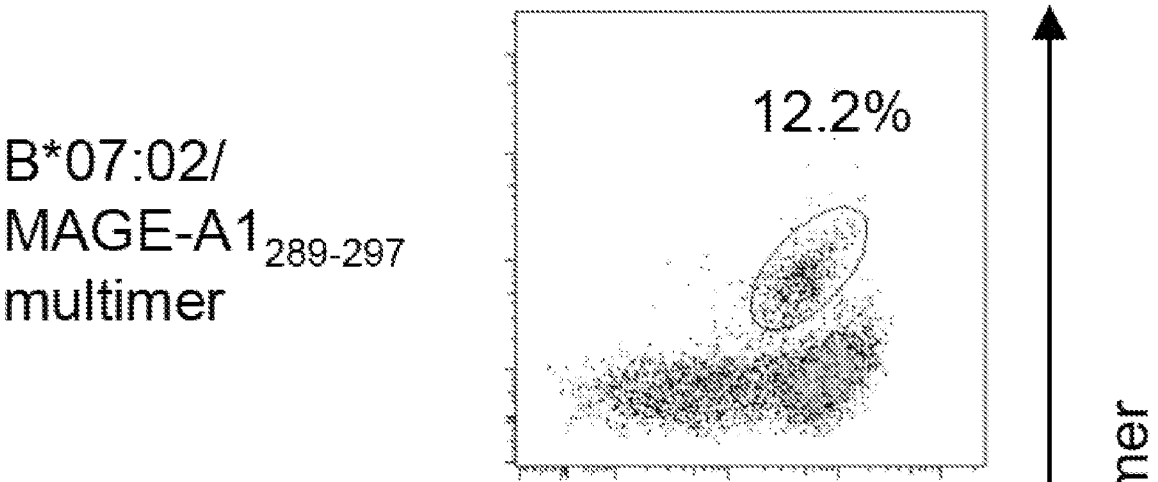

B*07:02/
MAGE-A1$_{289-297}$
multimer
12.2%

FIG. 9B

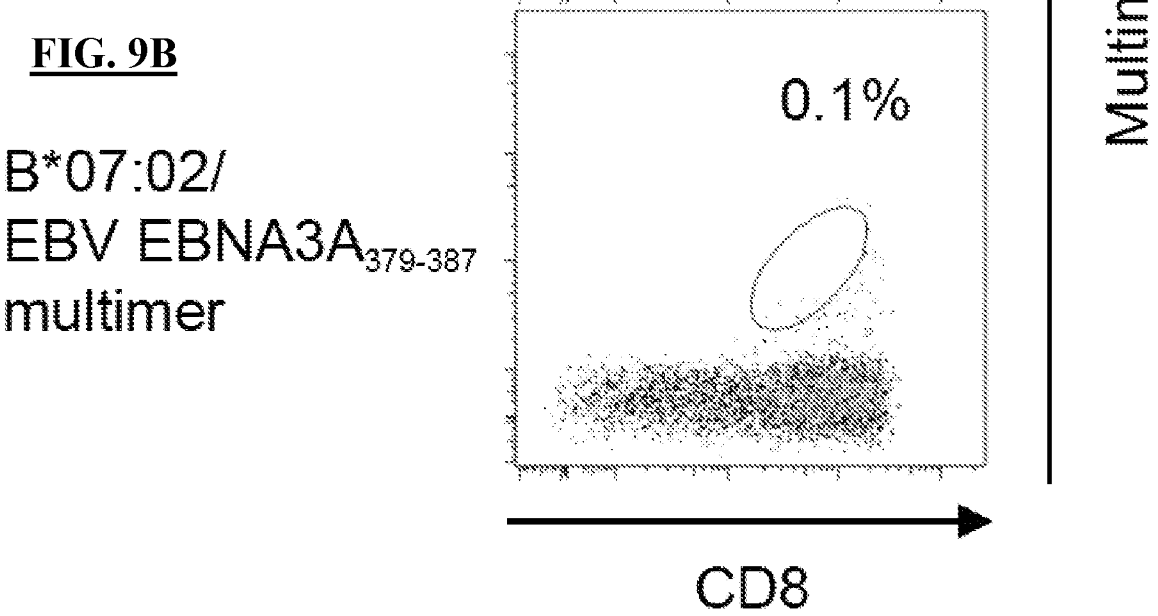
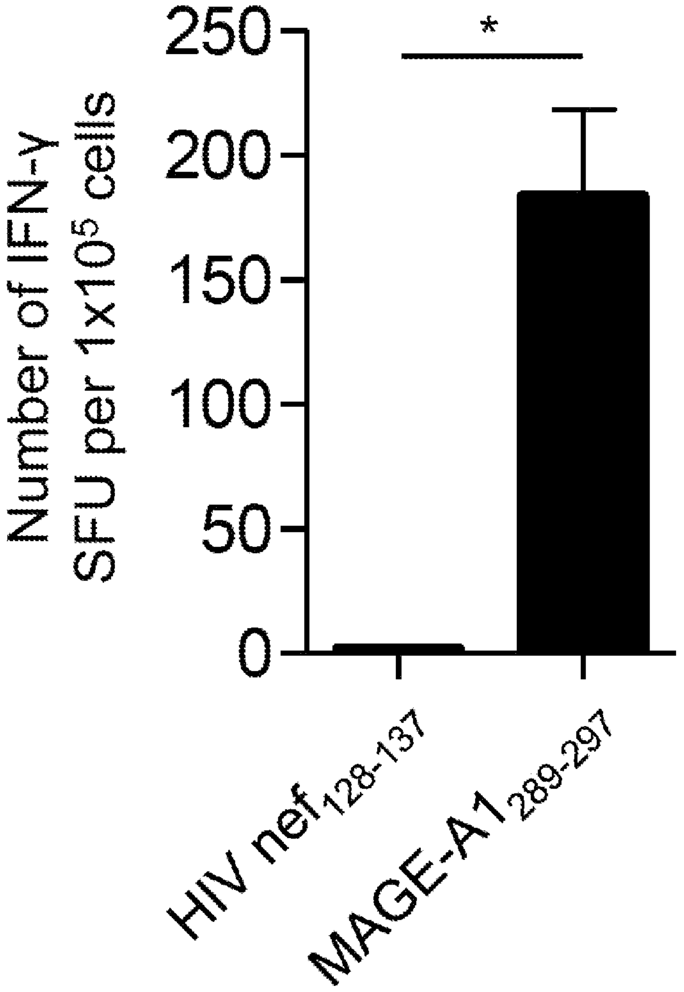

B*07:02/
EBV EBNA3A$_{379-387}$
multimer
0.1%
Multimer
CD8

FIG. 10


Number of IFN-γ
SFU per 1x10^5 cells
250
200
150
100
50
0
*
HIV nef128-137
MAGE-A1289-297

Jurkat76/CD8
transduced with

None

B*07:02/
MAGE-A1$_{289-297}$
TCR

B*07:02/
NY-ESO-1$_{60-72}$
TCR

B*07:02/
MAGE-A1$_{289-297}$
multimer

FIG. 11A

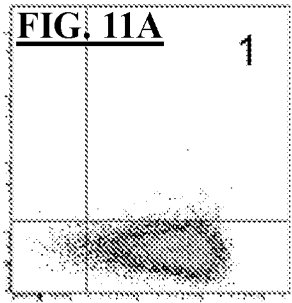


FIG. 11B

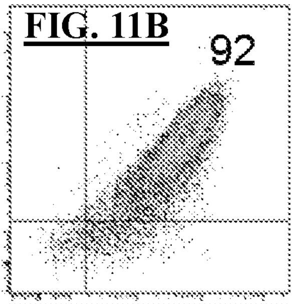
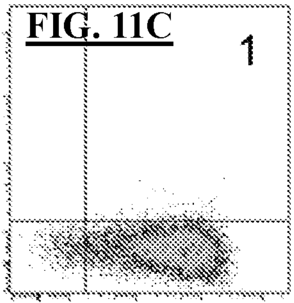


FIG. 11C



B*07:02/
NY-ESO-1$_{60-72}$
multimer

FIG. 11D

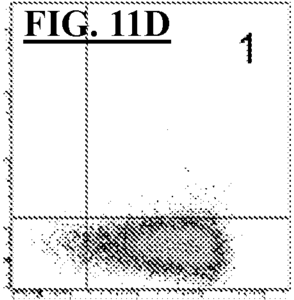


FIG. 11E

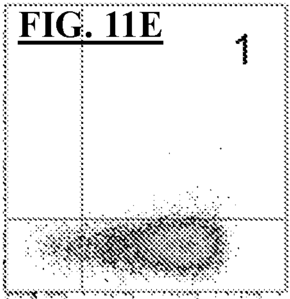
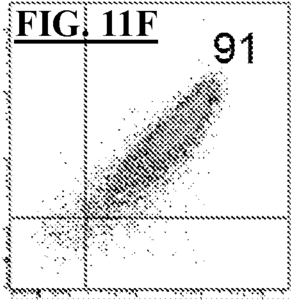


FIG. 11F



B*07:02/
unexchanged
multimer

FIG. 11G

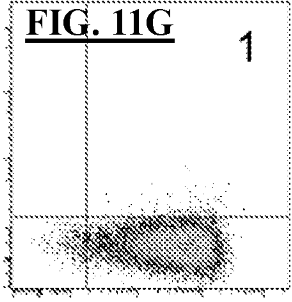


FIG. 11H

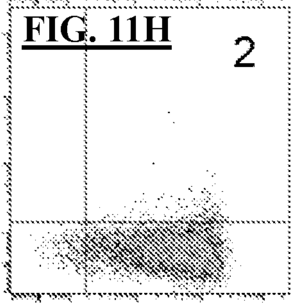
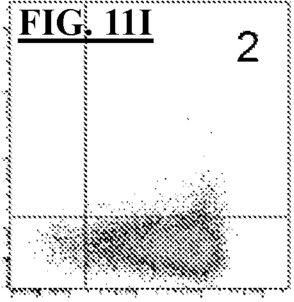


FIG. 11I



CD8

Multimer

Transduced with

None

B*07:02/
MAGE-A1$_{289-297}$
TCR

B*07:02/
MAGE-A1$_{289-297}$
multimer

B*07:02/
HIV nef$_{128-137}$
multimer

FIG. 12A

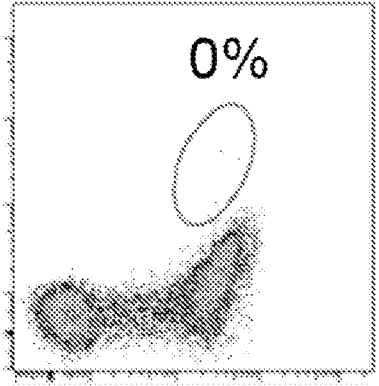


FIG. 12B

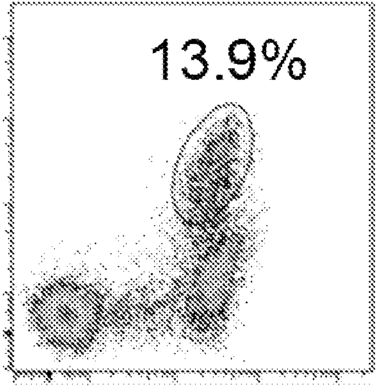


FIG. 12C

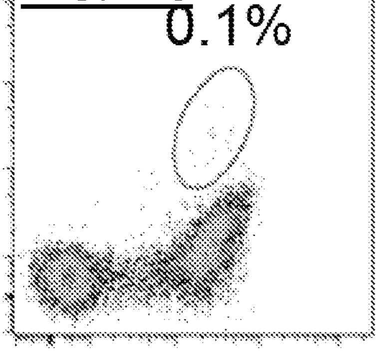


FIG. 12D

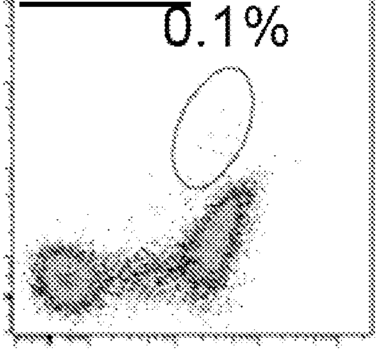


FIG. 13

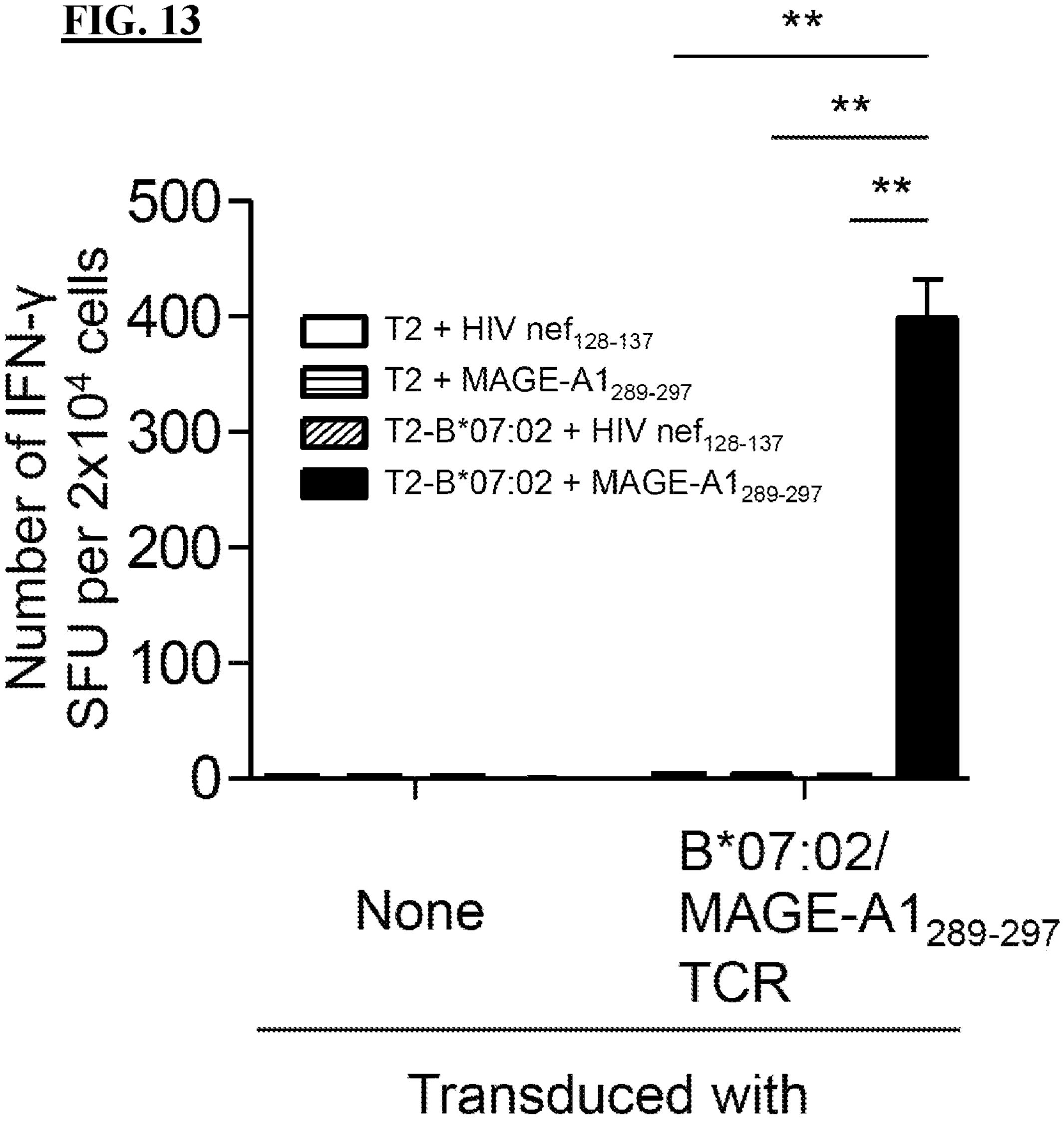

**
**
**
500
400
300
200
100
0
Number of IFN-γ SFU per 2x10⁴ cells
T2 + HIV nef128-137
T2 + MAGE-A1289-297
T2-B*07:02 + HIV nef128-137
T2-B*07:02 + MAGE-A1289-297
None
B*07:02/ MAGE-A1289-297 TCR
Transduced with

FIG. 14A

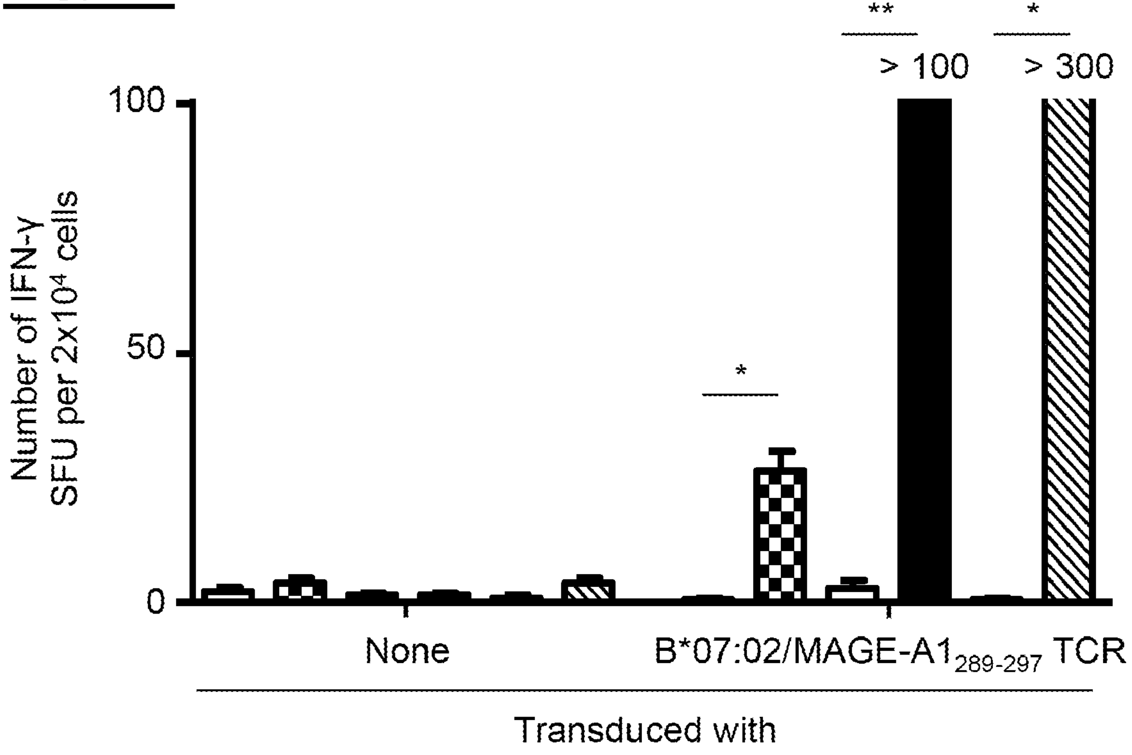


FIG. 14B

		B*07:02	MAGE-A1
□	Me275	-	+
▩	Me275/B*07:02	+	+
▤	SK-MEL-37	-	+
■	SK-MEL-37/B*07:02	+	+
▨	SK-MEL-21	+	-
▧	SK-MEL-21/MAGE-A1	+	+

FIG. 15A

Me275

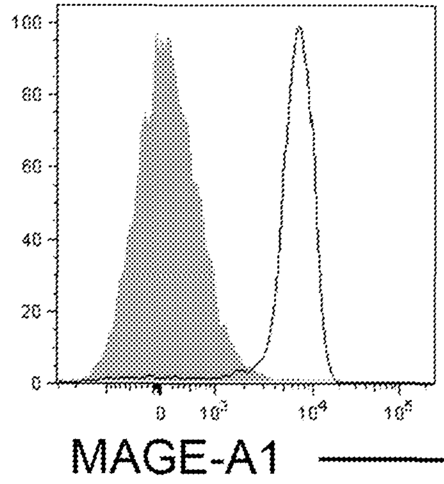


FIG. 15B

SK-MEL-37

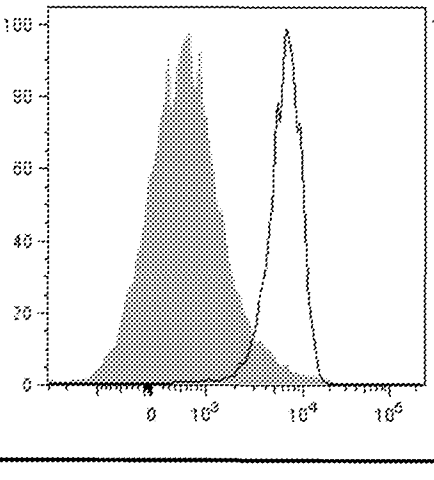


FIG. 15C

SK-MEL-21

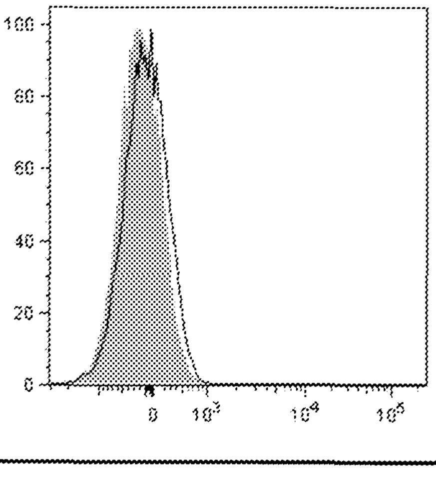


FIG. 15D

SK-MEL-21/
MAGE-A1

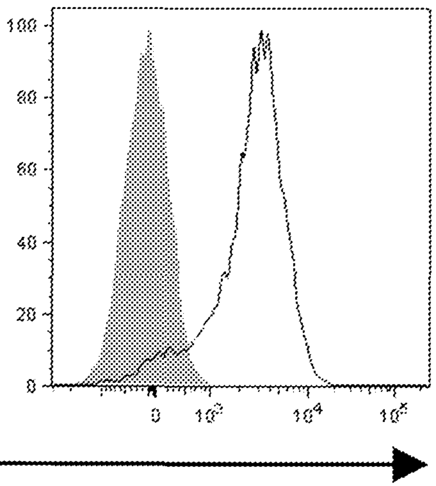


FIG. 16A

Me275

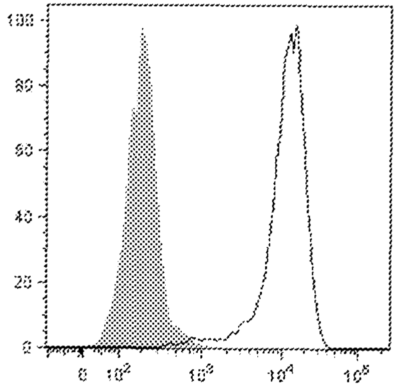


FIG. 16B

Me275/B*07:02

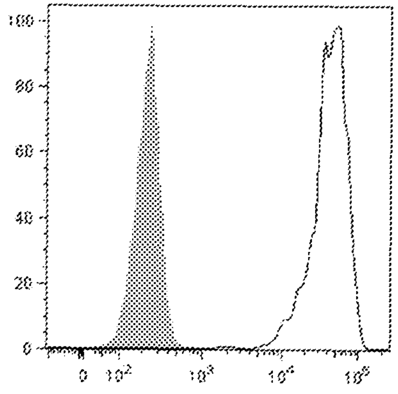


FIG. 16C

SK-MEL-37

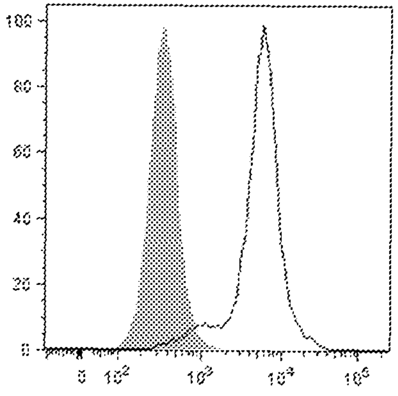
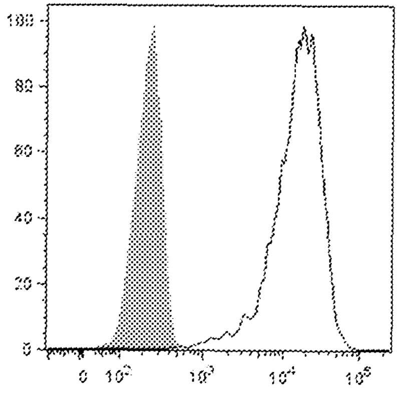


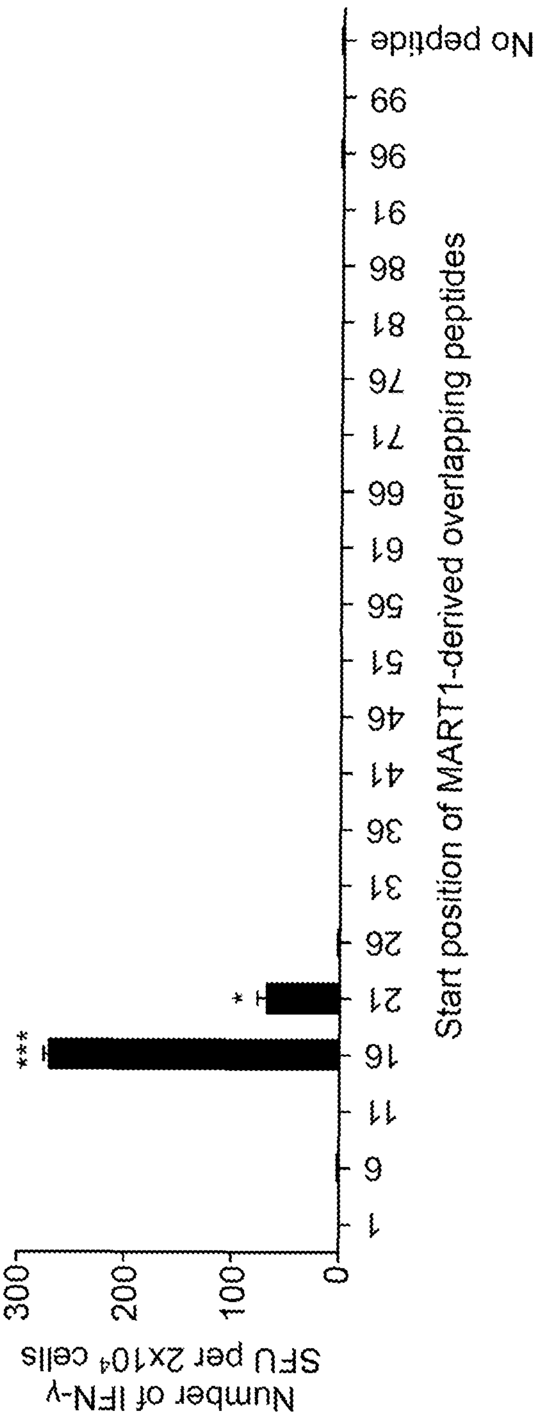
FIG. 16D

SK-MEL-37/B*07:02



ΔNGFR →

FIG. 17


Number of IFN-γ
SFU per 2x10⁴ cells
300
200
100
0
***
*
1
6
11
16
21
26
31
36
41
46
51
56
61
66
71
76
81
86
91
96
99
No peptide
Start position of MART1-derived overlapping peptides

B*18:01/ unexchanged multimer

B*18:01/ MART1$_{25\text{-}33}$ multimer

B*18:01/ HIV gag$_{161\text{-}170}$ multimer

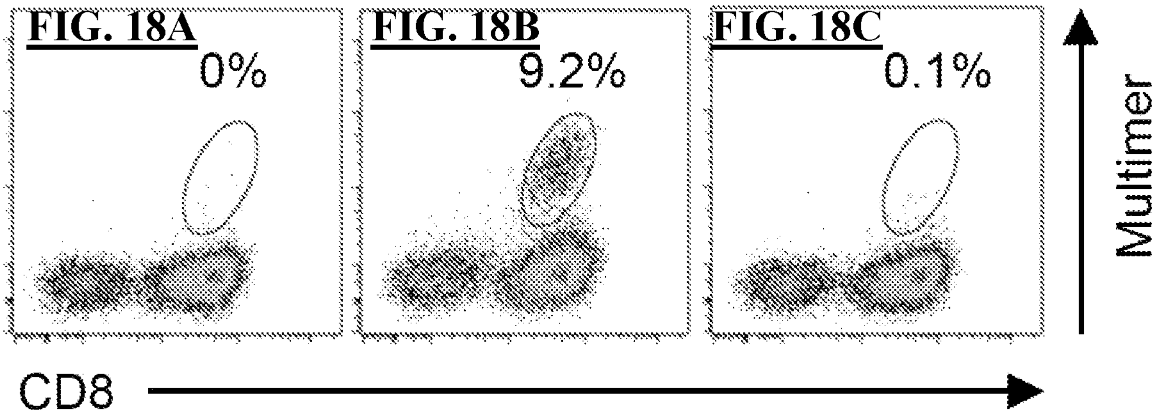
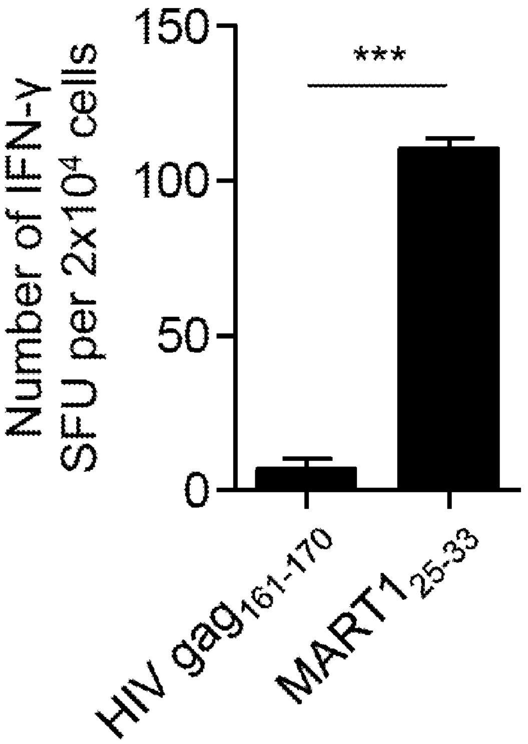


FIG. 18A

FIG. 18B

FIG. 18C

FIG. 19


Number of IFN-γ
SFU per 2x10⁴ cells
150
100
50
0
***
HIV gag161-170
MART1 25-33

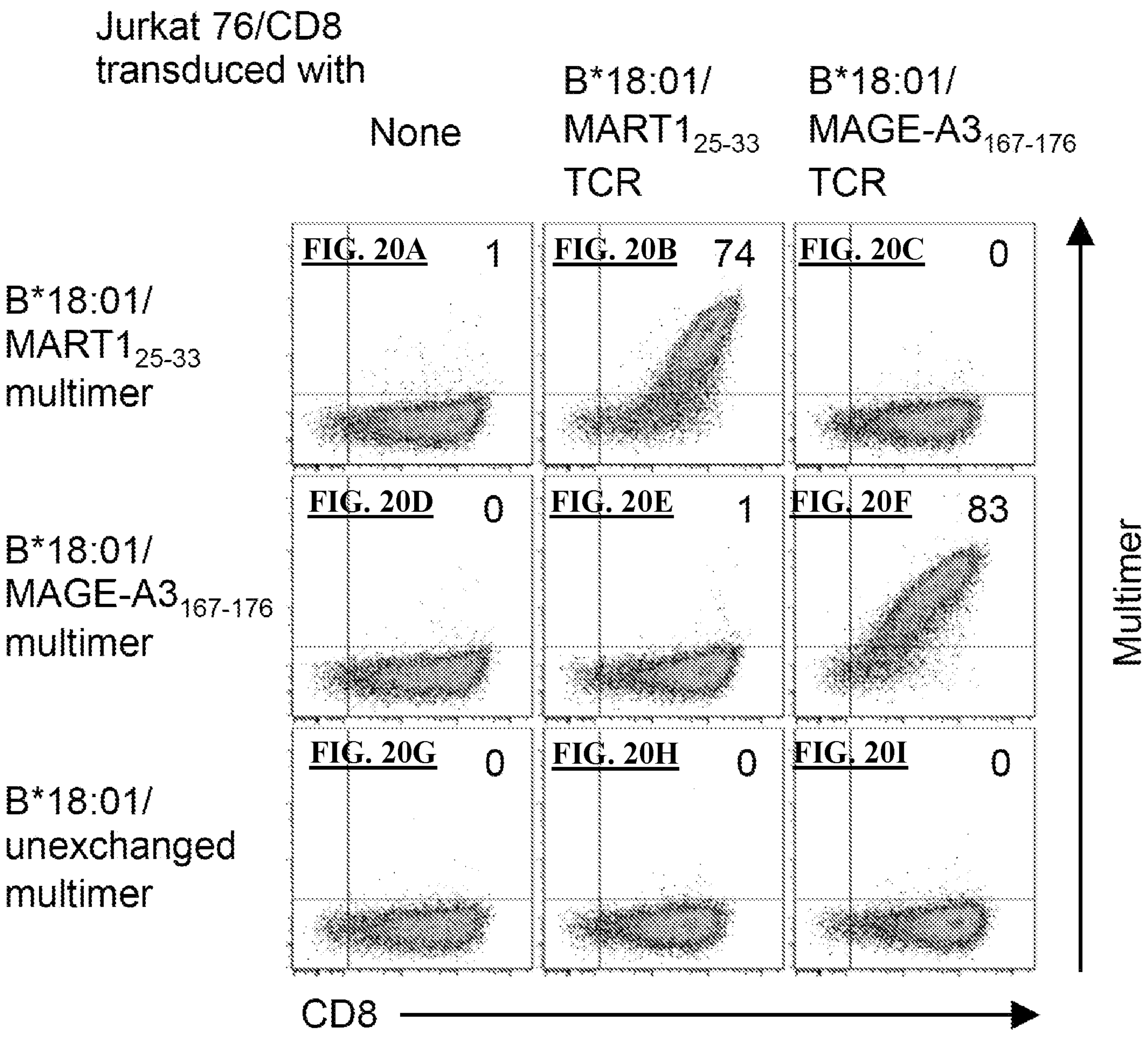


FIG. 20A
FIG. 20B
FIG. 20C
FIG. 20D
FIG. 20E
FIG. 20F
FIG. 20G
FIG. 20H
FIG. 20I

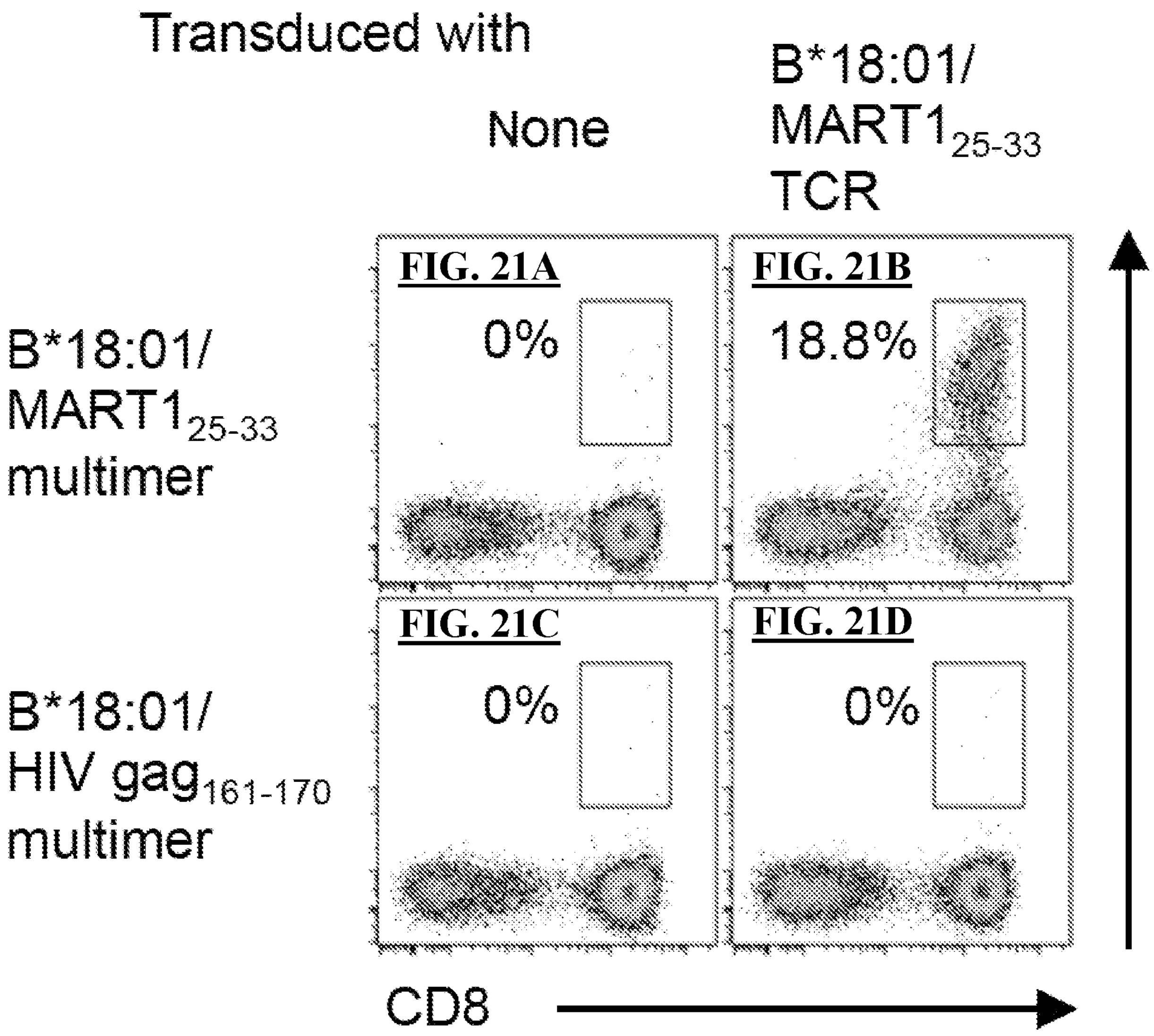


FIG. 21A
FIG. 21B
FIG. 21C
FIG. 21D

FIG. 22

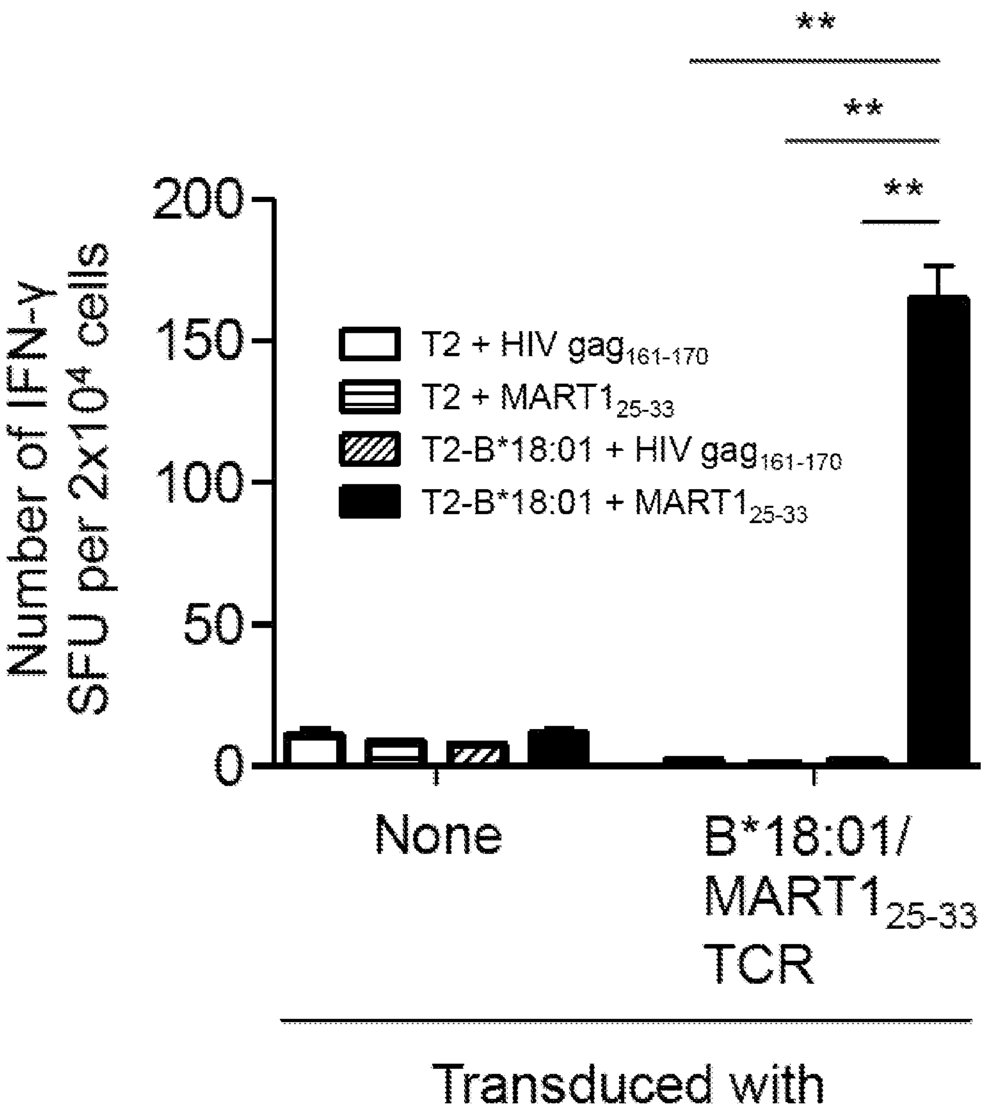

**
**
**
Number of IFN-γ SFU per 2x10^4 cells
200
150
100
50
0
T2 + HIV gag161-170
T2 + MART125-33
T2-B*18:01 + HIV gag161-170
T2-B*18:01 + MART125-33
None
B*18:01/ MART125-33 TCR
Transduced with

FIG. 23A

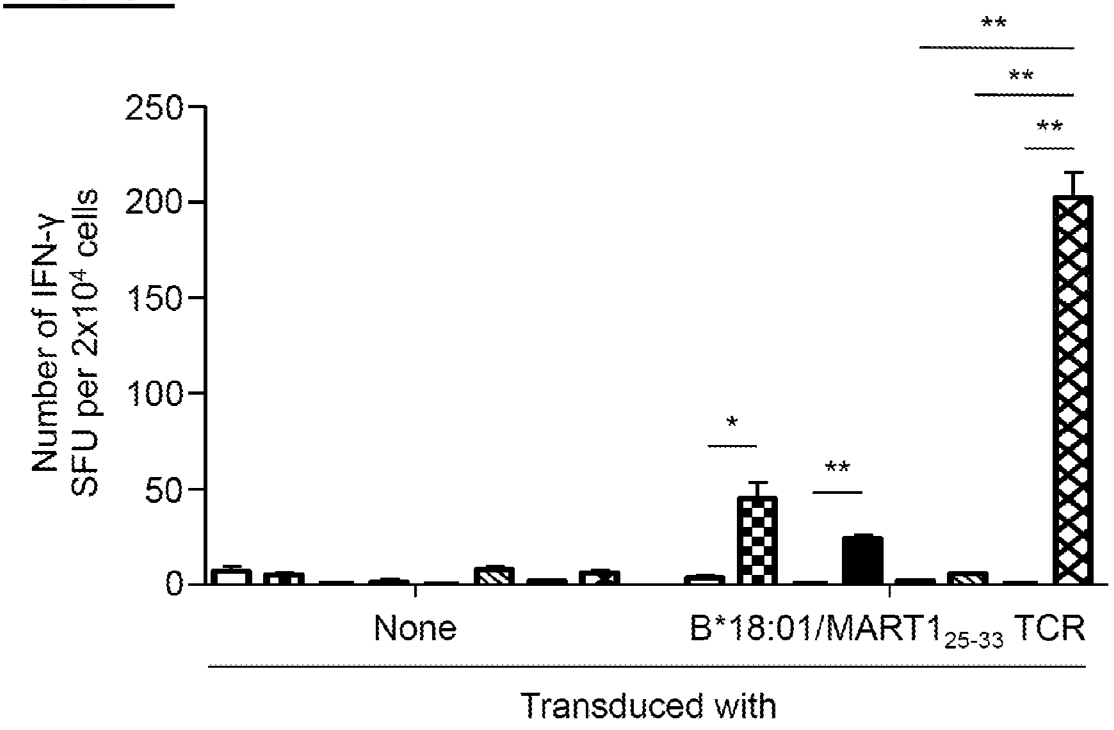


FIG. 23B

		B*18:01	MART1
□	Malem-3M	-	+
▦	Malme-3M/B*18:01	+	+
☰	SK-MEL-28	-	+
■	SK-MEL-28/B*18:01	+	+
▨	A375	-	-
▧	A375/B*18:01	+	-
⊞	A375/MART1	-	+
☒	A375/B*18:01/MART1	+	+

FIG. 24A

Malme-3M

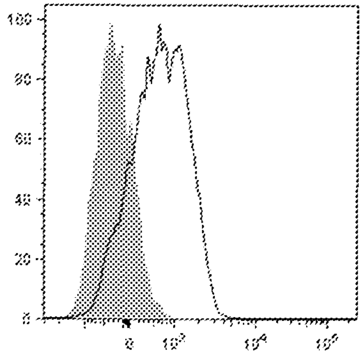


FIG. 24B

SK-MEL-28

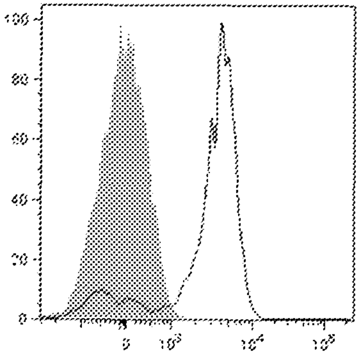


FIG. 24C

A375

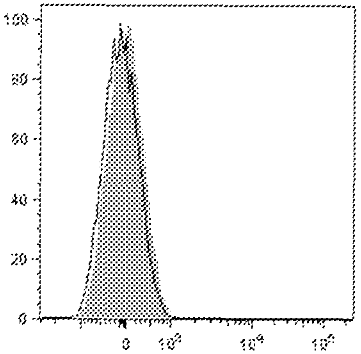


FIG. 24D

A375/
MART1

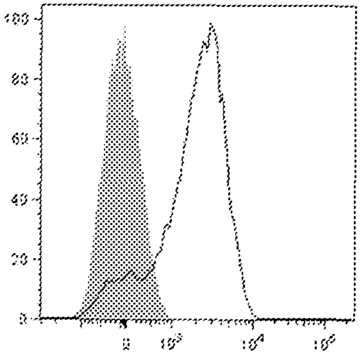


FIG. 24E

A375/B*18:01/
MART1

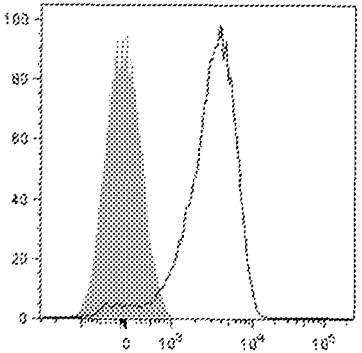


FIG. 25A

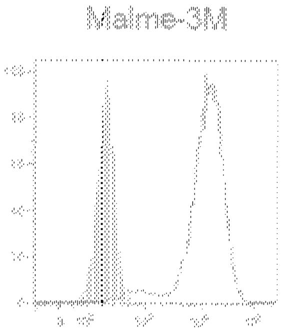


FIG. 25B

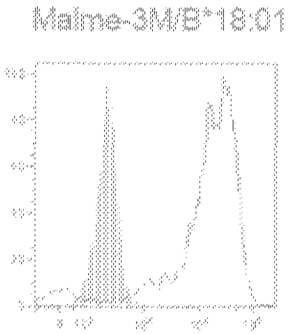


FIG. 25C

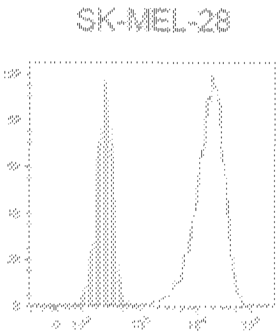


FIG. 25D

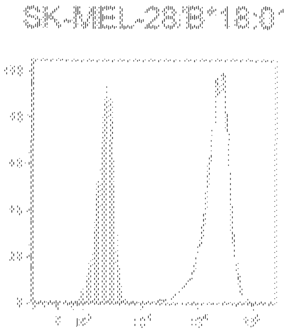


FIG. 25E

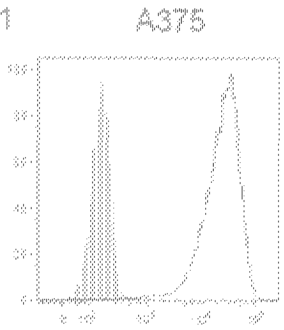
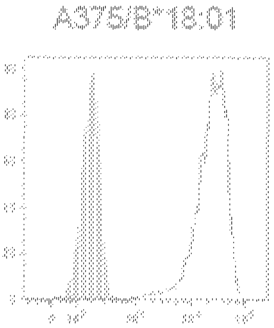


FIG. 25F



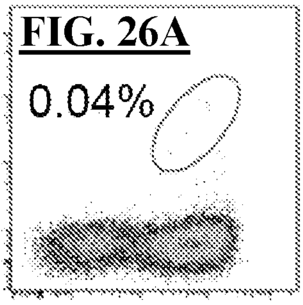
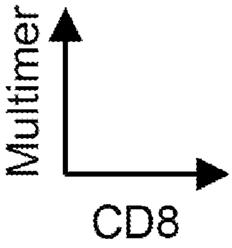


FIG. 26A



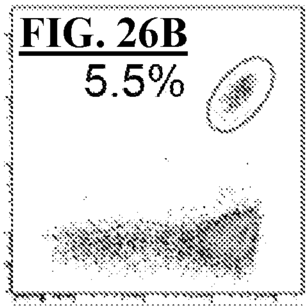


FIG. 26B

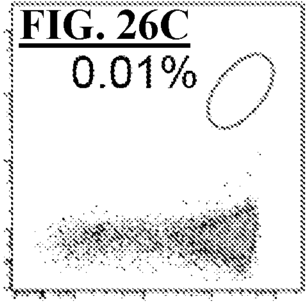
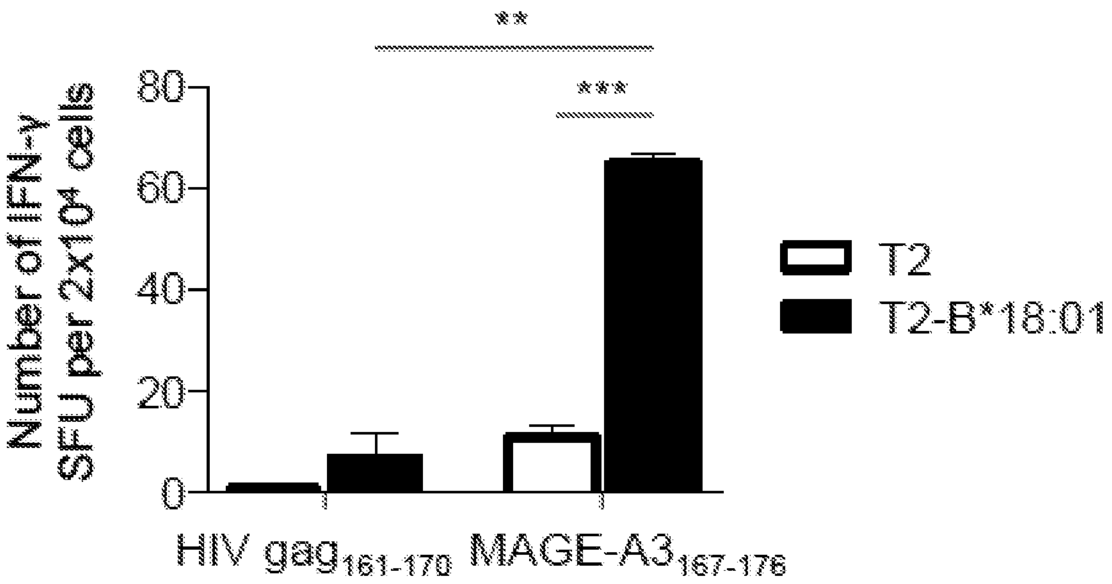


FIG. 26C

FIG. 27


**
***
80
60
40
20
0
Number of IFN-γ SFU per 2x10⁴ cells
HIV gag161-170
MAGE-A3167-176
T2
T2-B*18:01

Jurkat 76/CD8
transduced with

None

B*18:01/
MAGE-A3$_{167-176}$
TCR

B*18:01/
MART1$_{25-33}$
TCR

B*18:01/
MAGE-A3$_{167-176}$
multimer

FIG. 28A

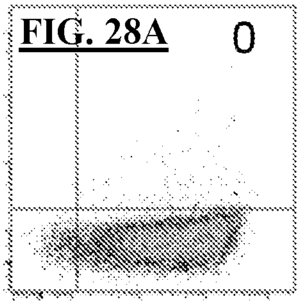


FIG. 28B

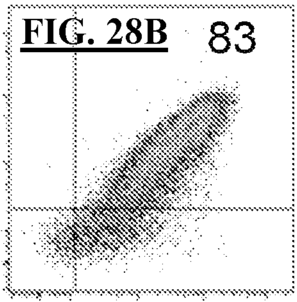
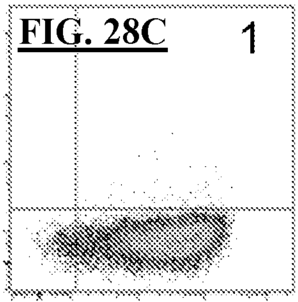


FIG. 28C



B*18:01/
MART1$_{25-33}$
multimer

FIG. 28D

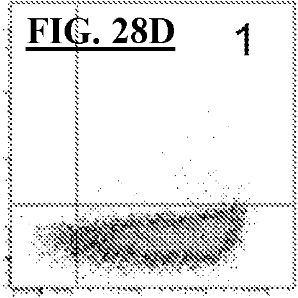


FIG. 28E

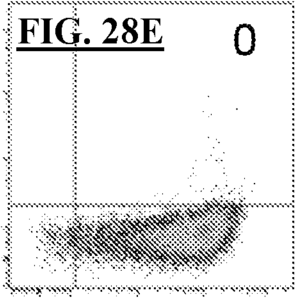
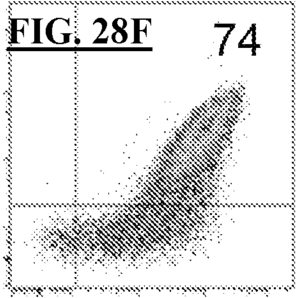


FIG. 28F



B*18:01/
unexchanged
multimer

FIG. 28G

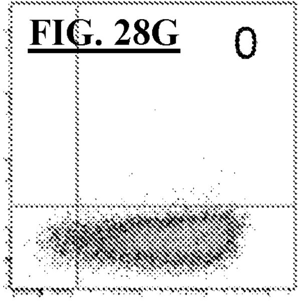


FIG. 28H

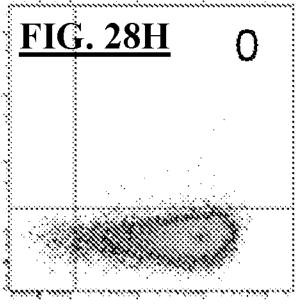
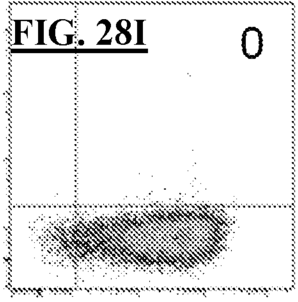


FIG. 28I



CD8

Multimer

FIG. 29A

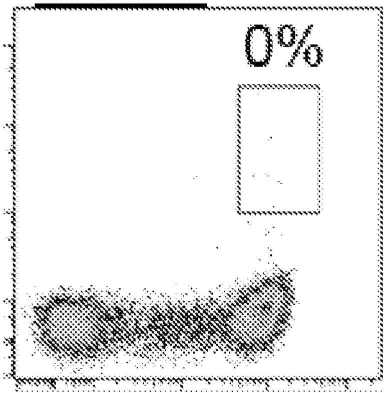


FIG. 29B

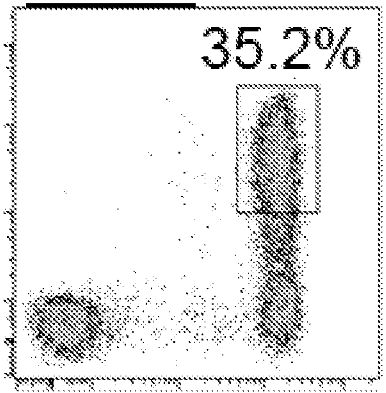


FIG. 29C

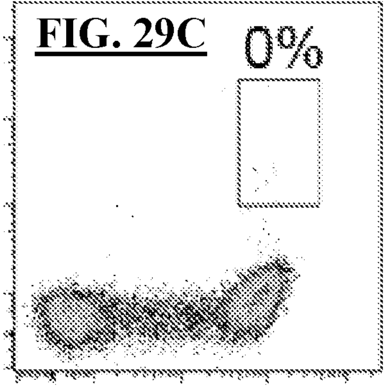


FIG. 29D

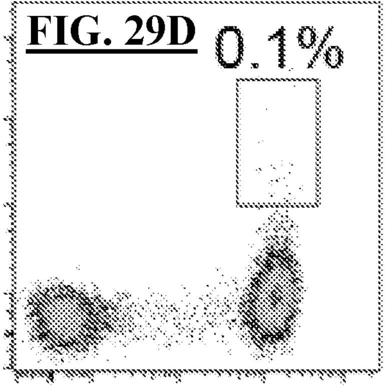


FIG. 30

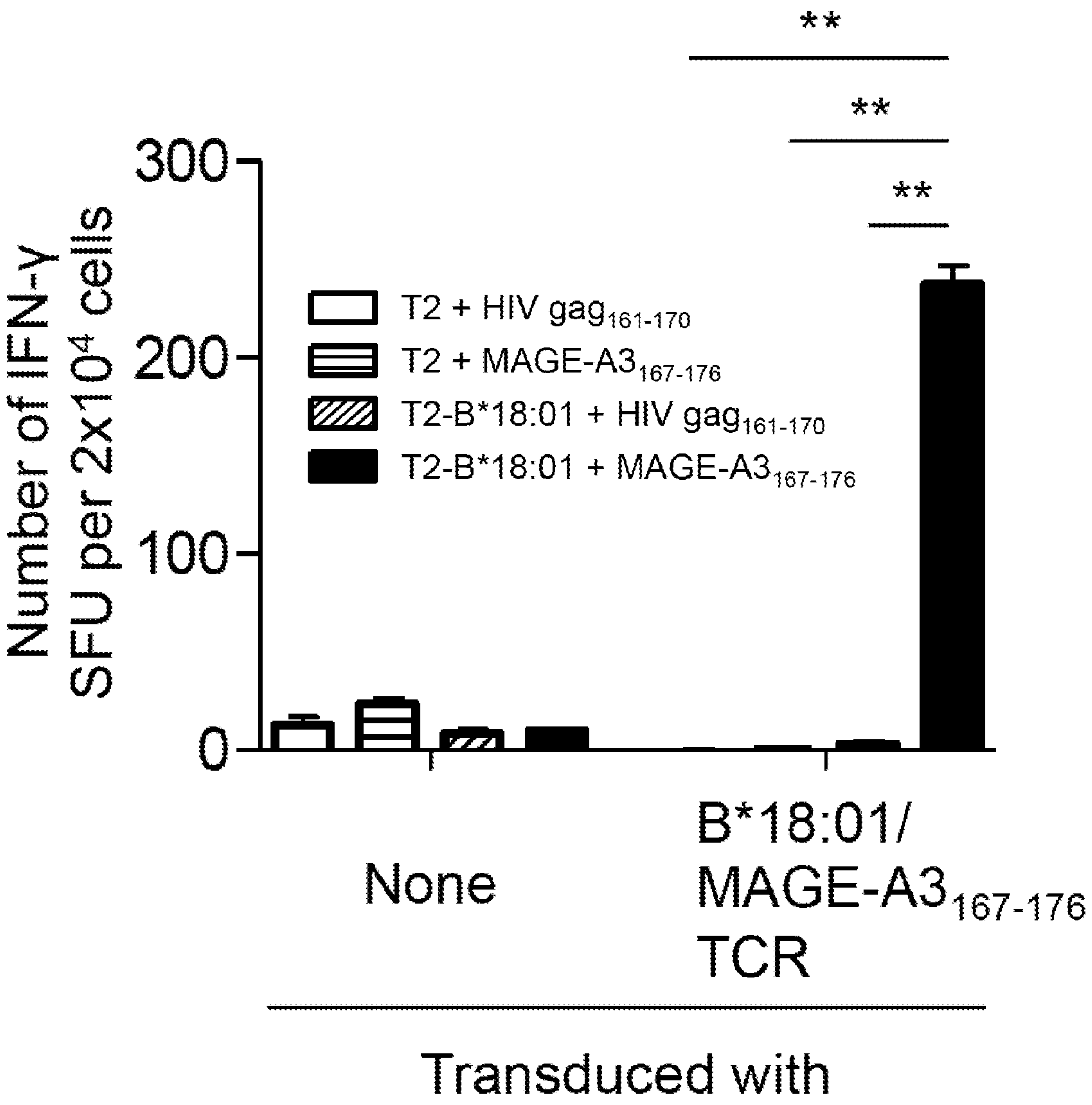

**
**
**
300
200
100
0
Number of IFN-γ SFU per 2x10^4 cells
T2 + HIV gag$_{161-170}$
T2 + MAGE-A3$_{167-176}$
T2-B*18:01 + HIV gag$_{161-170}$
T2-B*18:01 + MAGE-A3$_{167-176}$
None
B*18:01/ MAGE-A3$_{167-176}$ TCR
Transduced with

FIG. 31A

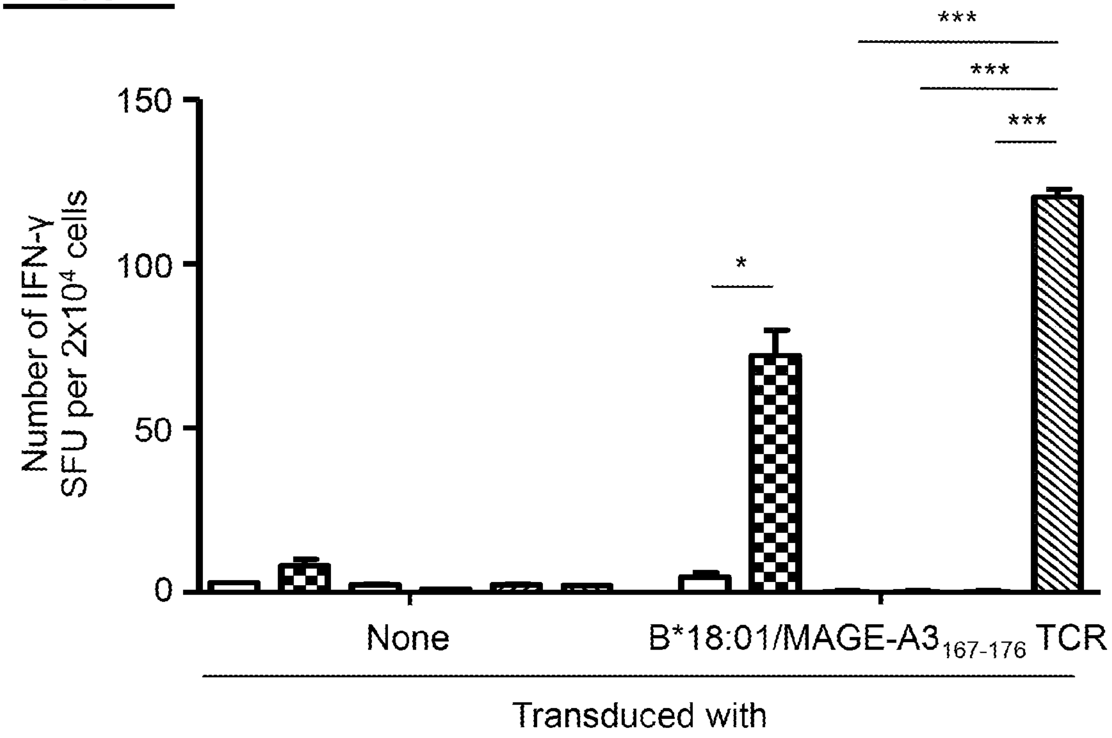


FIG. 31B

		B*18:01	MAGE-A3
□	SK-MEL-28	-	+
▦	SK-MEL-28/B*18:01	+	+
▤	HEK293T	-	-
■	HEK293T/B*18:01	+	-
▨	HEK293T/MAGE-A3	-	+
▧	HEK293T/B*18:01/MAGE-A3	+	+

FIG. 32

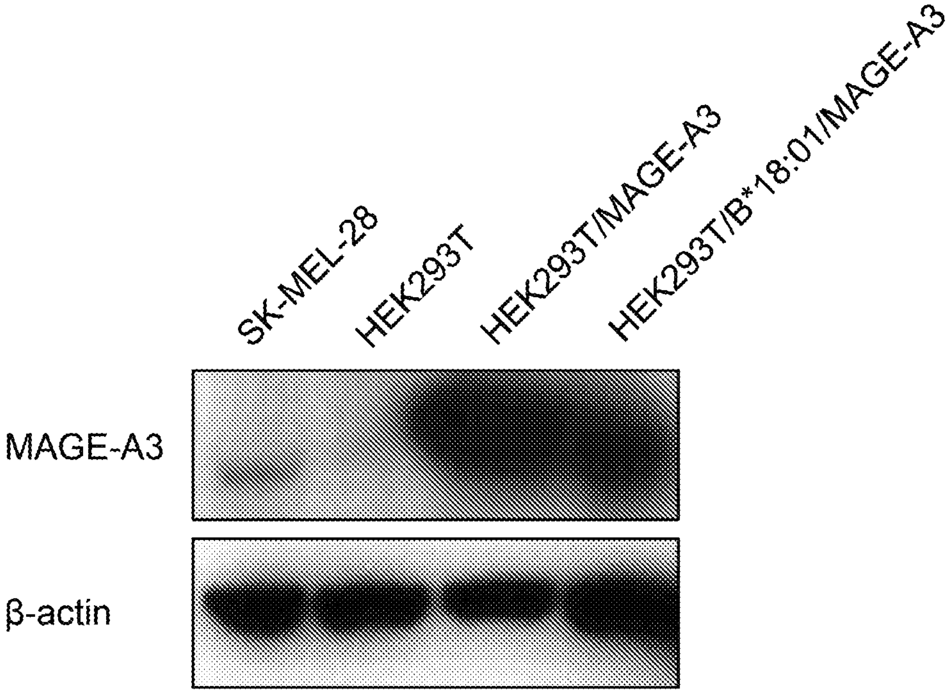

SK-MEL-28
HEK293T
HEK293T/MAGE-A3
HEK293T/B*18:01/MAGE-A3
MAGE-A3
β-actin

FIG. 33A

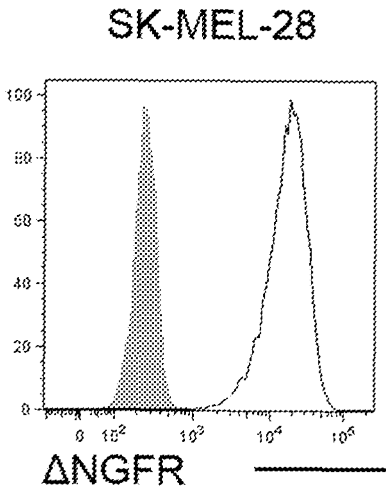


FIG. 33B

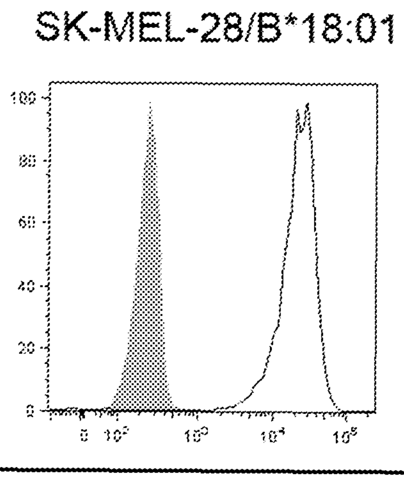


FIG. 33C

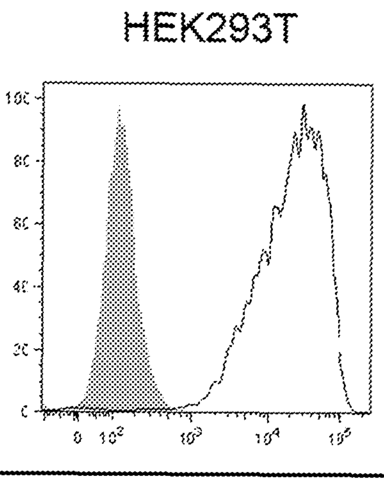


FIG. 33D

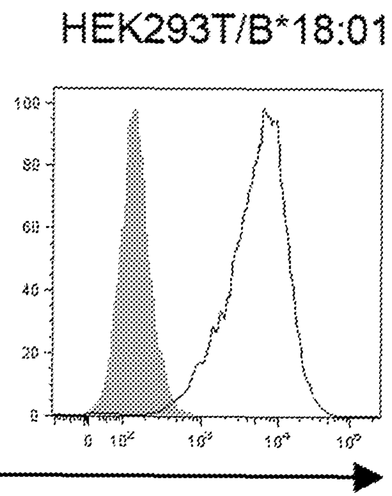


FIG. 34A

A*02:01/
SSX2$_{41-49}$
multimer

FIG. 34B

A*02:01/
HTLV-1 tax$_{11-19}$
multimer

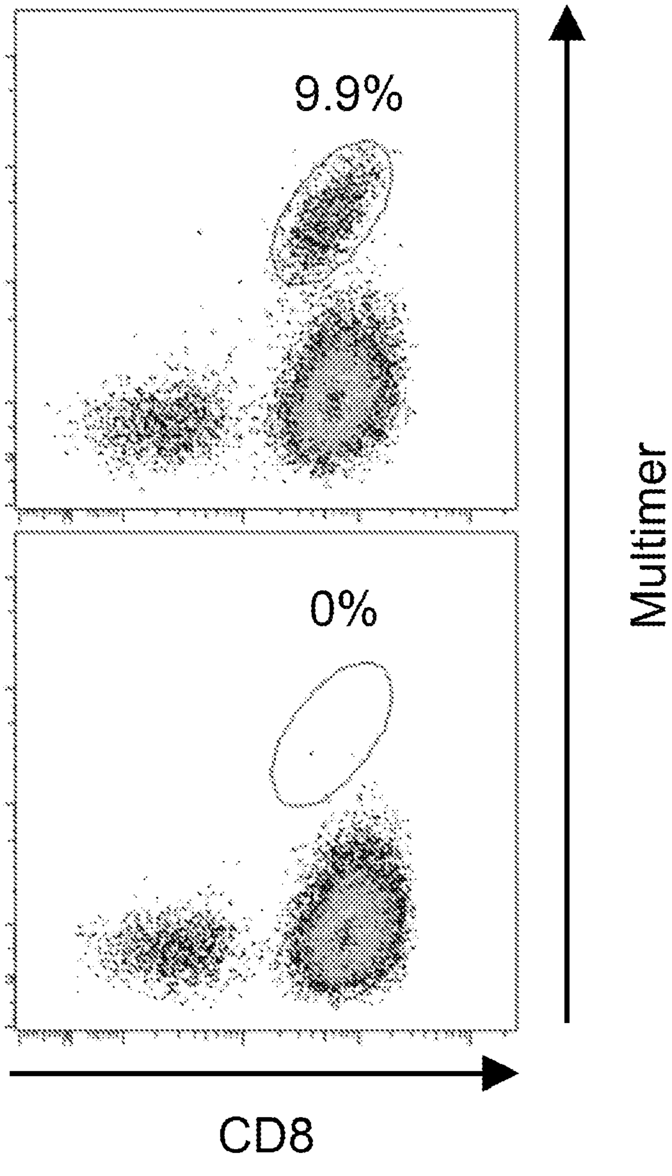
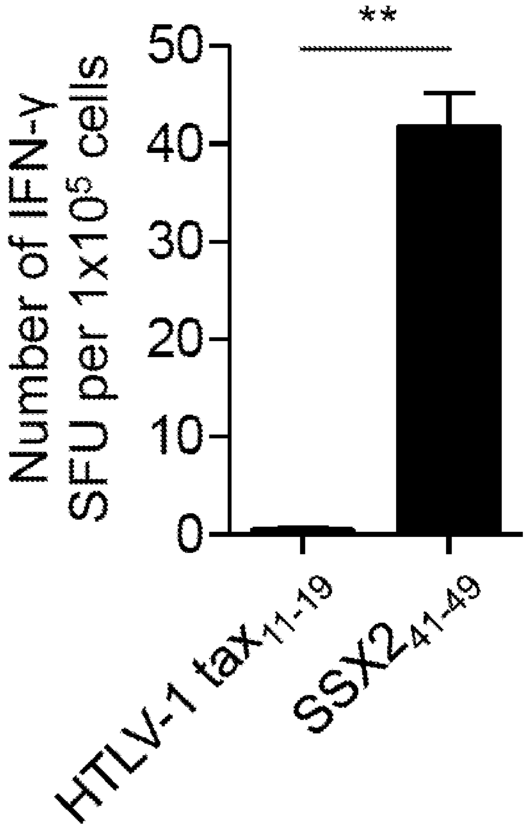


FIG. 35


Number of IFN-γ SFU per 1x10^5 cells
50
40
30
20
10
0
**
HTLV-1 tax11-19
SSX2 41-49

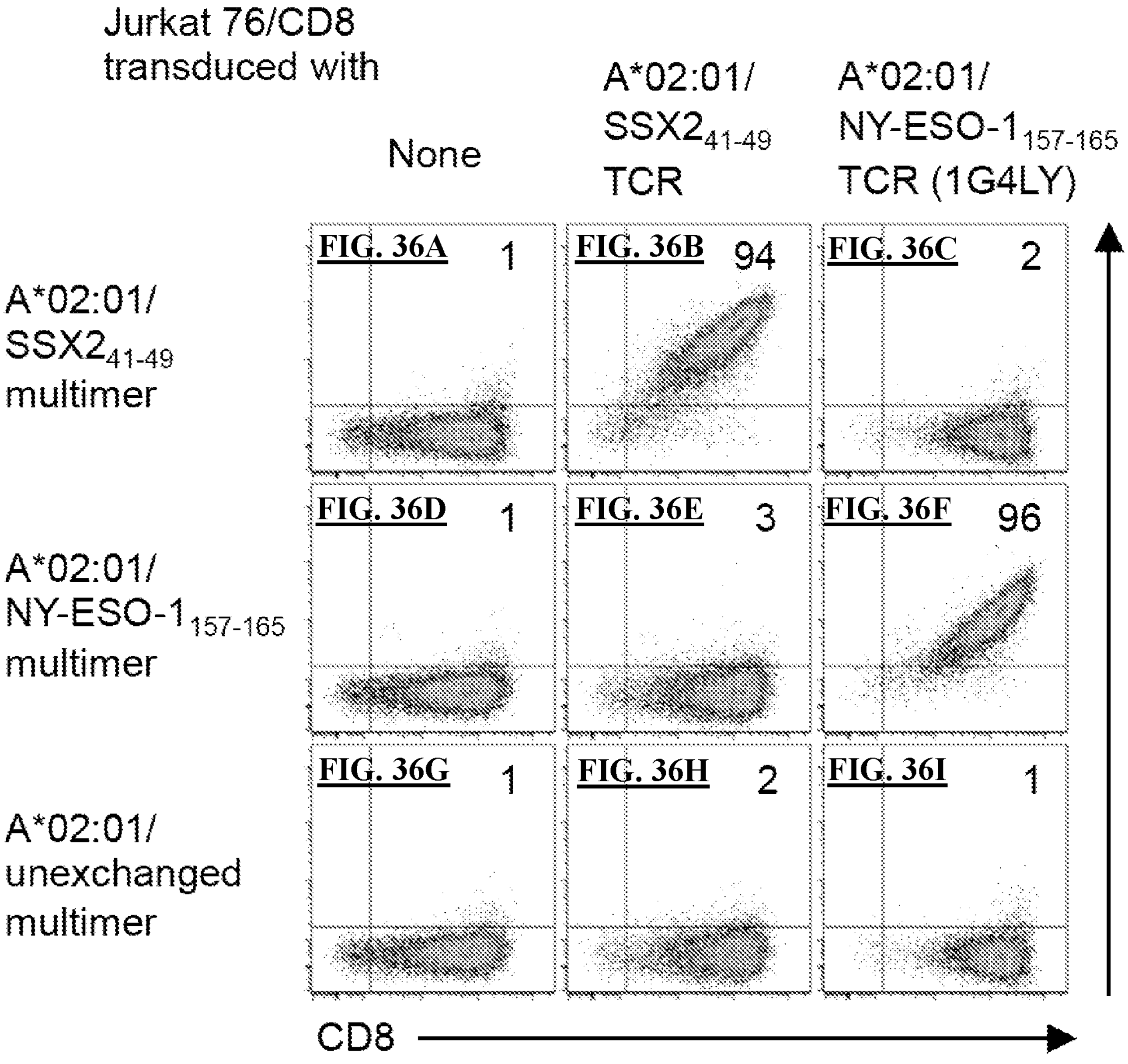


FIG. 36A FIG. 36B FIG. 36C FIG. 36D FIG. 36E FIG. 36F FIG. 36G FIG. 36H FIG. 36I

FIG. 37A

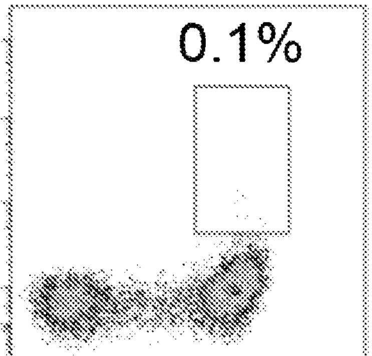


FIG. 37B

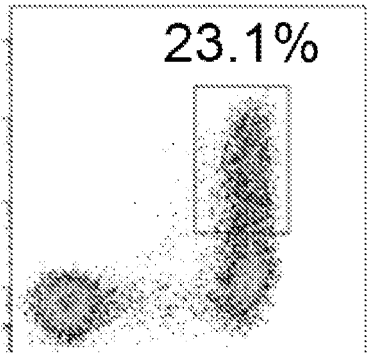


FIG. 37C

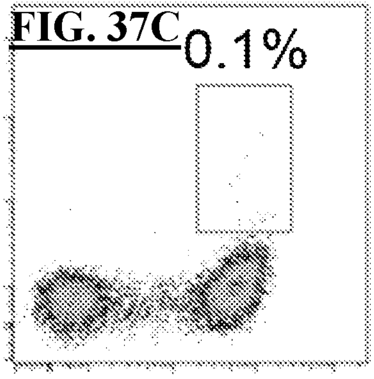


FIG. 37D

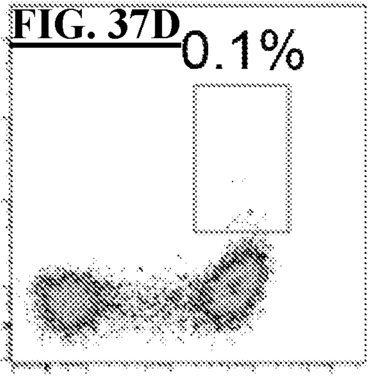


FIG. 38

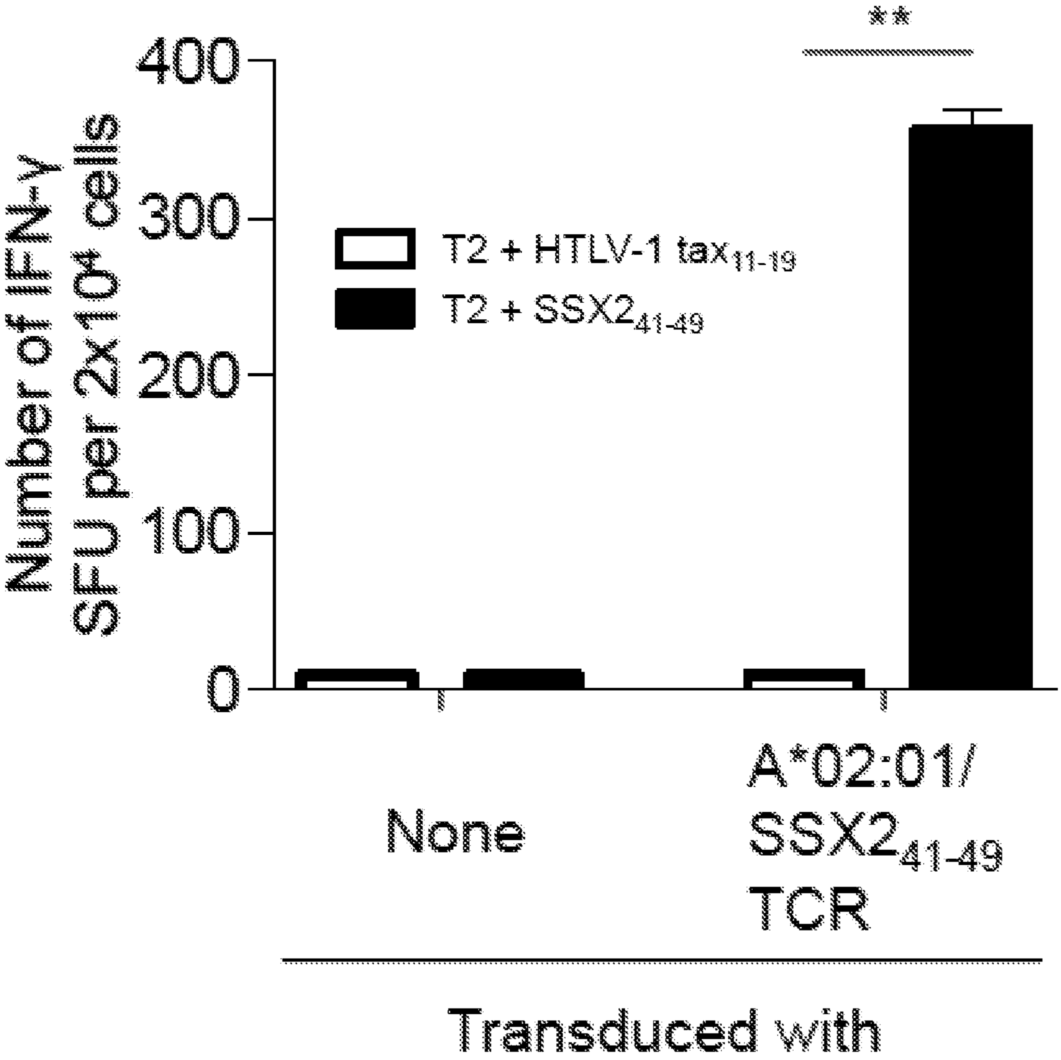

**
400
300
200
100
0
Number of IFN-γ SFU per 2x10⁴ cells
T2 + HTLV-1 tax11-19
T2 + SSX2 41-49
None
A*02:01/ SSX2 41-49 TCR
Transduced with

FIG. 39A

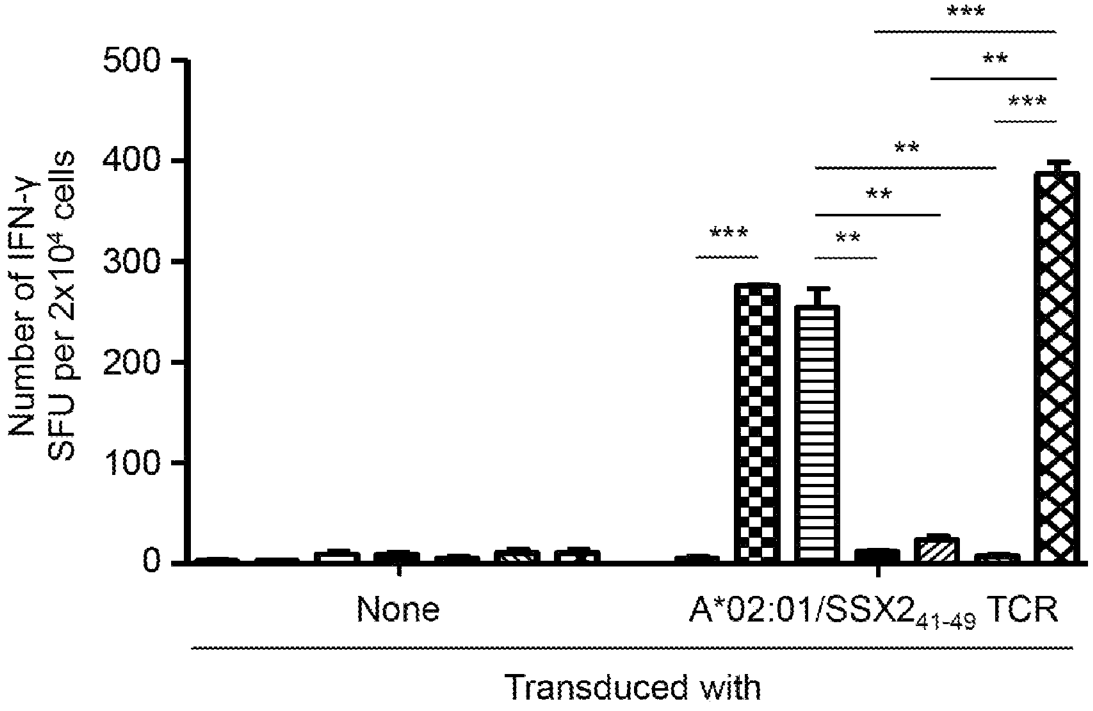


FIG. 39B

		A*02:01	SSX2
□	SK-MEL-21	+	-
▦	SK-MEL-21/SSX2	+	+
▤	SK-MEL-37	+	+
■	SK-MEL-28	-	-
▨	SK-MEL-28/A*02:01	+	-
▧	SK-MEL-28/SSX2	-	+
▩	SK-MEL-28/A*02:01/SSX2	+	+

FIG. 40

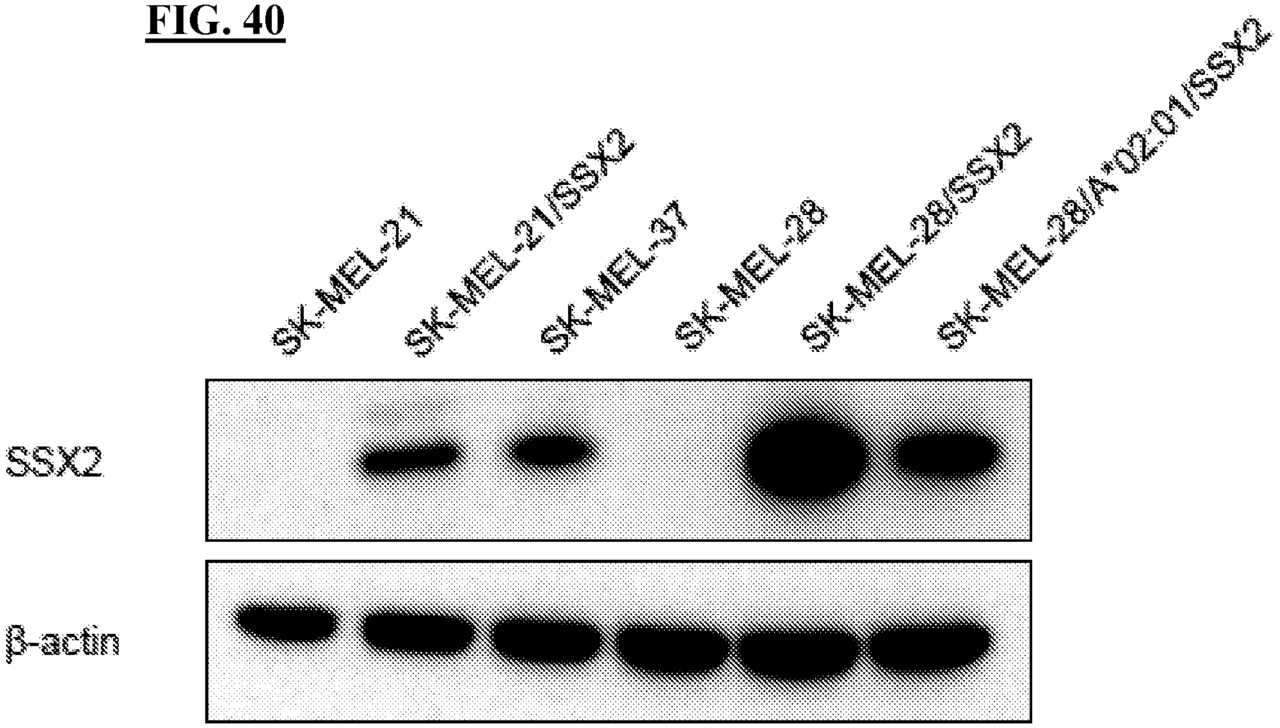
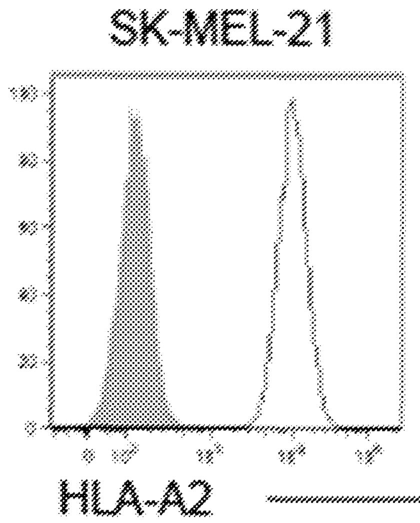
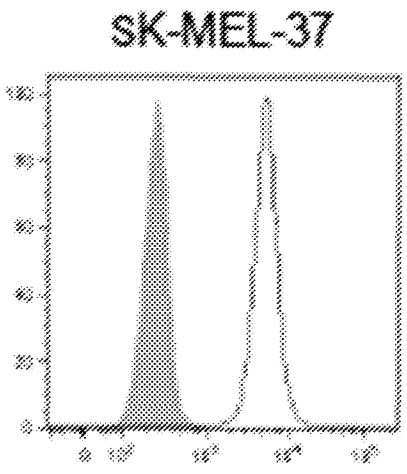

SK-MEL-21
SK-MEL-21/SSX2
SK-MEL-37
SK-MEL-28
SK-MEL-28/SSX2
SK-MEL-28/A*02:01/SSX2
SSX2
β-actin

FIG. 41A



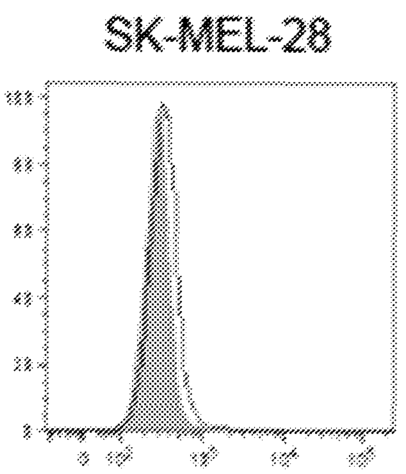
SK-MEL-21

FIG. 41B



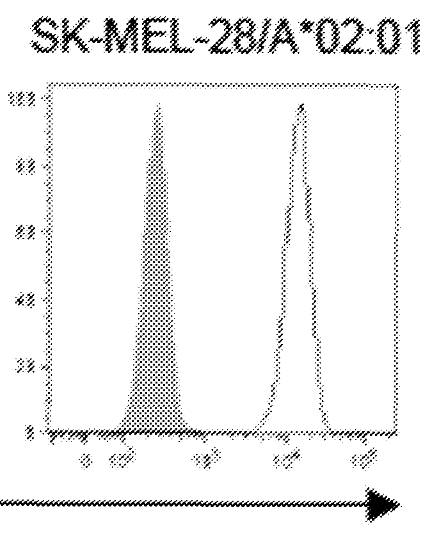
SK-MEL-37

FIG. 41C



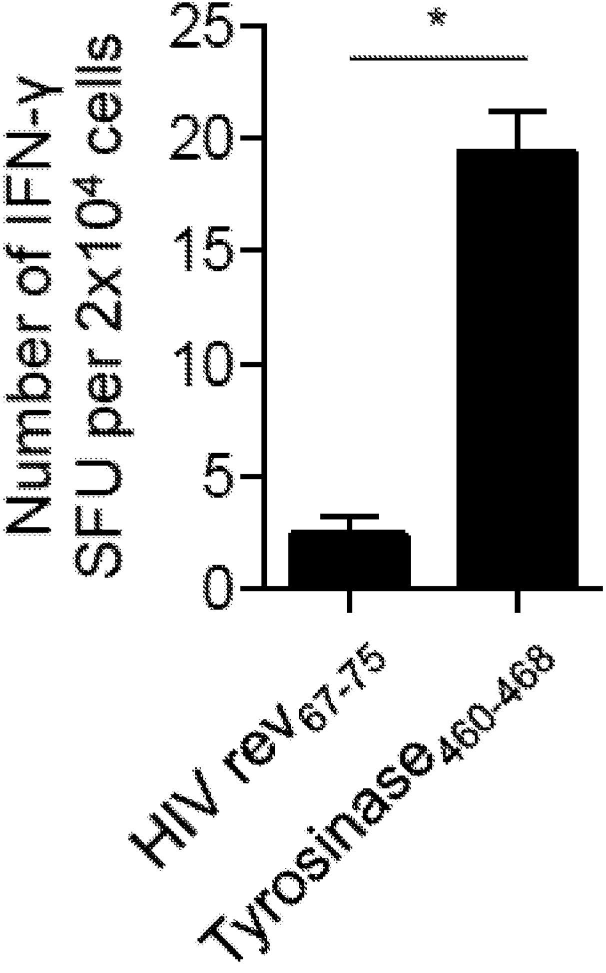
SK-MEL-28

FIG. 41D



SK-MEL-28/A*02:01

FIG. 2


Number of IFN-γ SFU per 2x10⁴ cells
25
20
15
10
5
0
*
HIV rev67-75
Tyrosinase460-468