USE OF BINDING PROTEINS FOR TREATMENT OF SOLID TUMORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial No. 63/631,385, filed on 08 April 2024, U.S. Provisional Application Serial No. 63/644,949, filed on 09 May 2024, U.S. Provisional Application Serial No. 63/653,125, filed on 29 May 2024, U.S. Provisional Application Serial No. 63/716,057, filed on 04 November 2024, and U.S. Provisional Application Serial No. 63/729,235, filed on 06 December 2024; the entire contents of each of said applications are incorporated herein in their entirety by this reference.

BACKGROUND

[0002] Solid tumors are difficult to treat for a number of reasons, including heterogeneity of malignant tissue. Tumor heterogeneity can result in partial responses to therapy and rapid relapse. Traditional therapeutics, and in particular traditional TCR products, have not fully addressed the treatment of solid tumors, including heterogenous solid tumors.

SUMMARY

[0003] The present application encompasses TCRs and combinations of TCRs for treatment of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer. Due at least in part to the heterogeneity of solid tumor cells, therapies used to treat solid tumors often provide only a partial response and can be followed by rapid relapse. Many first-generation TCRs were found to have a limited effective duration, in part because malignant cells can lack, decrease expression of, and/or decrease presentation of individual target antigens (or evolve to have these characteristics, before, during, or after treatment). For example, in 15% to 30% of tumors, cells lose at least one HLA. Checkpoint therapeutics can additionally fail due to low levels of endogenous tumor-targeted T cells. At least one solution of the present disclosure is multiplexing of TCRs in a single therapy or therapeutic regimen of engineered T cells. Further still, the present disclosure recognizes that TCRs targeting one or more of the most common HLAs can contribute to the utility of therapeutic products for treatment of a broad patient population. The present disclosure encompasses multiplexing of TCRs that target

antigens that are highly expressed by melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer and presented by a plurality of HLAs and such cancers are applicable to any aspect and embodiment thereof encompassed by the present disclosure.

[0004] In various embodiments, engineered T cells of the present disclosure can advantageously encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function, increasing therapeutic response, and/or decreasing the risk of relapse. In various embodiments, engineered T cells of the present disclosure can advantageously encode and/or express dominant negative TGFβRII (DN-TGFβRII). Expression of this dominant negative receptor can increase persistence of engineered T cells.

[0005] In at least one aspect, the present disclosure encompasses a method of treating a malignancy selected from the group consisting of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer in an adult human subject, the treatment including infusing one dose of one engineered T cell type (single-plex), two doses of one engineered T cell type (single-plex), or two doses of each of two engineered T cell types (multi-plex), where engineered T cell types are selected from the group consisting of:

[0006] 1) T cells engineered to express a TCR that binds MAGE-C2 peptide (RAREFMELL) when presented by HLA-B*07:02, if the cancer cells express MAGE-C2 and present MAGE-C2 peptide (RAREFMELL) by HLA-B*07:02 (TSC-201-B0702), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 7, a CDR2 including the amino acid sequence of SEQ ID NO: 8, and a CDR3 including the amino acid sequence of SEQ ID NO: 9, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 13, a CDR2 including the amino acid sequence of SEQ ID NO: 14, and a CDR3 including the amino acid sequence of SEQ ID NO: 15,

[0007] 2) T cells engineered to express a TCR that binds HPV16 E711-19 peptide (YMLDLQPET) when presented by HLA-A*02:01, if the cancer cells express HPV16 E7

and present HPV16 E711-19 peptide (YMLDLQPET) by HLA-A*02:01 (TSC-200-A0201), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 20, a CDR2 including the amino acid sequence of SEQ ID NO: 21, and a CDR3 including the amino acid sequence of SEQ ID NO: 22, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 26, a CDR2 including the amino acid sequence of SEQ ID NO: 27, and a CDR3 including the amino acid sequence of SEQ ID NO: 28,

[0008] 3) T cells engineered to express a TCR that binds MAGE-A1 peptide (VRFFFPSL) when presented by HLA-C*07:02, if the cancer cells express MAGE-A1 and present MAGE-A1 peptide (VRFFFPSL) by HLA-C*07:02 (TSC-204-C0702), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 33, a CDR2 including the amino acid sequence of SEQ ID NO: 34, and a CDR3 including the amino acid sequence of SEQ ID NO: 35, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 39, a CDR2 including the amino acid sequence of SEQ ID NO: 40, and a CDR3 including the amino acid sequence of SEQ ID NO: 41,

[0009] 4) T cells engineered to express a TCR that binds PRAME425-433 peptide (SLLQHLIGL) when presented by HLA-A*02:01, if the cancer cells express PRAME and present PRAME425-433 peptide (SLLQHLIGL) by HLA-A*02:01 (TSC-203-A0201), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 46, a CDR2 including the amino acid sequence of SEQ ID NO: 47, and a CDR3 including the amino acid sequence of SEQ ID NO: 48, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 52, a CDR2 including the amino acid sequence of SEQ ID NO: 53, and a CDR3 including the amino acid sequence of SEQ ID NO: 54,

[0010] 5) T cells engineered to express a TCR that binds MAGE-A1278-286 peptide (KVLEYVIKV) when presented by HLA-A*02:01, if the cancer cells express MAGE-A1 and present MAGE-A1278-286 peptide (KVLEYVIKV) by HLA-A*02:01 (TSC-204-A0201), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 59, a CDR2 including the amino acid sequence of SEQ ID NO: 60, and a CDR3 including the amino acid sequence of SEQ ID NO: 61, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 65, a CDR2 including the amino acid sequence of SEQ ID NO: 66, and a CDR3 including the amino acid sequence of SEQ ID NO: 67, and/or

[0011] 6) T cells engineered to express a TCR that binds MAGEA1161-169 peptide (EADPTGHSY) when presented by HLA-A*01:01, if the cancer cells express MAGE-A1 and present MAGEA1161-169 peptide (EADPTGHSY) by HLA-A*01:01 (TSC-204-A0101), where the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 72, a CDR2 including the amino acid sequence of SEQ ID NO: 73, and a CDR3 including the amino acid sequence of SEQ ID NO: 74, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 78, a CDR2 including the amino acid sequence of SEQ ID NO: 79, and a CDR3 including the amino acid sequence of SEQ ID NO: 80, and

[0012] where (i) single-plexing with one engineered cell type is selected from the group consisting of one dose of about 0.5x10^9 engineered T cells and one dose of about 2x10^9 engineered T cells, (ii) single-plexing with one engineered cell type is selected from the group consisting of two doses of about 4x10^9 engineered T cells per dose and two doses of about 10x10^9 engineered T cells per dose, or (iii) multi-plexing with two engineered cell types is selected from the group consisting of two doses of about 2x10^9 engineered T cells of each of two engineered T cell types per dose and two doses of about 5x10^9 engineered T cells of each of two engineered T cell types per dose.

[0013] In some embodiments:

[0014] 1)the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

[0015] 2) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

[0016] 3) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

[0017] 4) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

[0018] 5) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

[0019] 6) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

[0020] In some embodiments:

[0021] 1) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 16;

[0022] 2) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 29;

[0023] 3) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 42;

[0024] 4) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 55;

[0025] 5) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 68; and/or

[0026] 6) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 81.

[0027] In some embodiments:

[0028] 1) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 18;

[0029] 2) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 31;

[0030] 3) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 44;

[0031] 4) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 57;

[0032] 5) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or

[0033] 6) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

[0034] In some embodiments:

[0035] 1) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 18;

[0036] 2) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 31;

[0037] 3) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 44;

[0038] 4) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 57;

[0039] 5) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 70; and/or

[0040] 6) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 83.

[0041] In some embodiments, at least 40% of cells of the one dose or two doses of T cells include engineered T cells expressing a marker, optionally where the marker is Qtag-CD34.

[0042] In some embodiments, a method includes infusing one dose of one engineered T cell type (single-plex). In some embodiments, the one dose of one engineered T cell type (single-plex) includes about 0.5x10^9 engineered T cells. In some embodiments, the one dose of one engineered T cell type (single-plex) includes about 2x10^9 engineered T cells.

[0043] In some embodiments, a method includes infusing two doses of one engineered T cell type (single-plex). In some embodiments, each of the two doses of one

engineered T cell type includes about 4x10^9 engineered T cells per dose. In some embodiments, each of the two doses of one engineered T cell type includes about 10x10^9 engineered T cells.

[0044] In some embodiments, a method includes infusing two doses of each of two engineered T cell types (multi-plex). In some embodiments, each of the two doses of each of the two engineered T cell types includes about 2x10^9 engineered T cells per dose. In some embodiments, each of the two doses of each of the two engineered T cell types includes about 5x10^9 engineered T cells per dose.

[0045] In some embodiments, a subject having received the first dose of the one engineered T cell type further receives the second dose of the one engineered T cell type if a serious adverse event does not occur as a result of the first dose. In some embodiments, a subject having received the first dose of each of the two engineered T cell types further receives the second dose of each of the two engineered T cell types if a serious adverse event does not occur as a result of the first dose. In some embodiments, the first dose of the first T cell type and the first dose of the second T cell type are administered to the subject on the same day, optionally where the administration of the T cell types is sequential. In some embodiments, the second dose of the first T cell type and the second dose of the second T cell type are administered to the subject on the same day, optionally where the administration of the T cell types is sequential.

[0046] In some embodiments, T cells used to produce the cells of the engineered T cell type are derived from the subject by leukapheresis. In some embodiments, the subject is screened by germline DNA sequencing for the presence of an HLA that presents the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type. In some embodiments, the subject is screened by tumor cell DNA sequencing and/or immunohistochemistry for the presence of an HLA that presents the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type. In some embodiments, the subject is screened by tumor cell DNA sequencing and/or immunohistochemistry for the presence of the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type. In some embodiments, the subject undergoes lymphodepletion prior to administration of the first dose of the one engineered T cell type or of either of the two engineered T cell types. In some embodiments, the subject receives fludarabine and/or cyclophosphamide. In some embodiments, the subject undergoes lymphodepletion in which the subject receives cyclophosphamide (60 mg/kg on days -7 and -6) and fludarabine (30 mg/m^2 on days -7 to -3), where days are measured from

day 0 as the day of administration of T cell therapy. In some embodiments, the first dose of the one engineered T cell type or of both of the two engineered T cell types is administered about 25 days after leukapheresis. In some embodiments, the second dose of the one engineered T cell type or of each of the two engineered T cell types is administered to the subject about 28 days after the first dose.

[0047] In some embodiments, treatment eliminates tumor cells and/or inhibits tumor growth and/or disease progression. In some embodiments, the treatment causes a complete response and/or a decrease in the likelihood of relapse.

[0048] In some embodiments, cells of the one engineered T cell type and/or of each of the two engineered T cell types express CD8α, CD8β, DN-TGFβRII, and/or a selectable protein marker, optionally where the selectable protein marker is DHFR and further optionally where the CD8α, CD8β, and/or the selectable protein marker is fused to a CD34 enrichment tag. In some embodiments, cells are enriched using the CD34 enrichment tag. In some embodiments, the cells of the one engineered T cell type and/or of each of the two engineered T cell types include a vector encoding the TCR, optionally where the vector is a cloning vector, expression vector, or viral vector. In some embodiments, the vector further includes a nucleic acid sequence encoding CD8α, CD8β, DN-TGFβRII, and/or a selectable protein marker, optionally where the selectable protein marker is dihydrofolate reductase (DHFR). In some embodiments, the nucleic acid sequence encoding CD8α, CD8β, DN-TGFβRII, and/or the selectable protein marker is operably linked to a nucleic acid encoding a tag. In some embodiments, the nucleic acid encoding a tag is at the 5' upstream of the nucleic acid sequence encoding CD8 α, CD8β, and/or the selectable protein marker such that the tag is fused to the N-terminus of CD8α, CD8β, and/or the selectable protein marker. In some embodiments, the tag is a CD34 enrichment tag. In some embodiments, the nucleic acid encoding the binding protein, the nucleic acid sequence encoding TCRα, TCRβ, CD8α, CD8β, and/or the selectable protein marker are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide. In some embodiments, the self-cleaving peptide is P2A, E2A, F2A or T2A.

[0049] In some embodiments, a subject of a method of treating a malignancy as set forth herein meets the following criteria ("inclusion criteria"):

[0050] 1) diagnosed as having a solid tumor,

[0051] 2) tumor cells express an HLA that presents the peptide bound by each of the one or two engineered T cell types;

[0052] 3) does not display LOH of an HLA that presents the peptide bound by one or both of the one or two engineered T cell types;

[0053] 4) tumor cells express the peptide bound by each of the one or two engineered T cell types;

[0054] 5) at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;

[0055] 6) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1;

[0056] 7) at least 18 years of age;

[0057] 8) locally advanced (unresectable) or metastatic solid tumor for which there are no available curative treatment options, after failure of the standard of care systemic therapies for that particular indication;

[0058] 9) express one of the following HLA types: HLA-B*07:02, HLA-A*01:01 HLA-C*07:02, or HLA-A*02:01, optionally where expression is assessed by a genomics assay (*e.g.,* as in screening study TSCAN-003);

[0059] 10) tumor cells express one or more of the following: MAGE-A1, MAGE-C2, PRAME and HPV16-E7, optionally as assessed in the last 8 months in screening study TSCAN-003 (NCT05812027);

[0060] 11) able to understand and be willing to give informed consent; decision-impaired adults may consent with their legally authorized representative; and/or

[0061] 12) adequate bone marrow and organ function.

[0062] In some embodiments, the solid tumor is the solid tumor is melanoma (*e.g.,* cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer, head and neck cancer (*e.g.,* non-nasopharyngeal), sarcoma, thyroid cancer, ovarian cancer, cervical cancer, anal cancer, genital cancer, or anogenital cancer. In some embodiments, the solid tumor has not been adequately treated and/or cured by a standard of care therapy. In some embodiments, the standard of care therapy is a targeted therapy or a checkpoint inhibitor therapy, optionally where the targeted therapy or checkpoint inhibitor therapy is relevant for the particular disease afflicting the subject.

[0063] In some embodiments, a subject of a method of treating a malignancy as set forth herein meets the following criteria ("exclusion criteria"):

[0064] 1) does not demonstrate CNS metastases that are symptomatic or in need of treatment;

[0065] 2) does not demonstrate carcinomatous meningitis;

[0066] 3) has not demonstrated major cardiac pathology or stroke/transient ischemic attack (TIA);

[0067] 4) has not received systemic corticosteroids;

[0068] 5) is not concurrently receiving a cancer therapy for which they have not yet met washout requirements;

[0069] 6) has not demonstrated hypersensitivity to fludarabine or cyclophosphamide;

[0070] 7) does not encode and/or express an HLA type that inhibits binding of one or both of the one or two engineered T cell types with peptide;

[0071] 8) medical or psychological conditions that would make the participant unsuitable candidate for cell therapy, optionally where the suitability is at the discretion of a physician;

[0072] 9) history of myocardial infarction, cardiac angioplasty or stenting, unstable angina, cardiac arrhythmia requiring antiarrhythmic or procedure, or other clinically significant cardiac disease within 12 months of enrollment;

[0073] 10) history of stroke or transient ischemic attack (TIA) within 12 months of enrollment;

[0074] 11) systemic corticosteroid therapy >10 mg of prednisone daily or equivalent within 7 days of enrollment;

[0075] 12) history of severe hypersensitivity to fludarabine or cyclophosphamide or study product excipients including human serum albumin (HSA), Cryostor® (DMSO or Dextran 40), or Plasma-Lyte;

[0076] 13) untreated or symptomatic central nervous system (CNS) metastases or cytology proven carcinomatous meningitis;

[0077] 14) concurrent receipt of another anti-cancer therapy;

[0078] 15) presence of fungal, bacterial, viral, or other infection requiring anti-microbials for management;

[0079] 16) tumors that have HLA LOH using a central lab clinical trial assay of HLAs addressed by the monotherapy (singleplex) and/or T-Plex (multiplex) combination TCR-Ts in the protocol and have no available TCR-T options for intact HLAs in the participant's tumor; and/or

[0080] 17) regularly require supplemental oxygen.

[0081] In at least one aspect, the present disclosure encompasses a method of assessing the efficacy of a therapy for a malignancy selected from melanoma (*e.g.*, cutaneous

melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer, the method including: a) determining the presence or level of reactivity between T cells obtained from the subject and at least one immunogenic peptide or at least one stable MHC-peptide complex in which an HLA protein presents the immunogenic peptide, in a first sample obtained from the subject prior to providing at least a portion of the therapy, and b) determining the presence or level of reactivity between the at least one immunogenic peptide, or the at least one stable MHC-peptide complex, and T cells obtained from the subject present in a second sample obtained from the subject following provision of the therapy, where cells of the malignancy express the immunogenic peptide and the HLA protein, where the presence or a higher level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the malignancy, and/or where the absence or a reduced level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is not efficacious for treating the malignancy, where:

[0082] 1) the immunogenic peptide is MAGE-C2 peptide (RAREFMELL), the HLA protein is HLA-B*07:02, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 7, a CDR2 including the amino acid sequence of SEQ ID NO: 8, and a CDR3 including the amino acid sequence of SEQ ID NO: 9, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 13, a CDR2 including the amino acid sequence of SEQ ID NO: 14, and a CDR3 including the amino acid sequence of SEQ ID NO: 15,

[0083] 2) the immunogenic peptide is HPV16 E711-19 peptide (YMLDLQPET), the HLA protein is HLA-A*02:01, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 20, a CDR2 including the amino acid sequence of SEQ ID NO: 21, and a CDR3 including the amino acid sequence of SEQ ID NO: 22, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 26, a CDR2 including the amino acid sequence of SEQ ID NO: 27, and a CDR3 including the amino acid sequence of SEQ ID NO: 28,

[0084] 3) the immunogenic peptide is MAGE-A1 peptide (VRFFFPSL), the HLA protein is HLA-C*07:02, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 33, a CDR2 including the amino acid sequence of SEQ ID NO: 34, and a CDR3 including the amino acid sequence of SEQ ID NO: 35, and a TCR beta chain variable domain including a CDR1 including the

amino acid sequence of SEQ ID NO: 39, a CDR2 including the amino acid sequence of SEQ ID NO: 40, and a CDR3 including the amino acid sequence of SEQ ID NO: 41,

[0085] 4) the immunogenic peptide is PRAME425-433 peptide (SLLQHLIGL), the HLA protein is HLA-A*02:01, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 46, a CDR2 including the amino acid sequence of SEQ ID NO: 47, and a CDR3 including the amino acid sequence of SEQ ID NO: 48, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 52, a CDR2 including the amino acid sequence of SEQ ID NO: 53, and a CDR3 including the amino acid sequence of SEQ ID NO: 54,

[0086] 5) the immunogenic peptide is MAGE-A1278-286 peptide (KVLEYVIKV), the HLA protein is HLA-A*02:01, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 59, a CDR2 including the amino acid sequence of SEQ ID NO: 60, and a CDR3 including the amino acid sequence of SEQ ID NO: 61, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 65, a CDR2 including the amino acid sequence of SEQ ID NO: 66, and a CDR3 including the amino acid sequence of SEQ ID NO: 67, and

[0087] 6) the immunogenic peptide is MAGEA1161-169 peptide (EADPTGHSY), the HLA protein is HLA-A*01:01, and the TCR includes: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 72, a CDR2 including the amino acid sequence of SEQ ID NO: 73, and a CDR3 including the amino acid sequence of SEQ ID NO: 74, and/or a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 78, a CDR2 including the amino acid sequence of SEQ ID NO: 79, and a CDR3 including the amino acid sequence of SEQ ID NO: 80.

[0088] In some embodiments,

[0089] 1) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

[0090] 2) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

[0091] 3) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain

variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

[0092] 4) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

[0093] 5) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

[0094] 6) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

[0095] In some embodiments:

[0096] 1) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 16;

[0097] 2) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 29;

[0098] 3) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 42;

[0099] 4) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 55;

[0100] 5) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 68; and/or 6) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 81.

[0101] In some embodiments:

[0102] 1) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 18;

[0103] 2) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 31;

[0104] 3) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 44;

[0105] 4) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 57;

[0106] 5) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or

[0107] 6) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

[0108] In some embodiments,

[0109] 1) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 18;

[0110] 2) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 31;

[0111] 3) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 44;

[0112] 4) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 57;

[0113] 5) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 70; and/or

[0114] 6) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 83.

[0115] In some embodiments, level of reactivity is indicated by a) the presence of binding and/or b) T cell activation and/or effector function, optionally where the T cell activation or effector function is T cell proliferation, killing, or cytokine release. In some

embodiments, the binding, activation, and/or effector function is detected using fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay. In some embodiments, the level of reactivity is indicated by an inhibition of tumor cell growth. In some embodiments, a reduction in tumor cell growth between the first sample and the second sample is an indication that the therapy is efficacious for treating the malignancy. In some embodiments, the level of reactivity is indicated by a decrease in tumor cell number or tumor cell survival. In some embodiments, a reduction in tumor cell number or tumor cell survival between the first sample and the second sample is an indication that the therapy is efficacious for treating the malignancy.

[0116] In at least one aspect, the present disclosure encompasses a method of assessing the efficacy of a therapy for a malignancy selected from melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer, the method including: a) determining the presence or level of cells and/or cancer cells expressing an immunogenic peptide or at least one stable MHC-peptide complex in which an HLA protein presents the immunogenic peptide, in a first sample obtained from the subject prior to providing at least a portion of the therapy, and b) determining the presence or level of cells and/or cancer cells expressing an immunogenic peptide, or the at least one stable MHC-peptide complex, in a second sample obtained from the subject following provision of the therapy, where cells of the malignancy express the immunogenic peptide and the HLA protein, where the presence or a lower level in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the malignancy, and/or where the a higher level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is not efficacious for treating the malignancy, optionally where:

[0117] 1) the immunogenic peptide is MAGE-C2 peptide (RAREFMELL), the HLA protein is HLA-B*07:02, and the therapy includes infusing one dose or two doses of one engineered T cell type or two engineered T cell types according to the present disclosure each including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 7, a CDR2 including the amino acid sequence of SEQ ID NO: 8, and a CDR3 including the amino acid sequence of SEQ ID NO: 9, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID

NO: 13, a CDR2 including the amino acid sequence of SEQ ID NO: 14, and a CDR3 including the amino acid sequence of SEQ ID NO: 15,

[0118] 2) the immunogenic peptide is HPV16 E711-19 peptide (YMLDLQPET), the HLA protein is HLA-A*02:01, and the therapy includes infusing one dose or two doses of an engineered T cell type according to the present disclosure including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 20, a CDR2 including the amino acid sequence of SEQ ID NO: 21, and a CDR3 including the amino acid sequence of SEQ ID NO: 22, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 26, a CDR2 including the amino acid sequence of SEQ ID NO: 27, and a CDR3 including the amino acid sequence of SEQ ID NO: 28,

[0119] 3) the immunogenic peptide is MAGE-A1 peptide (VRFFFPSL), the HLA protein is HLA-C*07:02, and the therapy includes infusing one dose or two doses of an engineered T cell type according to the present disclosure including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 33, a CDR2 including the amino acid sequence of SEQ ID NO: 34, and a CDR3 including the amino acid sequence of SEQ ID NO: 35, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 39, a CDR2 including the amino acid sequence of SEQ ID NO: 40, and a CDR3 including the amino acid sequence of SEQ ID NO: 41,

[0120] 4) the immunogenic peptide is PRAME425-433 peptide (SLLQHLIGL), the HLA protein is HLA-A*02:01, and the therapy includes infusing one dose or two doses of an engineered T cell type according to the present disclosure including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 46, a CDR2 including the amino acid sequence of SEQ ID NO: 47, and a CDR3 including the amino acid sequence of SEQ ID NO: 48, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 52, a CDR2 including the amino acid sequence of SEQ ID NO: 53, and a CDR3 including the amino acid sequence of SEQ ID NO: 54,

[0121] 5) the immunogenic peptide is MAGE-A1278-286 peptide (KVLEYVIKV), the HLA protein is HLA-A*02:01, the therapy includes infusing one dose or two doses of an engineered T cell type according to the present disclosure including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 59, a CDR2 including the amino acid sequence of SEQ ID NO: 60, and a CDR3

including the amino acid sequence of SEQ ID NO: 61, and a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 65, a CDR2 including the amino acid sequence of SEQ ID NO: 66, and a CDR3 including the amino acid sequence of SEQ ID NO: 67, and

[0122] 6) the immunogenic peptide is MAGEA1161-169 peptide (EADPTGHSY), the HLA protein is HLA-A*01:01, and the therapy includes infusing one dose or two doses of an engineered T cell type according to the present disclosure including a TCR including: a TCR alpha chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 72, a CDR2 including the amino acid sequence of SEQ ID NO: 73, and a CDR3 including the amino acid sequence of SEQ ID NO: 74, and/or a TCR beta chain variable domain including a CDR1 including the amino acid sequence of SEQ ID NO: 78, a CDR2 including the amino acid sequence of SEQ ID NO: 79, and a CDR3 including the amino acid sequence of SEQ ID NO: 80.

[0123] In some embodiments:

[0124] 1) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

[0125] 2) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

[0126] 3) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

[0127] 4) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

[0128] 5) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

[0129] 6) the TCR alpha chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

[0130] In some embodiments:

[0131] 1) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 16;

[0132] 2) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 29;

[0133] 3) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 42;

[0134] 4) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 55;

[0135] 5) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 68; and/or

[0136] 6) the TCR alpha chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence includes the amino acid sequence of SEQ ID NO: 81.

[0137] In some embodiments:

[0138] 1) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 18;

[0139] 2) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 31;

[0140] 3) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 44;

[0141] 4) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 57;

[0142] 5) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or

[0143] 6) the TCR includes a TCR alpha chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain including an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

[0144] In some embodiments:

[0145] 1) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 18;

[0146] 2) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 31;

[0147] 3) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 44;

[0148] 4) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 57;

[0149] 5) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 70; and/or

[0150] 6) the TCR alpha chain includes the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain includes the amino acid sequence of SEQ ID NO: 83.

[0151] In various embodiments of methods encompassed herein, T cells include CD8+ T cells and CD4+ T cells.

DEFINITIONS

[0152] For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

[0153] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0154] As used herein, term "about", when used in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by

"about" in that context. For example, in some embodiments, the term "about" may encompass a range of values that within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referenced value. To provide another particular example, in the context of numbers of days, "about" refers to a range of a number of days that spans from three days less than a reference value to three days more than a reference value (*e.g.*, "about 25 days" refers to a range of 22-28 days).

[0155] As used herein, the term "administering", when applied to administration of T cells (*e.g.*, engineered T cell products) refers to the physical introduction of a composition comprising the T cells to a subject by infusion.

[0156] As used here, the term "adult" refers to a person of at least 18 years of age.

[0157] As used herein, the term "antigen" refers to any natural or synthetic immunogenic substance, such as a protein, peptide, or hapten. An antigen may be or include (i) a MAGEC2 antigen or fragment thereof; (ii) an HPV16 antigen or fragment thereof; (iii) a MAGEA1 antigen or fragment thereof; or (iv) a PRAME antigen or fragment thereof, against which protective or therapeutic immune responses are desired. Examples of antigens can include SEQ ID NO: 1-6, independently or when presented by an HLA (*e.g.* an indicated HLA, such as a protein of an indicated HLA allele)

[0158] The terms "complementarity determining region" and "CDR" are synonymous with "hypervariable region" or "HVR" and are known in the art to refer to non-contiguous sequences of amino acids within certain binding proteins, such as TCR variable regions, which confer antigen specificity and/or binding affinity. For TCRs, in general, there are three CDRs in each α-chain variable region (αCDR1, αCDR2, and αCDR3) and three CDRs in each β-chain variable region (βCDR1, βCDR2, and βCDR3). CDR3 is believed to be the main CDR responsible for recognizing processed antigen. CDR1 and CDR2 mainly interact with the MHC.

[0159] The term "coding region" refers to regions of a nucleotide sequence comprising codons that are translated into amino acid residues, whereas the term "non-coding region" refers to regions of a nucleotide sequence that are not translated into amino acids (*e.g.*, 5' and 3' untranslated regions).

[0160] As used herein, the term "costimulate" with reference to activated immune cells includes the ability of a costimulatory molecule to provide a second, non-activating receptor mediated signal (a "costimulatory signal") that induces proliferation or effector function. For example, a costimulatory signal may result in cytokine secretion, *e.g.*, in a T

cell that has received a T cell-receptor-mediated signal. Immune cells that have received a cell-receptor mediated signal, *e.g.,* via an activating receptor are referred to herein as "activated immune cells."

[0161] A "component of a TCR complex," as used herein, refers to a TCR chain (i.e ., TCRα, TCRβ, TCRγ or TCRδ), a CD3 chain (*i.e.,* CD3γ, CD3δ, CD3ε or CD3ζ), or a complex formed by two or more TCR chains or CD3 chains (*e.g.,* a complex of TCRα and TCRβ, a complex of TCRγ and TCRδ, a complex of CD3ε and CD3δ, a complex of CD3γ and CD3ε, or a sub-TCR complex of TCRα, TCRβ, CD3γ, CD3δ, and two CD3ε chains).

[0162] The term "determining a suitable treatment regimen for the subject" is taken to mean the determination of a treatment regimen (*i.e.,* a single therapy or a combination of different therapies that are used for the prevention and/or treatment of the viral infection in the subject) for a subject that is started, modified and/or ended based or essentially based or at least partially based on the results of the analysis according to the present invention. One example is starting an adjuvant therapy after surgery whose purpose is to decrease the risk of recurrence, another would be to modify the dosage of a particular chemotherapy. The determination can, in addition to the results of the analysis according to the present invention, be based on personal characteristics of the subject to be treated. In most cases, the actual determination of the suitable treatment regimen for the subject will be performed by the attending physician or doctor.

[0163] As used herein, the terms "HPV16 antigen" or "HPV16 $E7_{11-19}$ antigen" or " HPV16 $E7_{11-19}$ peptide antigen" or " HPV16 $E7_{11-19}$-containing peptide antigen" or "HPV16 $E7_{11-19}$ epitope" or "HPV16 $E7_{11-19}$ peptide epitope" or "HPV16 $E7_{11-19}$ peptide" refer to a naturally or synthetically produced peptide portion of an HPV16 E7 oncoprotein comprising, consisting of, or consisting essentially of the sequence YMLDLQPET (SEQ ID NO: 2).

[0164] The term "immune response" includes T cell mediated and/or B cell mediated immune responses. Exemplary immune responses include T cell responses, *e.g.,* cytokine production and cellular cytotoxicity. In addition, the term immune response includes immune responses that are indirectly effected by T cell activation, *e.g.,* antibody production (humoral responses) and activation of cytokine responsive cells, *e.g.,* macrophages.

[0165] As used herein, the term "linked" refers to the association of two or more molecules. The linkage may be covalent or non-covalent. The linkage also may be genetic (*i.e.,* recombinantly fused). Such linkages may be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

[0166] A "linker," in some embodiments, may refer to an amino acid sequence that connects two proteins, polypeptides, peptides, domains, regions, or motifs and may provide a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity *(e.g.,* scTCR) to a target molecule or retains signaling activity *(e.g.,* TCR complex). In some embodiments, a linker is comprised of about two to about 35 amino acids, for instance, or about four to about 20 amino acids or about eight to about 15 amino acids or about 15 to about 25 amino acids.

[0167] The term "MAGEA1" refers to a particular member of the melanoma antigen gene family clustered on human chromosome Xq28 (*e.g.*, chromosome X: 153,179,284-153,183,880 forward strand. GRCh38:CM000685.2) that is also known as cancer/testis antigen 1.1 (CT1.1); melanoma-associated antigen 1; MAGE1; melanoma antigen family A, 1 (directs expression of antigen MZ2-E); cancer/testis antigen family 1, member 1; melanoma-associated antigen MZ2-E; melanoma antigen family A1; cancer/testis antigen 1.1; melanoma antigen MAGE-1; MAGE-1 antigen; antigen Z2-E, MGC9326; and MAGE1A (Mao *et al.* (2019) *J. Hematol. Oncol.* 12:106; Fanipakdel *et al.* (2019) *J. Cell Physiol.* 234:12080-12086; Gu *et al.* (2018) *Thorac. Cancer* 9:431-438; Mecklenburg *et al.* (2017) *Clin. Cancer Res.* 23:1213-1219; Wang *et al.* (2016) *Biochem. Biophys. Res. Commun.* 473:959-965; Kozakova *et al.* (2015) *Cell Cycle* 14:920-930; Cannuyer *et al.* (2013) *PLoS One* 8:e5874; Pereira *et al.* (2012) *Oncol. Rep.* 27:1843-1848; Ogata *et al.* (2011) *Ann. Surg. Oncol.* 18:1195-1203; Roch *et al.* (2010) *Anticancer Res.* 30:1617-1623; Dango *et al.* (2010) *Lung Cancer* 67:290-295; van der Bruggen *et al.* (1991) *Science* 254:1643-1647). MAGEA1 is a melanoma antigen recognized by cytolytic T lymphocytes and is believed to be be involved in transcriptional regulation through interaction with SNW1 and recruiting histone deactelyase HDAC1, as well as in inhibiting notch intracellular domain (NICD) transactivation, embryonal development, association with some herediatyr disorders (*e.g.*, dyskeratosis congenital), and/or tumor transformation or aspects of tumor progression (*e.g.*, gastric carcinomas, hepatocellular carcinomas, etc.). MAGEA1 is not highly expressed in normal tissues, except for testis, and is expressed in tumors of various histological types, such as melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), head & neck cancer, lung cancer, sarcoma, thyroid cancer, cervical cancer, hepatocellular carcinoma, colorectal cancer, gastrointestinal cancer, colorectal cancer, gastrointestinal cancer, breast invasive carcinoma, and bladder urothelial carcinoma.

[0168] The term "MAGEA1" is intended to include fragments, variants (*e.g.,* allelic variants), and derivatives thereof. Representative human MAGEA1 cDNA and human

MAGEA1 protein sequences are well-known in the art and are publicly available from the National Center for Biotechnology Information (NCBI) (see, for example, ncbi.nlm.nih.gov/gene/4100). For example, human MAGEA1 (NP_004979.3) is encodable by the transcript (NM_004988.5). Nucleic acid and polypeptide sequences of MAGEA1 orthologs in organisms other than humans are well-known and include, for example, chimpanzee MAGEA1 (XM_529226.2 and XP_529226.2) and mouse MAGEA1 (Chromosome X:155088686-155089793; Ensembl mus musculus version 104.39 (GRCm39)).

[0169] Anti-MAGEA1 antibodies suitable for detecting MAGEA1 protein are well-known in the art and include, for example, antibodies AM32863PU, AM50138PU, AP06212PU, AP13128PU- TA312178, TA39275, TA339275, TA339276, and TA347677 (OriGene, Rockville, MD); antibodies orb167376 and orb11016 (Biorbyt, Cambridge, United Kingdom); antibodies A03570 and AO3570-1 (Boster Bio, Pleasanton, CA); antibodies E22-11B2-E9 and N1C3 (GeneTex, Irvince, CA); antibodies AFLGC-MAGEA1, MA5-37821, and MA1-91067 (Invitrogen, Waltham, MA); antibodies ABIN2782493 and ABIN2782494 (Antibodies-online, Limerick, PA); and antibodies MA454 and 6C1 (Santa Cruz Biotechnology, Dallas, TX). In addition, reagents are well-known for detecting MAGEA1 expression. Moreover, multiple siRNA, shRNA, CRISPR constructs for modulating MAGEA1 expression can be found in the commercial product lists of a variety of companies, such as open reading frame (ORF) clones MG212171, MR212171, MR212171L3, MR212171L3V, MR212171L4, MR212171L4V, RC202134, RC202134L3, RC202134L3V, RC202134L4, RC202134L4V, and RG202134 (OriGene, Rockville, MD), CRISPR knockouts GA102785, GA202555, KN202134, KN202134BN, KN202134LP, KN202134RB, KN402134, and KN509652 (OriGene, Rockville, MD), and RNA interference (RNAi) clones, such as siRNA and shRNA clones, including SR302776, TL311617, SR410578, TL311617V, TTL516288, TL516288V, TL704467, TL04467V, TR311617, TR516288, and TR704467 (OriGene, Rockville, MD). It is to be noted that the term can further be used to refer to any combination of features described herein regarding MAGEA1 molecules. For example, any combination of sequence composition, percentage identify, sequence length, domain structure, functional activity, *etc.* can be used to describe a MAGEA1 molecule encompassed by the present invention.

The term "MAGEA1 antigen" or "MAGEA1 peptide antigen" or "MAGEA1-containing peptide antigen" or "MAGEA1 epitope" or "MAGEA1 peptide epitope" or "MAGEA1 peptide" refers to a naturally or synthetically produced immunogenic portion of MAGEA1.

In some embodiments, MAGEA1 antigen protein can range in length from about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 amino acids, or any range in between, inclusive, such as 8-15 amino acids. In some embodiments, MAGEA1 antigen protein can form a complex with an MHC (*e.g.*, HLA) molecule such that a binding protein of this disclosure that recognizes a MAGEA1 peptide:MHC (*e.g.*, HLA) complex can bind (*e.g.*, specifically and/or selectively) to such a complex. Representative MAGEA1 peptide antigen sequence can be VRFFFPSL (SEQ ID NO: 3), KVLEYVIKV (SEQ ID NO: 5), or EADPTGHSY (SEQ ID NO: 6).

[0170] The term "MAGEC2" refers to a particular member of the melanoma antigen gene family clustered on human chromosome Xq26-q27 that is also known as cancer/testis antigen 10 (CT10), hepatocellular cancer antigen 587 (HCA587), and melanoma antigen, family E, 1, cancer/testis specific (MAGEE1) (Gure *et al.* (2000) *Int. J. Cancer* 85:726-732; Li *et al.* (2003) *Lab Invest.* 83:1185-1192; Ma *et al.* (2004) *Int. J. Cancer* 109:698-702; Godelaine *et al.* (2007) *Cancer Immunol. Immunother.* 56:753-759; Reiner *et al.* (2009) *Int. J. Cancer* 124:352-357; Doyle *et al.* (2010) *Mol. Cell* 39:93-974; von Boehmer *et al.* (2011) *PLoS One* 6, e21366; Wen *et al.* (2011) *Cancer Sci.* 102:1455-1461; de Carvalho *et al.* (2013) *Cancer Immunol. Immunother.* 62:191-195; Bhatia *et al.* (2013) *J. Invest. Dermatol.* 133:759-767); Yang *et al.* (2014) *Breast Cancer Res. Treat.* 145:23-32; and Kunert *et al.* (2016) *J. Immunol.* 197:2541-2552). MAGEC2 is believed to enhance ubiquitin ligase activity of RING-type zinc finger-containing E3 ubiquitin-protein ligases, such as by recruiting and/or stabilizing Ubl-conjugating enzymes (E2) at the E3:substrate complex. MAGEC2 enhances *in vitro* ubiquitin ligase activity of TRIM28 and stimulates p53/TP53 ubiquitination in presence of Ubl-conjugating enzyme UBE2H leading to p53/TP53 degradation. MAGEC2 is not expressed in normal tissues, except for testis, and is expressed in tumors of various histological types such as melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), head & neck cancer, lung cancer, sarcoma, thyroid cancer, cervical cancer, prostate cancer, multiple myeloma, hepatocellular carcinoma, breast invasive carcinoma, and bladder urothelial carcinoma.

[0171] The term "MAGEC2" is intended to include fragments, variants (*e.g.*, allelic variants), and derivatives thereof. Representative human MAGEC2 cDNA and human MAGEC2 protein sequences are well-known in the art and are publicly available from the National Center for Biotechnology Information (NCBI) (see, for example, ncbi.nlm.nih.gov/gene/51438). For example, human MAGEC2 (NP_057333.1) is encodable by the transcript (NM_016249.4). Nucleic acid and polypeptide sequences of MAGEC2

orthologs in organisms other than humans are well-known and include, for example, chimpanzee MAGEC2 (NM_001302428.1, NP_001289357.1, XM_016942653.1, and XP_016798142.1) and rhesus monkey MAGEC2 (NM_001265825.1, NP_001252754.1, XM_028841693.1, and XP_028697526.1).

[0172] Anti-MAGEC2 antibodies suitable for detecting MAGEC2 protein are well-known in the art and include, for example, antibodies TA315476 and TA342769 (OriGene, Rockville, MD); antibodies orb353181 and orb 125944 (Biorbyt, Cambridge, United Kingdom); antibodies A05335 and AO5335-1 (Boster Bio, Pleasanton, CA); and antibodies ABIN2788251 and ABIN2706502 (Antibodies-online, Limerick, PA). In addition, reagents are well-known for detecting MAGEC2 expression. Moreover, multiple siRNA, shRNA, CRISPR constructs for modulating MAGEC2 expression can be found in the commercial product lists of a variety of companies, such as open reading frame (ORF) clones SC07208 and RN211555 (OriGene, Rockville, MD) and CRISPR knockouts GA109805 and KN403064 (OriGene, Rockville, MD). It is to be noted that the term can further be used to refer to any combination of features described herein regarding MAGEC2 molecules. For example, any combination of sequence composition, percentage identify, sequence length, domain structure, functional activity, *etc.* can be used to describe a MAGEC2 molecule encompassed by the present invention.

[0173] The term "MAGEC2 antigen" or "MAGEC2 peptide antigen" or "MAGEC2-containing peptide antigen" or "MAGEC2 epitope" or "MAGEC2 peptide epitope" or "MAGEC2 peptide" refers to a naturally or synthetically produced immunogenic portion of MAGEC2. In some embodiments, MAGEC2 antigen protein can range in length from about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 amino acids, or any range in between, inclusive, such as 8-15 amino acids. In some embodiments, MAGEC2 antigen protein can form a complex with an MHC (*e.g.*, HLA) molecule such that a binding protein of this disclosure that recognizes a MAGEC2 peptide:MHC (*e.g.*, HLA) complex can bind (*e.g.*, specifically and/or selectively) to such a complex. A representative MAGEC2 peptide antigen sequence can be RAREFMELL (SEQ ID NO: 1).

[0174] "Major histocompatibility complex" (MHC) refers to glycoproteins that deliver peptide antigens to a cell surface. MHC class I molecules are heterodimers having a membrane spanning a chain (with three a domains) and a non-covalently associated b2 microglobulin. MHC class II molecules are composed of two transmembrane glycoproteins, a and b, both of which span the membrane. Each chain has two domains. MHC class I molecules deliver peptides originating in the cytosol to the cell surface, where a peptide

antigen-MHC (pMHC) complex is recognized by $CD8^+$ T cells. MHC class II molecules deliver peptides originating in the vesicular system to the cell surface, where they are recognized by $CD4^+$ T cells. Human MHC is referred to as human leukocyte antigen (HLA).

[0175] The terms "prevent," "preventing," "prevention," "prophylactic treatment," and the like refer to reducing the probability of developing a disease, disorder, or condition in a subject, who does not have, but is at risk of or susceptible to developing a disease, disorder, or condition.

[0176] The term "PRAME" refers to PRAME nuclear receptor transcriptional regulator, an antigen that is preferentially expressed in human melanomas and that is recognized by cytolytic T lymphocytes. It is not expressed in normal tissues, except testis. The encoded protein acts as a repressor of retinoic acid receptor, and likely confers a growth advantage to cancer cells via this function. Diseases associated with PRAME include, *e.g.*, melanoma, choroid cancer, non-small cell lung carcinomas, renal cell carcinoma (RCC), breast carcinoma, cervix carcinoma, colon carcinoma, sarcoma, neuroblastoma, head & neck cancer, ovarian cancer, as well as several types of leukemia. Human PRAME has multiple transcript variants resulted from alternative splicing, which are publicly known and can be obtained from the NCBI database. Representative human PRAME transcripts include, *e.g.*, transcript variant 1 (NM_006115.5) encoding isoform a (NP_006106.1); transcript variant 2 (NM_206953.3) encoding isoform a (NP_996836.1); transcript variant 3 (NM_206954.3) encoding isoform a (NP_996837.1); transcript variant 4 (NM_206955.3) encoding isoform a (NP_996838.1); transcript variant 5 (NM_206956.3) encoding isoform a (NP_996839.1); transcript variant 6 (NM_001291715.2) encoding isoform a (NP_001278644.1); transcript variant 7 (NM_001291716.2) encoding isoform a (NP_001278645.1); transcript variant 8 (NM_001291717.2) encoding isoform b (NP_001278646.1); transcript variant 9 (NM_001291719.2) encoding isoform b (NP_001278648.1); transcript variant 10 (NM_001318126.2) encoding isoform b (NP_001305055.1); and transcript variant 11 (NM_001318127.2) encoding isoform b (NP_001305056.1).

[0177] As used herein, the term " $PRAME_{425-433}$ antigen" or " $PRAME_{425-433}$ peptide antigen" or " $PRAME_{425-433}$-containing peptide antigen" or "$PRAME_{425-433}$ epitope" or "$PRAME_{425-433}$ peptide epitope" or "$PRAME_{425-433}$ peptide" refers to a naturally or synthetically produced peptide portion of a PRAME oncoprotein comprising, consisting of, or consisting essentially of the sequence SLLQHLIGL (SEQ ID NO: 4)

[0178] The term "prognosis" includes a prediction of the probable course and outcome of a viral infection or the likelihood of recovery from the disease. In some

embodiments, the use of statistical algorithms provides a prognosis of a viral infection in an individual. For example, the prognosis may be surgery, development of a clinical subtype of a viral infection, development of one or more clinical factors, or recovery from the disease.

[0179] As used herein, "percent identity" between amino acid sequences is synonymous with "percent homology," which can be determined using the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified by Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. The noted algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches are performed with the NBLAST program, score=100, wordlength=12, to obtain nucleotide sequences homologous to a polynucleotide described herein. BLAST protein searches are performed with the XBLAST program, score=50, wordlength=3, to obtain amino acid sequences homologous to a reference polypeptide. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul *et al.* (1997) *Nuc. Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) may be used.

[0180] The phrase "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body.

[0181] The term "specific binding" refers to binding protein binding to a predetermined antigen. Typically, the binding protein binds with an affinity (K_D) of approximately less than or equal to about $5x10^{-4}$ M, less than or equal to about $1x10^{-4}$ M, less than or equal to about $5x10^{-5}$ M, less than or equal to about $1x10^{-5}$ M, less than or equal to about $5x10^{-6}$ M, less than or equal to about $1x10^{-6}$ M, less than or equal to about $5x10^{-7}$ M, less than or equal to about $1x10^{-7}$ M, less than or equal to about $5x10^{-8}$ M, less than or equal to about $1x10^{-8}$ M, less than or equal to about $5x10^{-9}$ M, less than or equal to about $1x10^{-9}$ M, less than or equal to about $5x10^{-10}$ M, less than or equal to about $1x10^{-10}$ M, less than or equal to about $5x10^{-11}$ M, less than or equal to about $1x10^{-11}$ M, less than or equal to about $5x10^{-12}$ M, less than or equal to about $1x10^{-12}$ M, or even lower, or any range in between, inclusive, such as between about 1-50 micromolar, 1-100 micromolar, 0.1-500 micromolar, and the like,when determined by a binding assay, such as surface plasmon resonance (SPR) technology in a BIAcore™ assay instrument using an antigen of interest as the analyte and the binding protein as the ligand. In some embodiments, the binding protein binds to the

predetermined antigen with an affinity that is at least 1.1-, 1.2-, 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-, 2.5-, 3.0-, 3.5-, 4.0-, 4.5-, 5.0-, 6.0-, 7.0-, 8.0-, 9.0-, or 10.0-fold or greater than its affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "a binding protein recognizing an antigen" and "a binding protein specific for an antigen" are used interchangeably herein with the term "a binding protein which binds specifically to an antigen." Selective binding is a relative term referring to the ability of a binding protein to discriminate the binding of one antigen over another, such as a particular family member or antigen target over a related family member or antigen target. For example, analytical data provided in the Examples section demonstrate that binding proteins described herein specifically bind MAGEC2 immunogenic epitopes, HPV16 immunogenic epitopes, MAGEA1 immunogenic epitopes, or PRAME immunogenic epitopes and/or selectively bind a number of related epitopes (*e.g.*, immunogenic epitopes and closely related sequences) discriminating such targets from the vast majority of other possible epitopes available in the human genome.

[0182] The term "subject" refers to any healthy animal, mammal or human, or any animal, mammal or human afflicted with a disorder, *e.g.*, a cancer characterized by expression of MAGEC2, HPV16, MAGEA1, or PRAME by cells characteristic of the cancer. The term "subject" is interchangeable with "patient."

[0183] The term "survival" includes all of the following: survival until mortality, also known as overall survival (wherein said mortality may be either irrespective of cause or tumor related); "recurrence-free survival" (wherein the term recurrence shall include both localized and distant recurrence); metastasis free survival; disease free survival (wherein the term disease shall include cancer and diseases associated therewith). The length of said survival may be calculated by reference to a defined start point (*e.g.*, time of diagnosis or start of treatment) and end point (*e.g.*, death, recurrence or metastasis). In addition, criteria for efficacy of treatment may be expanded to include response to chemotherapy, probability of survival, probability of metastasis within a given time period, and probability of tumor recurrence.

[0184] As used herein, the term "T cell-mediated response" refers to a response mediated by T cells, including effector T cells (*e.g.*, $CD8^+$ cells) and helper T cells (*e.g.*, $CD4^+$ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation.

[0185] A "T cell" is an immune system cell that matures in the thymus and produces T cell receptors (TCRs). T cells may be naive (not exposed to antigen; increased expression of CD62L, CCR7, CD28, CD3, CD 127, and CD45RA, and decreased expression of CD45RO as compared to T_{CM}), memory T cells (T_M) (antigen-experienced and long-lived), and effector cells (antigen-experienced, cytotoxic). T_M may be further divided into subsets of central memory T cells (T_{CM}, increased expression of CD62L, CCR7, CD28, CD127, CD45RO, and CD95, and decreased expression of CD54RA as compared to naive T cells) and effector memory T cells (T_{EM}, decreased expression of CD62L, CCR7, CD28, CD45RA, and increased expression of CD127 as compared to naive T cells or T_{CM}). Effector T cells (T_E) refers to antigen-experienced CD8+ cytotoxic T lymphocytes that have decreased expression of CD62L ,CCR7, CD28, and are positive for granzyme and perforin as compared to T_{CM}. Other exemplary T cells include regulatory T cells, such as $CD4^+$ $CD25^+$ ($Foxp3^+$) regulatory T cells and Treg17 cells, as well as Trl, Th3, $CD8^+CD28$, and Qa-1 restricted T cells.

[0186] Conventional T cells, also known as Tconv or Teffs, have effector functions (*e.g.,* cytokine secretion, cytotoxic activity, anti-self-recognition, and the like) to increase immune responses by virtue of their expression of one or more T cell receptors. Tcons or Teffs are generally defined as any T cell population that is not a Treg and include, for example, naïve T cells, activated T cells, memory T cells, resting Tcons, or Tcons that have differentiated toward, for example, the Th1 or Th2 lineages. In some embodiments, Teffs are a subset of non-Treg T cells. In some embodiments, Teffs are CD4+ Teffs or CD8+ Teffs, such as CD4+ helper T lymphocytes (*e.g.,* Th0, Th1, Tfh, or Th17) and CD8+ cytotoxic T lymphocytes. As described further herein, cytotoxic T cells are CD8+ T lymphocytes. "Naïve Tcons" are $CD4^+$ T cells that have differentiated in bone marrow, and successfully underwent a positive and negative processes of central selection in a thymus, but have not yet been activated by exposure to an antigen. Naïve Tcons are commonly characterized by surface expression of L-selectin (CD62L), absence of activation markers such as CD25, CD44 or CD69, and absence of memory markers such as CD45RO. Naïve Tcons are therefore believed to be quiescent and non-dividing, requiring interleukin-7 (IL-7) and interleukin-15 (IL- 15) for homeostatic survival (see, at least WO 2010/101870). The presence and activity of such cells are undesired in the context of suppressing immune responses. Unlike Tregs, Tcons are not anergic and can proliferate in response to antigen-based T cell receptor activation (Lechler *et al.* (2001) *Philos. Trans. R. Soc. Lond. Biol. Sci.* 356:625-637).

[0187] "T effector" ("T_{eff}" or "T_E") cells refers to T cells (*e.g.*, CD4+ and CD8+ T cells) with cytolytic activities as well as T helper (Th) cells, which secrete cytokines and activate and direct other immune cells, but does not include regulatory T cells (Treg cells).

[0188] "T cell receptor" or "TCR" refers to an immunoglobulin superfamily member (having a variable binding domain, a constant domain, a transmembrane region, and a short cytoplasmic tail; *see, e.g.*, Janeway *et al.* (1997) *Curr. Biol. Publ.* 4:33) that is capable of binding (*e.g.*, specifically and/or selectively) to an antigen peptide bound to a MHC receptor. A TCR can be found on the surface of a cell or in soluble form and generally is comprised of a heterodimer having alpha and beta chains (also known as TCRα and TCRβ, respectively), or γ and δ chains (also known as TCRγ and TCRδ, respectively). Like immunoglobulins (*e.g.*, antibodies), the extracellular portion of TCR chains (*e.g.*, α-chain and β-chain) contain two immunoglobulin domains: a variable domain (*e.g.*, α-chain variable domain or V_α and β-chain variable domain or V_β; typically amino acids 1 to 116 based on Kabat numbering (Kabat *et al.* (1991) "Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services, Public Health Service National Institutes of Health, 5th ed.) at the N-terminal end, and one constant domain (*e.g.*, α-chain constant domain or C_α, typically amino acids 117 to 259 based on Kabat, β-chain constant domain or C_β, typically amino acids 117 to 295 based on Kabat) at the C-terminal end and adjacent to the cell membrane. Also like immunoglobulins, the variable domains contain complementary determining regions ("CDRs", also called hypervariable regions or "HVRs") separated by framework regions ("FRs") (*see, e.g.*, Fores *et al.* (1990) *Proc. Natl. Acad Sci. US.A.* 87:9138; Chothia *et al.* (1988) *EMBO J.* 7:3745; Lefranc *et al.* (2003) *Dev. Comp. Immunol.* 27:55). In some embodiments, a TCR is found on the surface of a T cell (or T lymphocyte) and associates with the CD3 complex. The source of a TCR encompassed by the present invention may be from various animal species, such as a human, mouse, rat, rabbit or other mammal.

[0189] The term "T cell receptor" or "TCR" should be understood to encompass full TCRs as well as antigen-binding portions or antigen-binding fragments thereof. In some embodiments, the TCR is an intact or full-length TCR, including TCRs in the αβ form or γδ form. In some embodiments, the TCR is an antigen-binding portion that is less than a full-length TCR but that binds to a specific peptide bound in an MHC molecule, such as binds to an MHC-peptide complex. In some cases, an antigen-binding portion or fragment of a TCR may contain only a portion of the structural domains of a full-length or intact TCR, but yet is able to bind the peptide epitope, such as MHC-peptide complex, to which the full TCR binds.

In some cases, an antigen-binding portion contains the variable domains of a TCR, such as variable α chain and variable β chain of a TCR, sufficient to form a binding site for binding to a specific MHC-peptide complex. Generally, the variable chains of a TCR contain complementarity determining regions (CDRs) involved in recognition of the peptide, MHC and/or MHC-peptide complex.

[0190] Nomenclature established by the International Immunogenetics Information System (IMGT) (see also Scaviner and Lefranc (2000) *Exp. Clin. Immunogenet.* 17:83-96 and 97-106; Folch and Lefranc (2000) *Exp. Clin. Immunogenet,* 17:107-114; T Cell Receptor Factsbook", (2001) LeFranc and LeFranc, Academic Press, ISBN 0-12-441352-8). The IMGT provides unique sequences used to describe a TCR, and sequences described herein may be identified by reference to such unique sequences provided herein. TCR sequences are publicly available at the IMGT database at imgt.org.

[0191] As described above, native alpha/beta heterodimeric TCRs have an alpha chain and a beta chain. Broadly, each chain comprises variable, joining and constant regions, and the beta chain also usually contains a short diversity region between the variable and joining regions, but this diversity region is often considered as part of the joining region. Each variable region comprises three hypervariable CDRs (Complementarity Determining Regions) embedded in a framework sequence. CDR3 is well-known to be the main mediator of antigen recognition. There are several types of alpha chain variable (Vα) regions and several types of beta chain variable (Vβ) regions distinguished by their framework, CDR1 and CDR2 sequences, and by a partly defined CDR3 sequence. The Vα types are referred to in IMGT nomenclature by a unique TRAV number. For example, "TRAV4" defines a TCR Vα region having unique framework and CDR1 and CDR2 sequences, and a CDR3 sequence which is partly defined by an amino acid sequence which is preserved from TCR to TCR but which also includes an amino acid sequence which varies from TCR to TCR. Similarly, "TRBV2" defines a TCR Vβ region having unique framework and CDR1 and CDR2 sequences, but with only a partly defined CDR3 sequence. It is known that there are 54 alpha variable genes, of which 44 are functional, and 67 beta variable genes, of which 42 are functional, within the alpha and beta loci, respectively.

[0192] The joining regions of the TCR are similarly defined by the unique IMGT TRAJ and TRBJ nomenclature, and the constant regions by the IMGT TRAC and TRBC nomenclature. The beta chain diversity region is referred to in IMGT nomenclature

by the abbreviation TRBD, and, as mentioned, the concatenated TRBD/TRBJ regions are often considered together as the joining region.

[0193] The gene pools that encode the TCR alpha and beta chains are located on different chromosomes and contain separate V, (D), J and C gene segments, which are brought together by rearrangement during T cell development. This leads to a very high diversity of T cell alpha and beta chains due to the large number of potential recombination events that occur between the 54 TCR alpha variable genes and 61 alpha J genes or between the 67 beta variable genes, two beta D genes and 13 beta J genes. The recombination process is not precise and introduces further diversity within the CDR3 region. Each alpha and beta variable gene may also comprise allelic variants, designated in IMGT nomenclature as TRAVxx*01 and *02, or TRBVx-x*01 and *02 respectively, thus further increasing the amount of variation. In the same way, some of the TRBJ sequences have two known variations. (Note that the absence of a "*" qualifier means that only one allele is known for the relevant sequence). The natural repertoire of human TCRs resulting from recombination and thymic selection has been estimated to comprise approximately 10^6 unique beta chain sequences, determined from CDR3 diversity (Arstila *et al.* (1999) *Science* 286:958-961) and could be even higher (Robins *et al.* (2009) *Blood* 114:4099-4107). Each beta chain is estimated to pair with at least 25 different alpha chains, thus generating further diversity (Arstila *et al.* (1999) Science 286:958-961).

[0194] The term "TCR alpha variable domain" therefore refers to the concatenation of TRAV and TRAJ regions; a TRAV region only; or TRAV and a partial TRAJ region, and the term TCR alpha constant domain refers to the extracellular TRAC region, or to a C-terminal truncated or full length TRAC sequence. Likewise the term "TCR beta variable domain" refers to the concatenation of TRBV and TRBD/TRBJ regions; to the TRBV and TRBD regions only; to the TRBV and TRBJ regions only; or to the TRBV and partial TRBD and/or TRBJ regions, and the term TCR beta constant domain refers to the extracellular TRBC region, or to a C-terminal truncated or full length TRBC sequence. These TCR alpha variable domain and TCR beta variable domain nomenclature similarly applies to the variable domains of TCR gamma and TCR delta chains, respectively, for gamma/delta TCRs. An ordinarily skilled artisan can obtain TRAV, TRAJ, TRAC, TRBV, TRBJ, and TRBC gene sequences, such as through the publicly available IMGT database.

[0195] The term "TCR complex" refers to a complex formed by the association of CD3 with TCR. For example, a TCR complex may be composed of a CD3γ chain, a CD3δ

chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRα chain, and a TCRβ chain. Alternatively, a TCR complex may be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRγ chain, and a TCRδ chain.

[0196] The term "therapeutic effect" refers to a local or systemic effect in animals, particularly mammals, and more particularly humans, caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal or human.

[0197] The terms "therapeutically effective amount" and "effective amount" means that amount of a substance that produces some desired effect, such as a desired local or systemic therapeutic effect, in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any treatment. In some embodiments, a therapeutically effective amount of a substance will depend on the substance's therapeutic index, solubility, pharmacokinetics, half-life, and the like. Toxicity and therapeutic efficacy of subject compounds may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD_{50} and the ED_{50}. In some embodiments, compositions that exhibit large therapeutic indices are used. In some embodiments, the LD_{50} (lethal dosage) may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more reduced for the agent relative to no administration of the agent. Similarly, the ED_{50} (*i.e.,* the concentration which achieves a half-maximal inhibition of symptoms) may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more increased for the agent relative to no administration of the agent. Also, similarly, the IC_{50} may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more increased for the agent relative to no administration of the agent. In some embodiments, T cell immune response in an assay may be increased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100%. In another embodiment, at least about a 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% decrease in a viral load may be achieved.

[0198] The term "treat" refers to the therapeutic management or improvement of a condition (*e.g.*, a disease or disorder) of interest. Treatment may include, but is not limited to, infusing an agent or composition (*e.g.*, a pharmaceutical composition) to a subject. Treatment is typically undertaken in an effort to alter the course of a disease (which term is used to indicate any disease, disorder, syndrome or undesirable condition warranting or potentially warranting therapy) in a manner beneficial to the subject. The effect of treatment may include reversing, alleviating, reducing severity of, delaying the onset of, curing, inhibiting the progression of, and/or reducing the likelihood of occurrence or recurrence of the disease or one or more symptoms or manifestations of the disease. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. A therapeutic agent may be administered to a subject who has a disease or is at increased risk of developing a disease relative to a member of the general population. In some embodiments, a therapeutic agent may be administered to a subject who has had a disease but no longer shows evidence of the disease. The agent may be administered *e.g.*, to reduce the likelihood of recurrence of evident disease. A therapeutic agent may be administered prophylactically, *i.e.*, before development of any symptom or manifestation of a disease. "Prophylactic treatment" refers to providing medical and/or surgical management to a subject who has not developed a disease or does not show evidence of a disease in order, *e.g.*, to reduce the likelihood that the disease will occur or to reduce the severity of the disease should it occur. The subject may have been identified as being at risk of developing the disease (*e.g.*, at increased risk relative to the general population or as having a risk factor that increases the likelihood of developing the disease.

[0199] The term "variable region" or "variable domain" refers to the domain of an immunoglobulin superfamily binding protein (*e.g.*, a TCR α-chain or β-chain (or γ chain and δ chain for γδ TCRs)) that is involved in binding of the immunoglobulin superfamily binding protein (*e.g.*, TCR) to antigen. The variable domains of the α-chain and β-chain (V_α and V_β, respectively) of a native TCR generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs. The V_α domain is encoded by two separate DNA segments, the variable gene segment and the joining gene segment (V-J); the V_β domain is encoded by three separate DNA segments, the variable gene segment, the

diversity gene segment, and the joining gene segment (V-D-J). A single V_α or V_β domain may be sufficient to confer antigen-binding specificity. Furthermore, TCRs that bind a particular antigen may be isolated using a V_α or V_β domain from a TCR that binds the antigen to screen a library of complementary V_α or V_β domains, respectively.

[0200] The term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In some embodiments, a vector is an episome, *i.e.*, a nucleic acid capable of extra-chromosomal replication. In some embodiments, vectors are those capable of autonomous replication and/or expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA loops, which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, as will be appreciated by those skilled in the art, the present invention is intended to include such other forms of expression vectors that serve equivalent functions and which become subsequently known in the art.

[0201] There is a known and definite correspondence between the amino acid sequence of a particular protein and the nucleotide sequences that can code for the protein, as defined by the genetic code (shown below). Likewise, there is a known and definite correspondence between the nucleotide sequence of a particular nucleic acid and the amino acid sequence encoded by that nucleic acid, as defined by the genetic code.

GENETIC CODE	
Alanine (Ala, A)	GCA, GCC, GCG, GCT
Arginine (Arg, R)	AGA, ACG, CGA, CGC, CGG, CGT
Asparagine (Asn, N)	AAC, AAT
Aspartic acid (Asp, D)	GAC, GAT
Cysteine (Cys, C)	TGC, TGT
Glutamic acid (Glu, E)	GAA, GAG
Glutamine (Gln, Q)	CAA, CAG
Glycine (Gly, G)	GGA, GGC, GGG, GGT
Histidine (His, H)	CAC, CAT

Isoleucine (Ile, I)	ATA, ATC, ATT
Leucine (Leu, L)	CTA, CTC, CTG, CTT, TTA, TTG
Lysine (Lys, K)	AAA, AAG
Methionine (Met, M)	ATG
Phenylalanine (Phe, F)	TTC, TTT
Proline (Pro, P)	CCA, CCC, CCG, CCT
Serine (Ser, S)	AGC, AGT, TCA, TCC, TCG, TCT
Threonine (Thr, T)	ACA, ACC, ACG, ACT
Tryptophan (Trp, W)	TGG
Tyrosine (Tyr, Y)	TAC, TAT
Valine (Val, V)	GTA, GTC, GTG, GTT
Termination signal (end)	TAA, TAG, TGA

[0202] An important and well-known feature of the genetic code is its redundancy, whereby, for most of the amino acids used to make proteins, more than one coding nucleotide triplet may be employed (illustrated above). Therefore, a number of different nucleotide sequences may code for a given amino acid sequence. Such nucleotide sequences are considered functionally equivalent since they result in the production of the same amino acid sequence in all organisms (although certain organisms may translate some sequences more efficiently than they do others). Moreover, occasionally, a methylated variant of a purine or pyrimidine may be found in a given nucleotide sequence. Such methylations do not affect the coding relationship between the trinucleotide codon and the corresponding amino acid.

[0203] For polypeptide amino acid sequence, corresponding nucleotide sequences that can encode the polypeptide can be deduced from the genetic code (which, because of its redundancy, will produce multiple nucleic acid sequences for any given amino acid sequence). Thus, description and/or disclosure herein of a nucleotide sequence which encodes a polypeptide should be considered to also include description and/or disclosure of the amino acid sequence encoded by the nucleotide sequence. Similarly, description and/or disclosure of a polypeptide amino acid sequence herein should be considered to also include description and/or disclosure of all possible nucleotide sequences that can encode the amino acid sequence.

BRIEF DESCRIPTION OF THE DRAWINGS

[0204] FIG. 1 includes an image of heterogeneous tumor cells and a schematic of heterogenous tumor cells. The cells in the image on the left from a heterogenous melanoma sample and are immunohistochemically stained for PRAME (purple) and MAGEC2 (blue). Tumor cells were noted to be positive for either PRAME or MAGEC2 or both. The schematic on the right shows the result of treatment of such a heterogenous melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer cell population with a therapy that targets PRAME-expressing cells but not others, resulting in relapse. Targeting single antigens is expected to result in partial responses in these tumors with rapid progression.

[0205] FIG. 2 includes a schematic image showing the positions of class I HLA alleles in the human genome and a chart showing common HLA alleles and their prevalence in certain populations.

[0206] FIG. 3 is a schematic illustration showing that multiplexed TCR T cell therapy can be used to treat heterogenous tumors, *e.g.*, tumors that are heterogenous for expression of a target antigen of one TCR T cell product or have lost HLA heterozygosity.

[0207] FIG. 4 is a schematic illustrating enhancement of cytotoxic T cell activity by helper T cells.

[0208] FIG. 5 is a schematic showing suppressive effects of TGFβ signaling.

[0209] FIG. 6 is a schematic showing restoration of T cell activities suppressed by TGFβ signaling in cells that express DN-TGFβRII.

[0210] FIG. 7 is a schematic showing that effects mediated by DN-TGFβRII can enhance persistence of engineered T cells.

[0211] FIG. 8 is a pair of graphs showing that T cells engineered to express DN-TGFβRII demonstrate greater cytokine production and greater proliferation in the presence of TGFβ as compared to T cells that do not express DN-TGFβRII.

[0212] FIG. 9 is a set of graphs showing the prevalence of the expression of certain antigens in head and neck, cervical (uterine cervix), melanoma, and NSCLC cancers.

[0213] FIG. 10 is pair of graphs showing that TSC-200-A0201 engineered TCR T cells eliminate target cells *in vitro* and *in vivo*, respectively.

[0214] FIG. 11 is pair of graphs showing that TSC-204-C0702 engineered TCR T cells eliminate target cells *in vitro* and *in vivo*, respectively.

[0215] FIG. 12 is pair of graphs showing that TSC-203-A0201 engineered TCR T cells eliminate target cells *in vitro* and *in vivo*, respectively.

[0216] FIG. 13 is pair of graphs showing that TSC-204-A0201 engineered TCR T cells eliminate target cells *in vitro* and *in vivo*, respectively.

[0217] FIG. 14 is a schematic of a heterogenous cell population including cells that express PRAME and cells that express MAGE-A1, and a graph indicating the effect of single TCR T cell products and multiplexed T cell products on such a heterogenous cell population.

[0218] FIG. 15 is schematic of a heterogenous cell population including cells that express PRAME and cells that express MAGE-A1 that is implanted into mice, and a graph indicating the effect of single TCR T cell products and multiplexed T cell products on the implanted tumor in the mouse.

[0219] FIG. 16 is a schematic illustration of a nucleic acid construct for expression of TCR alpha and beta chains and related sequences.

[0220] FIG. 17 is a schematic illustration of the production of a multiplexed TCR T cell therapy, in which two TCR T cell products are prepared from a single apheresis product for sequential administration to a subject.

[0221] FIG. 18 is a set of four images of heterogenous solid tumor samples stained for PRAME (green) and MAGE-A1 (red), or a combination thereof (referred to in the drawing as "T-plex").

[0222] FIG. 19 is a graph showing that TCR T cells that express CD8α and CD8β produce higher levels of cytokine that TCR T cells that do not express CD8α and CD8β.

[0223] FIG. 20 is a graph showing that TCR T cells that express DN-TGFβRII demonstrate greater T cell persistence and greater reduction of tumor volume in mice than a reference TCR T cell population that does not express DN-TGFβRII.

[0224] FIG. 21 is a schematic illustrating a dosing scheme in which TCR T cell products are tested individually at one or two dose levels, and in combination at one or two dose levels.

[0225] FIG. 22 is a schematic illustration of the procedure for treatment of subjects by infusing T cell products.

[0226] FIG. 23 is a graph showing estimates of HLA loss of heterozygosity in samples from NSCLC, melanoma, and head & neck tumors, for each of HLA-A, HLA-B, and HLA-C.

[0227] FIG. 24 is a schematic showing potential for complete response and long-term remission or cure when a heterogenous solid tumor is treated with multiplexed TCR T cell therapy.

[0228] FIG. 25 is a schematic showing the process by which subjects are screen as potential recipients for TCR T cell therapy.

[0229] FIG. 26 is a pair of graphs showing that TCR T cells that express CD8α and CD8β produce higher levels of cytokine that TCR T cells that do not express CD8α and CD8β.

[0230] FIG. 27 is a set of panels providing information regarding a phase 1 trial relating to infusing of TCRs of the present disclosure to human subjects as a multiplexed, enhanced T cell receptor-engineered T cell therapy (TCR-T) for solid tumors.

[0231] FIG. 28 is a set of panels providing information regarding a phase 1 trial relating to infusing of TCRs of the present disclosure to human subjects as a multiplexed, enhanced T cell receptor-engineered T cell therapy (TCR-T) for solid tumors.

[0232] FIG. 29 is a set of panels providing information regarding a phase 1 trial relating to infusing of TCRs of the present disclosure to human subjects as a multiplexed, enhanced T cell receptor-engineered T cell therapy (TCR-T) for solid tumors.

[0233] FIG. 30 is a schematic representation of the vector pNVVD187 (TSC-201-B0702 npDNA Transposon; SEQ ID NO: 103).

[0234] FIG. 31 is a schematic representation of the vector pNVVD160 (TSC-200-A0201 npDNA Transposon; SEQ ID NO: 104).

[0235] FIG. 32 is a schematic representation of the vector PNVVD142 (TSC-204-C0702 npDNA Transposon; SEQ ID NO: 105).

[0236] FIG. 33 is a schematic representation of the vector pNVVD134 (TSC-203-A0201 npDNA Transposon; SEQ ID NO: 106).

[0237] FIG. 34 is a schematic representation of the vector pNVVD136 (TSC-204-A0201 npDNA Transposon; SEQ ID NO: 107).

[0238] FIG. 35 is a schematic representation of the vector pNVVD236 (TSC-204-A0101 npDNA Transposon; SEQ ID NO: 108).

[0239] FIG. 36 is a set of panels providing information regarding a phase 1 trial relating to a first-in-human clinical trial for use of TCRs of the present disclosure in a singleplex or a multiplex, enhanced T cell receptor-engineered T cell (TCR-T) therapy for solid tumors.

[0240] FIG. 37 is a set of panels providing information regarding a phase 1 trial relating to a first-in-human clinical trial for use of TCRs of the present disclosure in a singleplex or a multiplex, enhanced T cell receptor-engineered T cell (TCR-T) therapy for solid tumors.

[0241] FIG. 38 is a set of panels providing information regarding a phase 1 trial relating to a first-in-human clinical trial for use of TCRs of the present disclosure in a singleplex or a multiplex, enhanced T cell receptor-engineered T cell (TCR-T) therapy for solid tumors.

[0242] FIGs. 39A-39C are schematics showing that ImmunoBank of TCRs enables T-Plex, a multiplexed TCR-T cell therapy for solid tumors.

[0243] FIGs. 40A-40D show that targets of T-Plex were found co-expressed in solid tumors and were typically presenting intra-tumor heterogeneity.

[0244] FIGs. 41A-41D show a proof-of-concept (POC) study, which demonstrates that T-Plex addressed intra-tumor heterogeneity *in vitro*. FIG. 41A is a schematic showing developing models to demonstrate the concept of T-Plex. FIG. 41B shows measure of residual tumor cells after co-culture. FIG. 41C shows selecting target cells as a function of antigen and HLA.

[0245] FIGs. 42A-42D show a proof-of-concept (POC) study, which demonstrates that T-Plex addressed intra-tumor heterogeneity *in vivo*.

[0246] FIGs. 43A-43D show that T-Plex presented additive and synergistic activities.

[0247] FIG. 44 shows representative dosed patient data for TSC-203-A0201 PRAME TCR-T therapy demonstrating dose-dependent TCR-T cell activation (*e.g.*, antigen-driven TCR-T cell expansion based on interferon gamma secretion).

DETAILED DESCRIPTION

[0248] The present disclosure encompasses TCRs as set forth in Table 1 that bind (*e.g.*, specifically and/or selectively) to a peptide-MHC (pMHC) complex comprising (i) a MAGEC2 immunogenic peptide presented by HLA-B*0702; (ii) an HPV16 immunogenic peptide presented by HLA-A*0201; (iii) a MAGEA1 immunogenic peptide presented by HLA-B*0702; (iv) a PRAME immunogenic peptide presented by HLA-A*0201; (v) a MAGEA1 immunogenic peptide presented by HLA-A*0201; and/or (vi) a MAGEA1 immunogenic peptide presented by HLA-A*0101. The present disclosure further encompasses T cells that encode and/or express TCRs. In various embodiments, infusing of T cells that encode and/or express one or more TCCs of Table 1 to subjects can treat

melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and/or anogenital cancer and/or prevent relapse. Any TCR described herein (*e.g.*, listed by sequence in Table 1, described in the specification, exemplified in the working examples, listed in the figures, etc.) in combination with any other TCR described herein (*e.g.*, listed by sequence in Table 1, described in the specification, exemplified in the working examples, listed in the figures, etc.).

[0249] The present disclosure encompasses, among other things, methods of treating a malignancy selected from the group consisting of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and/or anogenital cancer.

TCRs and Engineered T Cells

[0250] TCRs of the present disclosure include the TCRs for which CDR, variable domain, constant domain, and full chain sequences are set forth in Table 1 below. In various embodiments, the present disclosure provides a T cell, or population of T cells, engineered to encode and express a TCR set forth in Table 1. Engineered T cell products of the present disclosure include products referred to as TSC-201-B0702, TSC-200-A0201, TSC-204-C0702, TSC-203-A0201, TSC-204-A0201, and TSC-204-A0101. Engineered T cell products of the present disclosure can include CD8+ and/or CD4+ T cells.

TSC-201-B0702

[0251] In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 7, an alpha chain CDR2 according to SEQ ID NO: 8, and an alpha chain CDR3 according to SEQ ID NO: 9, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1 according to SEQ ID NO: 13, a beta chain CDR2 according to SEQ ID NO: 14, and a beta chain CDR3 according to SEQ ID NO: 15, *e.g.*, in a beta chain variable domain.

[0252] In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 10 and a beta chain variable domain according to SEQ ID NO: 16. In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR

that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 10 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 16. In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 10 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 16.

[0253] In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 12and a beta chain according to SEQ ID NO: 18. In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 12and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 18. In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 12and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 18.

[0254] In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-201-B0702 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-201-B0702 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

[0255] TSC-201-B0702 also encompasses products disclosed in International Application Publication No.: WO 2022/221479, which is incorporated herein by reference in its entirety, with respect to its disclosure of TCRs and uses thereof, and in particular with respect to TSC-201-B0702.

TSC-200-A0201

[0256] In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 20, an alpha chain CDR2 according to SEQ ID NO: 21, and an alpha chain CDR3 according to SEQ ID NO: 22, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1 according to SEQ ID NO: 26, a beta chain CDR2 according to SEQ ID NO: 27, and a beta chain CDR3 according to SEQ ID NO: 28, *e.g.*, in a beta chain variable domain.

[0257] In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 23 and a beta chain variable domain according to SEQ ID NO: 29. In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 23 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 29. In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 23 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 29.

[0258] In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 25 and a beta chain according to SEQ ID NO: 31. In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 25 and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 31. In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 25 and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 31.

[0259] In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-200-A0201 engineered T cells can allow CD4+ helper T cells to participate in target

recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-200-A0201 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

[0260] TSC-200-A0201 also encompasses products disclosed in International Application Publication No.: WO 2023/086477 and corresponding US Application Publication No.: 2023/0272049, which are incorporated herein by reference in its entirety, with respect to disclosure of TCRs and uses thereof, and in particular with respect to TSC-200-A0201.

TSC-204-C0702

[0261] In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 33, an alpha chain CDR2 according to SEQ ID NO: 34, and an alpha chain CDR3 according to SEQ ID NO: 35, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1 according to SEQ ID NO: 39, a beta chain CDR2 according to SEQ ID NO: 40, and a beta chain CDR3 according to SEQ ID NO: 41, *e.g.*, in a beta chain variable domain.

[0262] In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 36 and a beta chain variable domain according to SEQ ID NO: 42. In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 36 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 42. In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 36 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 42.

[0263] In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 38 and a beta chain according to SEQ ID NO: 44. In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at

least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 38 and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 44. In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 38 and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 44.

[0264] In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-204-C0702 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-204-C0702 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

[0265] TSC-204-C0702 also encompasses products disclosed in International Application Publication No.: WO 2023/086480 and corresponding US Application Publication No.: 2023-0270832, which are incorporated herein by reference in their entirety, with respect to disclosure of TCRs and uses thereof, and in particular with respect to TSC-204-C0702.

TSC-203-A0201

[0266] In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 46, an alpha chain CDR2 according to SEQ ID NO: 47, and an alpha chain CDR3 according to SEQ ID NO: 48, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1 according to SEQ ID NO: 52, a beta chain CDR2 according to SEQ ID NO: 53, and a beta chain CDR3 according to SEQ ID NO: 54, *e.g.*, in a beta chain variable domain.

[0267] In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 49 and a beta chain variable domain according to SEQ ID NO: 55. In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 49 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at

least 98%, or at least 99% identity with SEQ ID NO: 55. In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 49 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 55.

[0268] In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 51 and a beta chain according to SEQ ID NO: 57. In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 51 and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 57. In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 51 and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 57.

[0269] In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-203-A0201 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-203-A0201 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

[0270] TSC-203-A0201 also encompasses products disclosed in International Application No.: PCT/US23/76068, which is incorporated herein by reference in its entirety, with respect to its disclosure of TCRs and uses thereof, and in particular with respect to TSC-203-A0201.

TSC-204-A0201

[0271] In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 59, an alpha chain CDR2 according to SEQ ID NO: 60, and an alpha chain CDR3 according to SEQ ID NO: 61, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1

according to SEQ ID NO: 65, a beta chain CDR2 according to SEQ ID NO: 66, and a beta chain CDR3 according to SEQ ID NO: 67, *e.g.*, in a beta chain variable domain.

[0272] In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 62 and a beta chain variable domain according to SEQ ID NO: 68. In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 62 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 68. In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 62 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 68.

[0273] In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 64 and a beta chain according to SEQ ID NO: 70. In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 64 and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 70. In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 64 and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 70.

[0274] In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-204-A0201 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-204-A0201 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

[0275] TSC-204-A0201 also encompasses products disclosed in International Application No.: PCT/US23/76072, which is incorporated herein by reference in its entirety, with respect to its disclosure of TCRs and uses thereof, and in particular with respect to TSC-204-A0201.

TSC-204-A0101

[0276] In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain CDR1 according to SEQ ID NO: 72, an alpha chain CDR2 according to SEQ ID NO: 73, and an alpha chain CDR3 according to SEQ ID NO: 74, *e.g.*, in an alpha chain variable domain, and includes a beta chain CDR1 according to SEQ ID NO: 78, a beta chain CDR2 according to SEQ ID NO: 79, and a beta chain CDR3 according to SEQ ID NO: 80, *e.g.*, in a beta chain variable domain.

[0277] In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain according to SEQ ID NO: 75 and a beta chain variable domain according to SEQ ID NO: 81. In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 75 and a beta chain variable domain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 81. In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 75 and a beta chain variable domain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 81.

[0278] In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain according to SEQ ID NO: 77 and a beta chain according to SEQ ID NO: 83. In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR that includes an alpha chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 77 and a beta chain having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity with SEQ ID NO: 83. In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express a TCR

that includes an alpha chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 77 and a beta chain having no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid differences with SEQ ID NO: 83.

[0279] In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or express CD8α and CD8β. Expression of CD8α and CD8β coreceptors by TSC-204-A0101 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. In various embodiments, TSC-204-A0101 includes engineered T cells that encode and/or expression of DN-TGFβRII. Expression of DN-TGFβRII can increase persistence of engineered T cells in a subject.

Table 1. Exemplary TCR Amino Acid Sequences

Agent	**Alpha/ Beta**	**Element**	**Sequence**	**SEQ ID NO:**
TSC-201-B0702 MAGE-C2/HLA-B*0702 TCR MAGEC2_184-6 MGTM codon optimized sequence (also known as "184-6", "6", "TCR 6", TCR expressed by "TSC-201-	Alpha TRAV22/ TRAJ44/ MGTM modified TRAC	CDR1	**DSVNN**	7
		CDR2	**IPSGT**	8
		CDR3	**CAVTGTASKLTF**	9
		V_α	MKRILGALLGLLSAQVCCVRGIQVEQSP PDLILQEGANSTLRCNFSDSVNNLQWF HQNPWGQLINLFYIPSGTKQNGRLSATT VATERYSLLYISSSQTTDSGVYFCAVTG TASKLTFGTGTRLQVTLD	10
		C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv yitdktvldmrsmdfksnsavawsnksdfacanafnnsii pedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkv agfnllmtlrlwss	11
		Chain	MKRILGALLGLLSAQVCCVRGIQVEQSP PDLILQEGANSTLRCNFSDSVNNLQWF HQNPWGQLINLFYIPSGTKQNGRLSATT VATERYSLLYISSSQTTDSGVYFCAVTG TASKLTFGTGTRLQVTLDiqnpdpavyqlrds kssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmd fksnsavawsnksdfacanafnnsiipedtffpssdvpcdv klveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	12
	Beta TRBV7-9/TRBJ2-7/ MGTM	CDR1	**SEHNR**	13
		CDR2	**FQNEAQ**	14
		CDR3	**CASSKGIFEQYF**	15
		V_β	MGTSLLCWMALCLLGADHADTGVSQD PRHKITKRGQNVTFRCDPISEHNRLYW YRQTLGQGPEFLTYFQNEAQLEKSRLLS	16

B07", and TCR expressed by "TSC-201-B0702")	modified TRBC1		DRFSAERPKGSFSTLEIQRTEQGDSAMY LCASSKGIFEQYFGPGTRLTVTE	
		C_β	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvel swwvngkevhsgvstdpqplkeqpalndsryclssrlrvs atfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsae awgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	17
		Chain	MGTSLLCWMALCLLGADHADTGVSQD PRHKITKRGQNVTFRCDPISEHNRLYW YRQTLGQGPEFLTYFQNEAQLEKSRLLS DRFSAERPKGSFSTLEIQRTEQGDSAMY LCASSKGIFEQYFGPGTRLTVTEdlnkvfpp evavfepskaeiahtqkatlvclatgffpdhvelswwvngk evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprn hfrcqvqfyglsendewtqdrakpvtqivsaeawgradcg itsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrk df	18
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MGTSLLCWMALCLLGADHADTGVSQD PRHKITKRGQNVTFRCDPISEHNRLYW YRQTLGQGPEFLTYFQNEAQLEKSRLLS DRFSAERPKGSFSTLEIQRTEQGDSAMY LCASSKGIFEQYFGPGTRLTVTEdlnkvfpp evavfepskaeiahtqkatlvclatgffpdhvelswwvngk evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprn hfrcqvqfyglsendewtqdrakpvtqivsaeawgradcg itsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrk df*ggsgrakrsgsgatnfsllkqagdveenpgp*MKRILG ALLGLLSAQVCCVRGIQVEQSPPDLILQ EGANSTLRCNFSDSVNNLQWFHQNPW GQLINLFYIPSGTKQNGRLSATTVATER YSLLYISSSQTTDSGVYFCAVTGTASKL TFGTGTRLQVTLDiqnpdpavyqlrdskssdksv clftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsav awsnksdfacanafnnsiipedtffpssdvpcdvklveksf etdtnlnfqnllvivlrilllkvagfnllmtlrlwss	19
TSC-200-A0201 E7-11-28 MGTM codon optimized	Alpha TRAV25/ TRAJ37/ MGTM modified TRAC	CDR1	**TTLSN**	20
		CDR2	**LVKSGEV**	21
		CDR3	**CAGIGSSNTGKLIF**	22
		V_α	MLLITSMLVLWMQLSQVNGQQVMQIP QYQHVQEGEDFTTYCNSS**TTLSN**IQWY KQRPGGHPVFLIQ**LVKSGEV**KKQKRLT FQFGEAKKNSSLHITATQTTDVGTYF**CA GIGSSNTGKLIF**GQGTTLQVKPD	23
		C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv yitdktvldmrsmdfksnsavawsnksdfacanafnnsii	24

sequence (also known as "TCR28" or "28" or "TCR-200-A02")			pedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	
		Chain	MLLITSMLVLWMQLSQVNGQQVMQIPQYQHVQEGEDFTTYCNSS**TTLSN**IQWYKQRPGGHPVFLIQ**LVKSGEV**KKQKRLTFQFGEAKKNSSLHITATQTTDVGTYF**CAGIGSSNTGKLIF**GQGTTLQVKPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	25
	Beta TRBV2/TRBJ2-7/MGTM modified TRBC	CDR1	**SNHLY**	26
		CDR2	**FYNNEI**	27
		CDR3	**CAITGRVSYEQYF**	28
		V_β	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEVILRCVPI**SNHLY**FYWYRQILGQKVEFLVS**FYNNEI**SEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYF**C****AITGRVSYEQYF**GPGTRLTVTE	29
		C_β	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf	30
		Chain	MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEVILRCVPI**SNHLY**FYWYRQILGQKVEFLVS**FYNNEI**SEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYF**C****AITGRVSYEQYF**GPGTRLTVTEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf	31
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MDTWLVCWAIFSLLKAGLTEPEVTQTPSHQVTQMGQEVILRCVPI**SNHLY**FYWYRQILGQKVEFLVS**FYNNEI**SEKSEIFDDQFSVERPDGSNFTLKIRSTKLEDSAMYF**C****AITGRVSYEQYF**GPGTRLTVTEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf*gsgrakrsgsgatnfsllkqagdveenpgp*MLLITSMLVLWMQLSQVNGQQVMQIPQYQHVQEGEDFTTYCNSS**TTLSN**IQWYKQRPGGHPVFLIQ**LVKSGEV**KKQKRLTFQFGEAKKNSSLHITATQTTDVGTYF**CAGIGSS**	32

			NTGKLIFGQGTTLQVKPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	
TSC-204-C0702 MAGEA1 TCR 32-41 MGTM codon optimized sequence (also known as "TCR41" or "41" or "TCR-204-C07")	Alpha TRAV27/ TRAJ52/ MGTM modified TRAC	CDR1	**SVFSS**	33
		CDR2	**VVTGGEV**	34
		CDR3	**CAGDESISYGKLTF**	35
		V_α	MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEPGEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYL**CAGDESISYGKLTF**GQGTILTVHPN	36
		C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	37
		Chain	MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEPGEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYL**CAGDESISYGKLTF**GQGTILTVHPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	38
	Beta TRBV12-4/TRBJ1-4/MGTM modified TRBC1	CDR1	**SGHDY**	39
		CDR2	**FNNNVP**	40
		CDR3	**CASSFLGWNEKLFF**	41
		V_β	MGSWTLCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEVTLRCKPI**SGHDY**LFWYRQTMMRGLELLIY**FNNNVP**IDDSGMPEDRFSAKMPNASFSTLKIQPSEPRDSAVYF**CASSFLGWNEKLFF**GSGTQLSVLE	42
		C_β	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf	43
		Chain	MGSWTLCCVSLCILVAKHTDAGVIQSPRHEVTEMGQEVTLRCKPI**SGHDY**LFWYRQTMMRGLELLIY**FNNNVP**IDDSGMPEDRFSAKMPNASFSTLKIQPSEPRDSAVYF**CASSFLGWNEKLFF**GSGTQLSVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea	44

			wgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MGSWTLCCVSLCILVAKHTDAGVIQSP RHEVTEMGQEVTLRCKPI**SGHDY**LFWY RQTMMRGLELLIY**FNNNVP**IDDSGMPE DRFSAKMPNASFSTLKIQPSEPRDSAVY F**CASSFLGWNEKLFF**GSGTQLSVLEdln kvfppevavfepskaeiahtqkatlvclatgffpdhvelsw wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatf wqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea wgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf*gsgrakrsgsgatnfsllkqagdveenpgp* MVLKFSVSILWIQLAWVSTQLLEQSPQF LSIQEGENLTVYCNSS**SVFSS**LQWYRQE PGEGPVLLVT**VVTGGEV**KKLKRLTFQF GDARKDSSLHITAAQPGDTGLYL**CAGD ESISYGKLTF**GQGTILTVHPNiqnpdpavyq lrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmr smdfksnsavawsnksdfacanafnnsiipedtffpssdvp cdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlw ss	45
TSC-203-A0201 PRAME-425-366 MGTM codon optimized sequence (also known as “366”, “TCR 366”, TCR expressed by “TSC-203-A02”, and TCR expressed by	Alpha TRAV38-2DV8/TRAJ50/MGTM modified TRAC	CDR1	**TSESDYY**	46
		CDR2	**QEAYKQQN**	47
		CDR3	**CAYRKTSYDKVIF**	48
		V_α	MACPGFLWALVISTCLEFSMAQTVTQS QPEMSVQEAETVTLSCTYD**TSESDYY**L FWYKQPPSRQMILVIR**QEAYKQQN**ATE NRFSVNFQKAAKSFSLKISDSQLGDAA MYF**CAYRKTSYDKVIF**GPGTSLSVIPN	49
		C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv yitdktvldmrsmdfksnsavawsnksdfacanafnnsii pedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkv agfnllmtlrlwss	50
		Chain	MACPGFLWALVISTCLEFSMAQTVTQS QPEMSVQEAETVTLSCTYD**TSESDYY**L FWYKQPPSRQMILVIR**QEAYKQQN**ATE NRFSVNFQKAAKSFSLKISDSQLGDAA MYF**CAYRKTSYDKVIF**GPGTSLSVIPNi qnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvy itdktvldmrsmdfksnsavawsnksdfacanafnnsiipe dtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvag fnllmtlrlwss	51
	Beta TRBV13/TRBJ2-	CDR1	**PRHDT**	52
		CDR2	**FYEKMQ**	53
		CDR3	**CASSFARLEGRDNEQFF**	54
		V_β	MLSPDLPDSAWNTRLLCRVMLCLLGA GSVAAGVIQSPRHLIKEKRETATLKCYP	55

"TSC-203-A0201")	1/MGTM modified TRBC		I**PRHDT**VYWYQQGPGQDPQFLIS**FYEK MQ**SDKGSIPDRFSAQQFSDYHSELNMS SLELGDSALYF**CASSFARLEGRDNEQF F**GPGTRLTVLE	
		Cβ	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvel swwvngkevhsgvstdpqplkeqpalndsryclssrlrvs atfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsae awgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	56
		Chain	MLSPDLPDSAWNTRLLCRVMLCLLGA GSVAAGVIQSPRHLIKEKRETATLKCYP I**PRHDT**VYWYQQGPGQDPQFLIS**FYEK MQ**SDKGSIPDRFSAQQFSDYHSELNMS SLELGDSALYF**CASSFARLEGRDNEQF F**GPGTRLTVLEdlnkvfppevavfepskaeiahtqk atlvclatgffpdhvelswwvngkevhsgvstdpqplkeq palndsryclssrlrvsatfwqnprnhfrcqvqfyglsende wtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilye illgkatlyavlvsalvlmamvkrkdf	57
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MLSPDLPDSAWNTRLLCRVMLCLLGA GSVAAGVIQSPRHLIKEKRETATLKCYP I**PRHDT**VYWYQQGPGQDPQFLIS**FYEK MQ**SDKGSIPDRFSAQQFSDYHSELNMS SLELGDSALYF**CASSFARLEGRDNEQF F**GPGTRLTVLEdlnkvfppevavfepskaeiahtqk atlvclatgffpdhvelswwvngkevhsgvstdpqplkeq palndsryclssrlrvsatfwqnprnhfrcqvqfyglsende wtqdrakpvtqivsaeawgradcgitsasyhqgvlsatilye illgkatlyavlvsalvlmamvkrkdf*gsgrakrsgsgatnf sllkqagdveenpgp*MACPGFLWALVISTCLE FSMAQTVTQSQPEMSVQEAETVTLSCT YD**TSESDYY**LFWYKQPPSRQMILVIR**Q EAYKQQN**ATENRFSVNFQKAAKSFSL KISDSQLGDAAMYF**CAYRKTSYDKVIF** GPGTSLSVIPNiqnpdpavyqlrdskssdksvclftdf dsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsn ksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnl nfqnllvivlrilllkvagfnllmtlrlwss	58
TSC-204-A0201 MAGEA1-278-1479 MGTM	Alpha TRAV20/ TRAJ26/ MGTM	CDR1	**VSGLRG**	59
		CDR2	**LYSAGEE**	60
		CDR3	**CAVSYGQNFVF**	61
		Vα	MEKMLECAFIVLWLQLGWLSGEDQVT QSPEALRLQEGESSSLNCSYT**VSGLRG**L FWYRQDPGKGPEFLFT**LYSAGEE**KEKE RLKATLTKKESFLHITAPKPEDSATYL**C AVSYGQNFVF**GPGTRLSVLPY	62

codon optimized sequence (also known as clone "MAGEA1-1479," "TCR 1479", "1479", TCR expressed by "TSC-204-A02", and TCR expressed by "TSC-204-A0201")	modified TRAC	C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv yitdktvldmrsmdfksnsavawsnksdfacanafnnsii pedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkv agfnllmtlrlwss	63
		Chain	MEKMLECAFIVLWLQLGWLSGEDQVT QSPEALRLQEGESSSLNCSYT**VSGLRG**L FWYRQDPGKGPEFLFT**LYSAGEE**KEKE RLKATLTKKESFLHITAPKPEDSATYL**C AVSYGQNFVF**GPGTRLSVLPYiqnpdpavy qlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldm rsmdfksnsavawsnksdfacanafnnsiipedtffpssdv pcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl wss	64
	Beta TRBV5-8/TRBJ1-1/MGTM modified TRBC	CDR1	**SGHTS**	65
		CDR2	**YDEGEE**	66
		CDR3	**CASSLGQLNTEAFF**	67
		V_β	MGPRLLFWALLCLLGTGPVEAGVTQSP THLIKTRGQQATLRCSPI**SGHTS**VYWY QQALGLGLQFLLW**YDEGEE**RNRGNFP PRFSGRQFPNYSSELNVNALELEDSALY L**CASSLGQLNTEAFF**GQGTRLTVVE	68
		C_β	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvel swwvngkevhsgvstdpqplkeqpalndsryclssrlrvs atfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsae awgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	69
		Chain	MGPRLLFWALLCLLGTGPVEAGVTQSP THLIKTRGQQATLRCSPI**SGHTS**VYWY QQALGLGLQFLLW**YDEGEE**RNRGNFP PRFSGRQFPNYSSELNVNALELEDSALY L**CASSLGQLNTEAFF**GQGTRLTVVEdln kvfppevavfepskaeiahtqkatlvclatgffpdhvelsw wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatf wqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea wgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	70
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MGPRLLFWALLCLLGTGPVEAGVTQSP THLIKTRGQQATLRCSPI**SGHTS**VYWY QQALGLGLQFLLW**YDEGEE**RNRGNFP PRFSGRQFPNYSSELNVNALELEDSALY L**CASSLGQLNTEAFF**GQGTRLTVVEdln kvfppevavfepskaeiahtqkatlvclatgffpdhvelsw wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatf wqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea wgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf*gsgrakrsgseatnfsllkqagdveenpgp* MEKMLECAFIVLWLQLGWLSGEDQVT QSPEALRLQEGESSSLNCSYT**VSGLRG**L	71

			FWYRQDPGKGPEFLFT**LYSAGEE**KEKE RLKATLTKKESFLHITAPKPEDSATYL**C AVSYGQNFVF**GPGTRLSVLPYiqnpdpavy qlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldm rsmdfksnsavawsnksdfacanafnnsiipedtffpssdv pcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl wss	
TSC-204-A0101 MAGEA1-161-458 MGTM codon optimized sequence (also known as clone "MAGEA1-458", "TCR 458", "458", TCR expressed by "TSC-204-A01", TCR expressed by "TSC-204-A01:01", and TCR expressed by "TSC-204-A0101")	Alpha TRAV21/ TRAJ47/ MGTM modified TRAC	CDR1	**DSAIYN**	72
		CDR2	**IQSSQRE**	73
		CDR3	**CAVQYGNKLVF**	74
		V_α	METLLGLLILWLQLQWVSSKQEVTQIP AALSVPEGENLVLNCSFT**DSAIYN**LQW FRQDPGKGLTSLLL**IQSSQRE**QTSGRLN ASLDKSSGRSTLYIAASQPGDSATYL**CA VQYGNKLVF**GAGTILRVKSY	75
		C_α	iqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv yitdktvldmrsmdfksnsavawsnksdfacanafnnsii pedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkv agfnllmtlrlwss	76
		Chain	METLLGLLILWLQLQWVSSKQEVTQIP AALSVPEGENLVLNCSFT**DSAIYN**LQW FRQDPGKGLTSLLL**IQSSQRE**QTSGRLN ASLDKSSGRSTLYIAASQPGDSATYL**CA VQYGNKLVF**GAGTILRVKSYiqnpdpavy qlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldm rsmdfksnsavawsnksdfacanafnnsiipedtffpssdv pcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl wss	77
	Beta TRBV5-4/TRBJ2-7/MGTM modified TRBC	CDR1	**SGHNT**	78
		CDR2	**YYREEE**	79
		CDR3	**CASSTDITYEQYF**	80
		V_β	MGPGLLCWALLCLLGAGSVETGVTQSP THLIKTRGQQVTLRCSSQ**SGHNT**VSWY QQALGQGPQFIFQ**YYREEE**NGRGNFPP RFSGLQFPNYSSELNVNALELDDSALYL **CASSTDITYEQYF**GPGTRLTVTE	81
		C_β	dlnkvfppevavfepskaeiahtqkatlvclatgffpdhvel swwvngkevhsgvstdpqplkeqpalndsryclssrlrvs atfwqnprnhfrcqvqfygisendewtqdrakpvtqivsae awgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvl mamvkrkdf	82
		Chain	MGPGLLCWALLCLLGAGSVETGVTQSP THLIKTRGQQVTLRCSSQ**SGHNT**VSWY QQALGQGPQFIFQ**YYREEE**NGRGNFPP RFSGLQFPNYSSELNVNALELDDSALYL **CASSTDITYEQYF**GPGTRLTVTEdlnkvfp pevavfepskaeiahtqkatlvclatgffpdhvelswwvng	83

			kevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnpr nhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc gitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkr kdf	
	Complete Beta+Alpha ORF-Encoded Protein Sequence		MGPGLLCWALLCLLGAGSVETGVTQSP THLIKTRGQQVTLRCSSQ**SGHNT**VSWY QQALGQGPQFIFQ**YYREEE**NGRGNFPP RFSGLQFPNYSSELNVNALELDDSALYL **CASSTDITYEQYF**GPGTRLTVTEdlnkvfp pevavfepskaeiahtqkatlvclatgffpdhvelswwvng kevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnpr nhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc gitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkr kdf*gsgrakrsgsgatnfsllkqagdveenpgp*METLL GLLILWLQLQWVSSKQEVTQIPAALSVP EGENLVLNCSFT**DSAIYN**LQWFRQDPG KGLTSLLL**IQSSQRE**QTSGRLNASLDKS SGRSTLYIAASQPGDSATYL**CAVQYGN KLVF**GAGTILRVKSYiqnpdpavyqlrdskssd ksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksn savawsnksdfacanafnnsiipedtffpssdvpcdvklve ksfetdtnlnfqnllvivlrilllkvagfnllmtlrlwss	84

Nucleic Acids and Vectors

[0280] In at least one aspect encompassed by the present invention, provided herein are nucleic acid molecules that encode a TCR of Table 1. In at least one aspect encompassed by the present invention, provided herein are nucleic acid molecules of Table 2 that encode a TCR.

[0281] In various embodiments, a TCR or fragment thereof of Table 1 is encoded an alpha chain nucleic acid sequence of SEQ ID NO: 85, a beta chain nucleic acid sequence of SEQ ID NO: 86, and/or a complete ORF of SEQ ID NO: 87 encoding a beta chain and an alpha chain. In various embodiments, a TCR or fragment thereof of Table 1 is encoded an alpha chain nucleic acid sequence of SEQ ID NO: 88, a beta chain nucleic acid sequence of SEQ ID NO: 89, and/or a complete ORF of SEQ ID NO: 90 encoding a beta chain and an alpha chain. In various embodiments, a TCR or fragment thereof of Table 1 is encoded an alpha chain nucleic acid sequence of SEQ ID NO: 91, a beta chain nucleic acid sequence of SEQ ID NO: 92, and/or a complete ORF of SEQ ID NO: 93 encoding a beta chain and an alpha chain. In various embodiments, a TCR or fragment thereof of Table 1 is encoded an alpha chain nucleic acid sequence of SEQ ID NO: 94, a beta chain nucleic acid sequence of SEQ ID NO: 95, and/or a complete ORF of SEQ ID NO: 96 encoding a beta chain and an alpha chain. In various embodiments, a TCR or fragment thereof of Table 1 is encoded an

alpha chain nucleic acid sequence of SEQ ID NO: 97, a beta chain nucleic acid sequence of SEQ ID NO: 98, and/or a complete ORF of SEQ ID NO: 99 encoding a beta chain and an alpha chain. In various embodiments, a TCR or fragment thereof of Table 1 is encoded an alpha chain nucleic acid sequence of SEQ ID NO: 100, a beta chain nucleic acid sequence of SEQ ID NO: 101, and/or a complete ORF of SEQ ID NO: 102 encoding a beta chain and an alpha chain.

[0282] In particular, the present disclosure encompasses nucleic acid vectors that include constructs as shown in **FIG. 16**, where the sequences encoding the TCRα and TCRβ chains encode the TCR chains of a TCR of Table 1. As shown in **FIG. 16**, a promoter is operably linked with the coding sequence that encodes TCRα and TCRβ chains, as well as CD8α and CD8β. The amino acid sequences of the TCRα and TCRβ chains are separated by a self-cleaving peptide (P2A). CD8α and CD8β coreceptors allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. CD8α and CD8β are likewise separated by a self-cleaving peptide (P2A), and the CD8α polypeptide includes an N-terminal CD34 epitope tag that enables purification of engineered T cells as well as tracking in the subject. A separate promoter is operably linked with and controls expression of DN-TGFβRII. The vector further includes a selection gene. The shown sequences of **FIG. 16** are flanked by transposon Terminal Inverted Repeats (TIRs).

Table 2. Exemplary TCR-Encoding Nucleic Acid Sequences

Agent	Alpha/ Beta	Sequence	SEQ ID NO:
TSC-201-B0702 MAGE-C2/HLA-B*0702 TCR MAGEC2_184-6 MGTM	Alpha TRAV22 /TRAJ44/ MGTM modified TRAC	ATGAAGAGAATCCTGGGCGCCCTGCTGGGACTGC TGTCTGCCCAAGTCTGTTGTGTGCGGGGCATCCA GGTGGAACAGAGCCCTCCAGATCTGATCCTGCAA GAGGGCGCCAACAGCACCCTGAGATGCAACTTC AGCGACTCCGTGAACAACCTGCAGTGGTTCCACC AGAATCCTTGGGGCCAGCTGATCAACCTGTTCTA CATCCCCAGCGGCACCAAGCAGAACGGCAGACT GTCTGCTACCACCGTGGCCACCGAGAGATACAGC CTGCTGTACATCAGCAGCAGCCAGACCACCGATT CCGGCGTCTACTTCTGCGCAGTGACTGGTACCGC TTCAAAACTGACATTTGGGACTGGAACAAGACTT CAGGTCACGCTCGACatccagaaccccgaccccgccgtgtaccag ctgagggactccaagtccagcgacaagagcgtgtgtctgtttacggacttcgaca gccagaccaacgtgagtcaaagcaaggacagcgacgtctacataacggataag accgtgctggacatgcggagcatggacttcaagagcaacagcgccgtggcctg	85

codon optimized sequence (also known as "184-6", "6", "TCR 6", TCR expressed by "TSC-201-B07", and TCR expressed by "TSC-201-B0702")		gtccaacaagagcgacttcgcctgcgccaacgccttcaacaacagcatcatccc cgaggacaccttcttccccagcagcgacgtgccctgcgacgtgaaactggtgga gaagtccttcgagacagacaccaatctgaactttcagaacctgctggtgatcgtgc tgcggattctgctgctgaaagtggccggcttcaatctgctgatgaccctgcggctg tggagcagc	
	Beta TRBV7-9/TRBJ2-7/ MGTM modified TRBC1	ATGGGAACCTCTCTGCTGTGCTGGATGGCCCTGT GTCTGCTGGGAGCCGATCATGCCGATACGGGAGT GTCCCAGGATCCTCGGCACAAGATTACCAAGAGG GGCCAGAACGTGACCTTCCGCTGTGACCCTATCA GCGAGCACAACCGGCTGTATTGGTACAGACAGA CACTCGGCCAGGGGCCTGAATTTCTCACATACTT CCAGAACGAAGCCCAGCTGGAAAAGTCCCGGCT GCTGAGCGATAGATTTTCCGCCGAGAGGCCCAAG GGCTCCTTCAGCACTCTGGAAATTCAGCGCACCG AGCAGGGCGACTCTGCCATGTATCTGTGCGCATC CTCTAAGGGCATTTTTGAGCAATATTTTGGGCCG GGCACCAGGCTCACGGTCACAGAAgatctgaacaaggtgt tcctccagaggtggccgtgttcgagccttctaaggccgagatcgcccacacac aaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgtggaact gtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacggatccccca gcctctgaaagaacagcctgccctgaacgacagccggtactgcctgagctccag actgagagtgtccgccaccttctggcagaaccccccggaaccacttcagatgcca ggtgcagttttacggcctgagcgagaacgacgagtggacccaggacagagcca agcccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgcggc atcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtacgaa atcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgctgat ggccatggtcaagcggaaggacttt	86
	Complete Beta+Alpha ORF-Encoded Protein Sequence	ATGGGAACCTCTCTGCTGTGCTGGATGGCCCTGT GTCTGCTGGGAGCCGATCATGCCGATACGGGAGT GTCCCAGGATCCTCGGCACAAGATTACCAAGAGG GGCCAGAACGTGACCTTCCGCTGTGACCCTATCA GCGAGCACAACCGGCTGTATTGGTACAGACAGA CACTCGGCCAGGGGCCTGAATTTCTCACATACTT CCAGAACGAAGCCCAGCTGGAAAAGTCCCGGCT GCTGAGCGATAGATTTTCCGCCGAGAGGCCCAAG GGCTCCTTCAGCACTCTGGAAATTCAGCGCACCG AGCAGGGCGACTCTGCCATGTATCTGTGCGCATC CTCTAAGGGCATTTTTGAGCAATATTTTGGGCCG GGCACCAGGCTCACGGTCACAGAAgatctgaacaaggtgt tcctccagaggtggccgtgttcgagccttctaaggccgagatcgcccacacac aaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgtggaact gtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacggatccccca gcctctgaaagaacagcctgccctgaacgacagccggtactgcctgagctccag actgagagtgtccgccaccttctggcagaaccccccggaaccacttcagatgcca ggtgcagttttacggcctgagcgagaacgacgagtggacccaggacagagcca agcccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgcggc atcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtacgaa atcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgctgat	87

		ggccatggtcaagcggaaggactttggcagcggc*agagccaaaaggtccgg gagcggtgcgacaaacttagcctgttgaaacaagccggcgacgttgaagag aaccccggacct*ATGAAGAGAATCCTGGGCGCCCTGCT GGGACTGCTGTCTGCCCAAGTCTGTTGTGTGCGG GGCATCCAGGTGGAACAGAGCCCTCCAGATCTGA TCCTGCAAGAGGGCGCCAACAGCACCCTGAGAT GCAACTTCAGCGACTCCGTGAACAACCTGCAGTG GTTCCACCAGAATCCTTGGGGCCAGCTGATCAAC CTGTTCTACATCCCCAGCGGCACCAAGCAGAACG GCAGACTGTCTGCTACCACCGTGGCCACCGAGAG ATACAGCCTGCTGTACATCAGCAGCAGCCAGACC ACCGATTCCGGCGTCTACTTCTGCGCAGTGACTG GTACCGCTTCAAAACTGACATTTGGGACTGGAAC AAGACTTCAGGTCACGCTCGACatccagaaccccgaccccc gccgtgtaccagctgagggactccaagtccagcgacaagagcgtgtgtctgttta cggacttcgacagccagaccaacgtgagtcaaagcaaggacagcgacgtctac ataacggataagaccgtgctggacatgcggagcatggacttcaagagcaacag cgccgtggcctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaa cagcatcatccccgaggacaccttcttccccagcagcgacgtgccctgcgacgt gaaactggtggagaagtccttcgagacagacaccaatctgaactttcagaacctg ctggtgatcgtgctgcggattctgctgctgaaagtggccggcttcaatctgctgat gaccctgcggctgtggagcagc	
TSC-200-A0201 E7-11-28 MGTM codon optimized sequence (also known as “TCR28” or “28” or “TCR-200-A02”)	Alpha TRAV25 /TRAJ37/ MGTM modified TRAC	ATGCTGCTGATCACCTCCATGCTGGTGCTGTGGA TGCAGCTGAGCCAAGTGAACGGCCAGCAAGTGA TGCAGATCCCTCAGTACCAGCACGTGCAAGAAGG CGAGGACTTCACCACCTACTGCAACAGCAGC**ACC ACACTGAGCAAC**ATCCAGTGGTACAAGCAGCGG CCTGGCGGACACCCTGTGTTTCTGATCCAG**CTGG TCAAGTCCGGCGAAGTG**AAGAAGCAGAAGCGG CTGACCTTCCAGTTCGGCGAGGCCAAGAAGAACA GCAGCCTGCACATCACCGCCACACAGACCACAG ATGTGGGCACCTACTTCT**TGCGCTGGCATCGGTA GCAGCAACACCGGTAAGCTCATCTTT**GGGCAA GGGACAACTTTACAAGTAAAACCAGacatccagaaccccgaccccgccgtgtaccagctgagggactccaagtccagcgacaagagcgtgtgtctgtttacggacttcgacagccagaccaacgtgagtcaaagcaaggacagcgacgtctacataacggataagaccgtgctggacatgcggagcatggacttcaagagcaacagcgccgtggcctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaacagcatcatccccgaggacaccttcttccccagcagcgacgtgccctgcgacgtgaaactggtggagaagtccttcgagacagacaccaatctgaactttcagaacctgctggtgatcgtgctgcggattctgctgctgaaagtggccggcttcaatctgctgatgaccctgcggctgtggagcagc	88

	Beta TRBV2/ TRBJ2- 7/MGTM modified TRBC	ATGGATACCTGGCTCGTGTGTTGGGCCATCTTTA GCCTGCTGAAGGCCGGACTGACCGAGCCTGAAGT GACCCAGACTCCAAGCCATCAAGTGACTCAGATG GGGCAAGAAGTCATTCTGCGTTGCGTGCCCATC**A** **GCAACCACCTGTAC**TTTTATTGGTATCGCCAGAT CCTGGGCCAGAAAGTGGAATTCCTGGTGTCC**TTC** **TACAACAATGAGATC**TCCGAGAAGTCCGAGATC TTCGACGACCAGTTCTCCGTGGAAAGACCCGACG GCAGCAACTTCACACTGAAGATCCGGTCTACCAA ACTTGAGGACTCCGCTATGTATTTT**TGTGCAATC** **ACAGGTCGCGTTTCATATGAGCAATATTTC**GG GCCGGGCACCAGGCTCACGGTCACAGAAgatctcaata aagtgttcccccctgaggttgcggtgtttgagccgtccaaagcggagattgcccca cacacagaaagcgactttggtttgtttggcgacaggcttttttccctgaccacgtaga gctgtcttggtgggtcaacggcaaggaggttcacagcggtgtgtcaacggatcc ccagcctctgaaagaacagcctgccctgaacgacagccggtactgcctgagctc cagactgagagtgtccgccaccttctggcagaaccccccggaaccacttcagatg ccaggtgcagttttacggcctgagcgagaacgacgagtggacccaggacagag ccaagcccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgc ggcatcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtac gaaatcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgc tgatggccatggtcaagcggaaggacttt	89
	Complete Beta+Alp ha ORF- Encoded Protein Sequence	ATGGATACCTGGCTCGTGTGTTGGGCCATCTTTA GCCTGCTGAAGGCCGGACTGACCGAGCCTGAAGT GACCCAGACTCCAAGCCATCAAGTGACTCAGATG GGGCAAGAAGTCATTCTGCGTTGCGTGCCCATCA GCAACCACCTGTACTTTTATTGGTATCGCCAGAT CCTGGGCCAGAAAGTGGAATTCCTGGTGTCCTTC TACAACAATGAGATCTCCGAGAAGTCCGAGATCT TCGACGACCAGTTCTCCGTGGAAAGACCCGACGG CAGCAACTTCACACTGAAGATCCGGTCTACCAAA CTTGAGGACTCCGCTATGTATTTTTGTGCAATCAC AGGTCGCGTTTCATATGAGCAATATTTCGGGCCG GGCACCAGGCTCACGGTCACAGAAgatctcaataaagtgtt ccccccctgaggttgcggtgtttgagccgtccaaagcggagattgcccacacaca gaaagcgactttggtttgtttggcgacaggcttttttccctgaccacgtagagctgtc ttggtgggtcaacggcaaggaggttcacagcggtgtgtcaacggatccccagcc tctgaaagaacagcctgccctgaacgacagccggtactgcctgagctccagact gagagtgtccgccaccttctggcagaaccccccggaaccacttcagatgccaggt gcagttttacggcctgagcgagaacgacgagtggacccaggacagagccaag cccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgcggcatc accagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtacgaaatc ctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgctgatgg ccatggtcaagcggaaggactttggcagcggc*agagccaaaaaggtccggga* *gcggtgcgacaaacttagcctgttgaaacaagccggcgacgttgaagagaa* *ccccggacct*ATGCTGCTGATCACCTCCATGCTGGTGC TGTGGATGCAGCTGAGCCAAGTGAACGGCCAGC AAGTGATGCAGATCCCTCAGTACCAGCACGTGCA AGAAGGCGAGGACTTCACCACCTACTGCAACAG CAGCACCACACTGAGCAACATCCAGTGGTACAA	90

		GCAGCGGCCTGGCGGACACCCTGTGTTTCTGATC CAGCTGGTCAAGTCCGGCGAAGTGAAGAAGCAG AAGCGGCTGACCTTCCAGTTCGGCGAGGCCAAGA AGAACAGCAGCCTGCACATCACCGCCACACAGA CCACAGATGTGGGCACCTACTTCTGCGCTGGCAT CGGTAGCAGCAACACCGGTAAGCTCATCTTTGGG CAAGGGACAACTTTACAAGTAAAACCAGACatccag aaccccgaccccgccgtgtaccagctgagggactccaagtccagcgacaaga gcgtgtgtctgtttacggacttcgacagccagaccaacgtgagtcaaagcaagg acagcgacgtctacataacggataagaccgtgctggacatgcggagcatggact tcaagagcaacagcgccgtggcctggtccaacaagagcgacttcgcctgcgcc aacgccttcaacaacagcatcatccccgaggacaccttcttccccagcagcgac gtgcccctgcgacgtgaaactggtggagaagtccttcgagacagacaccaatctg aactttcagaacctgctggtgatcgtgctgcggattctgctgctgaaagtggccgg cttcaatctgctgatgaccctgcggctgtggagcagc	
TSC-204-C0702 MAGEA1 TCR 32-41 MGTM codon optimized sequence (also known as "TCR41" or "41" or "TCR-204-C07")	Alpha TRAV27 /TRAJ52/ MGTM modified TRAC	ATGGTCCTGAAATTCTCCGTGTCCATTCTTTGGAT TCAGTTGGCATGGGTGAGCACCCAGCTGCTGGAG CAGAGCCCTCAGTTTCTTAGCATCCAAGAGGGAG AAAATCTCACTGTGTACTGCAACTCCTCA**AGTGT TTTCTCCAGC**CTTCAATGGTACAGACAGGAGCC TGGGGAAGGTCCTGTCCTCCTGGTGACA**GTTGTT ACTGGTGGAGAA**GTGAAGAAGCTGAAGAGACTT ACCTTTCAGTTTGGTGATGCAAGAAAGGACAGTT CTCTCCACATCACTGCAGCCCAGCCTGGTGATAC AGGCCTCTACCTC**TGTGCAGGAGATGAAAGTAT TAGCTATGGAAAGCTGACATTT**GGACAAGGGA CCATCTTGACTGTCCATCCAaacatccagaaccccgaccccg ccgtgtaccagctgagggactccaagtccagcgacaagagcgtgtgtctgtttac ggacttcgacagccagaccaacgtgagtcaaagcaaggacagcgacgtctaca taacggataagaccgtgctggacatgcggagcatggacttcaagagcaacagc gccgtggcctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaac agcatcatccccgaggacaccttcttccccagcagcgacgtgcccctgcgacgtg aaactggtggagaagtccttcgagacagacaccaatctgaactttcagaacctgc tggtgatcgtgctgcggattctgctgctgaaagtggccggcttcaatctgctgatg accctgcggctgtggagcagc	91
	Beta TRBV12 - 4/TRBJ1-4/MGTM modified TRBC1	ATGGGCTCCTGGACCCTCTGCTGTGTGTCCCTTTG CATCCTGGTTGCAAAGCACACAGATGCTGGAGTT ATCCAGTCACCCCGGCACGAGGTGACAGAGATG GGACAAGAAGTGACTCTGAGATGTAAACCAATT**T CAGGACATGACTAC**CTTTTCTGGTACAGACAGA CCATGATGCGGGGACTGGAGTTGCTCATTTAC**TT CAACAACAACGTTCCT**ATTGATGATTCAGGGAT GCCCGAGGATCGCTTCTCAGCTAAGATGCCTAAT GCATCATTCTCCACTCTGAAGATCCAGCCCTCAG AACCCAGGGACTCAGCTGTGTACTTC**TGTGCCA GCAGTTTTCTCGGCTGGAATGAAAAACTGTTC TTT**GGCAGTGGAACCCAGCTCTCTGTCTTGgaagatc tgaacaaggtgttccctccagaggtggccgtgttcgagccttctaaggccgagat cgcccacacacaaaaagccacccctcgtgtgcctggccaccggcttttttccccga ccacgtggaactgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtc	92

		aacggatccccagcctctgaaagaacagcctgccctgaacgacagccggtact gcctgagctccagactgagagtgtccgccaccttctggcagaacccccggaacc acttcagatgccaggtgcagttttacggcctgagcgagaacgacgagtggaccc aggacagagccaagcccgtgacacaaatcgtgtctgccgaagcctggggaag agccgattgcggcatcaccagcgcctcctatcaccagggcgtgctgagcgcca caatcctgtacgaaatcctgctgggcaaggccaccctgtacgccgtgctggtgtc tgctctggtgctgatggccatggtcaagcggaaggacttt	
	Complete Beta+Alpha ORF-Encoded Protein Sequence	ATGGGCTCCTGGACCCTCTGCTGTGTGTCCCTTTG CATCCTGGTTGCAAAGCACACAGATGCTGGAGTT ATCCAGTCACCCCGGCACGAGGTGACAGAGATG GGACAAGAAGTGACTCTGAGATGTAAACCAATT**T CAGGACATGACTAC**CTTTTCTGGTACAGACAGA CCATGATGCGGGGACTGGAGTTGCTCATTTAC**TT CAACAACAACGTTCCT**ATTGATGATTCAGGGAT GCCCGAGGATCGCTTCTCAGCTAAGATGCCTAAT GCATCATTCTCCACTCTGAAGATCCAGCCCTCAG AACCCAGGGACTCAGCTGTGTACTTC**TGTGCCA GCAGTTTTCTCGGCTGGAATGAAAAACTGTTC TTT**GGCAGTGGAACCCAGCTCTCTGTCTTGgaagatc tgaacaaggtgttccctccagaggtggccgtgttcgagccttctaaggccgagat cgcccacacacaaaaagccacccctcgtgtgcctggccaccggcttttttccccga ccacgtggaactgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtc aacggatccccagcctctgaaagaacagcctgccctgaacgacagccggtact gcctgagctccagactgagagtgtccgccaccttctggcagaacccccggaacc acttcagatgccaggtgcagttttacggcctgagcgagaacgacgagtggaccc aggacagagccaagcccgtgacacaaatcgtgtctgccgaagcctggggaag agccgattgcggcatcaccagcgcctcctatcaccagggcgtgctgagcgcca caatcctgtacgaaatcctgctgggcaaggccaccctgtacgccgtgctggtgtc tgctctggtgctgatggccatggtcaagcggaaggacttt*GGCAGCGGC AGAGCCAAAAGGTCCGGGAGCGGTGCGACAAACTT TAGCCTGTTGAAACAAGCCGGCGACGTTGAAGAGAA CCCCGGACCT*ATGGTCCTGAAATTCTCCGTGTCCA TTCTTTGGATTCAGTTGGCATGGGTGAGCACCCA GCTGCTGGAGCAGAGCCCTCAGTTTCTTAGCATC CAAGAGGGAGAAAATCTCACTGTGTACTGCAACT CCTCA**AGTGTTTTCTCCAGC**CTTCAATGGTACA GACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGT GACA**GTTGTTACTGGTGGAGAA**GTGAAGAAGC TGAAGAGACTTACCTTTCAGTTTGGTGATGCAAG AAAGGACAGTTCTCTCCACATCACTGCAGCCCAG CCTGGTGATACAGGCCTCTACCTC**TGTGCAGGA GATGAAAGTATTAGCTATGGAAAGCTGACATT T**GGACAAGGGACCATCTTGACTGTCCATCCAaacat ccagaaccccgaccccgccgtgtaccagctgagggactccaagtccagcgaca agagcgtgtgtctgtttacggacttcgacagccagaccaacgtgagtcaaagcaa ggacagcgacgtctacataacggataagaccgtgctggacatgcggagcatgg acttcaagagcaacagcgccgtggcctggtccaacaagagcgacttcgcctgc gccaacgccttcaacaacagcatcatccccgaggacaccttcttccccagcagc gacgtgccctgcgacgtgaaactggtggagaagtccttcgagacagacaccaat	93

		ctgaactttcagaacctgctggtgatcgtgctgcggattctgctgctgaaagtggc cggcttcaatctgctgatgaccctgcggctgtggagcagc	
TSC-203-A0201 PRAME-425-366 MGTM codon optimized sequence (also known as "366", "TCR 366", TCR expressed by "TSC-203-A02", and TCR expressed by "TSC-203-A0201")	Alpha TRAV38-2DV8/TRAJ50/MGTM modified TRAC	ATGGCCTGTCCTGGCTTCCTGTGGGCCCTTGTGAT CAGCACTTGCCTGGAATTCAGCATGGCTCAGACA GTCACCCAGTCTCAGCCCGAAATGAGCGTCCAAG AGGCTGAAACCGTGACTCTGTCTTGTACCTACGA C**ACCTCCGAGAGCGATTACTAC**CTCTTTTGGTA TAAGCAACCGCCGTCCAGGCAAATGATCCTCGTG ATCCGG**CAAGAAGCTTACAAACAGCAGAAT**GC TACCGAAAACCGGTTCTCCGTCAATTTTCAGAAA GCCGCTAAGAGCTTTAGCCTGAAAATCTCCGACT CTCAGCTCGGCGACGCTGCTATGTATTTC**TGTGC CTACCGCAAAACTTCTTACGATAAAGTCATTTT T**GGGCCAGGGACAAGCTTATCAGTCATTCCAAaca tccagaaccccgaccccgccgtgtaccagctgagggactccaagtccagcgac aagagcgtgtgtctgtttacggacttcgacagccagaccaacgtgagtcaaagca aggacagcgacgtctacataacggataagaccgtgctggacatgcggagcatg gacttcaagagcaacagcgccgtggcctggtccaacaagagcgacttcgcctg cgccaacgccttcaacaacagcatcatccccgaggacaccttcttccccagcag cgacgtgccctgcgacgtgaaactggtggagaagtccttcgagacagacacca atctgaactttcagaacctgctggtgatcgtgctgcggattctgctgctgaaagtgg ccggcttcaatctgctgatgaccctgcggctgtggagcagc	94
	Beta TRBV13/TRBJ2-1/MGTM modified TRBC	ATGCTGAGCCCCGACCTGCCTGACAGCGCTTGGA ATACCAGACTCCTGTGCAGAGTGATGCTGTGCCT GCTTGGAGCTGGAAGTGTGGCTGCTGGTGTCATT CAGTCCCCAAGGCACCTGATCAAAGAGAAGAGA GAGACAGCCACTCTGAAGTGCTACCCCATT**CCTA GACACGACACG**GTCTATTGGTATCAGCAAGGAC CTGGACAGGACCCTCAGTTCCTGATCAGC**TTCTA CGAGAAGATGCAG**AGCGACAAGGGCAGCATCC CCGACAGATTTTCTGCCCAGCAGTTCAGCGACTA CCACAGCGAGCTGAACATGAGCAGCCTGGAACT GGGCGATAGCGCCCTGTACTTC**TGTGCCTCTTCT TTCGCACGCCTGGAAGGTCGCGATAATGAACA ATTTTTTT**GGGCCAGGGACACGGCTCACCGTGCTA Gaagatctgaacaaggtgttcctccagaggtggccgtgttcgagccttctaagg ccgagatcgcccacacacaaaaagccacccctcgtgtgcctggccaccggctttt ccccgaccacgtggaactgtcttggtgggtcaacggcaaagaggtgcactccg gcgtgtcaacggatccccagcctctgaaagaacagcctgccctgaacgacagc cggtactgcctgagctccagactgagagtgtccgccaccttctggcagaacccc cggaaccacttcagatgccaggtgcagttttacggcctgagcgagaacgacgag tggacccaggacagagccaagccccgtgacacaaatcgtgtctgccgaagcctg gggaagagccgattgcggcatcaccagcgcctcctatcaccagggcgtgctga gcgccacaatcctgtacgaaatcctgctgggcaaggccaccctgtacgccgtgc tggtgtctgctctggtgctgatggccatggtcaagcggaaggacttt	95

	Complete Beta+Alpha ORF-Encoded Protein Sequence	ATGCTGAGCCCCGACCTGCCTGACAGCGCTTGGA ATACCAGACTCCTGTGCAGAGTGATGCTGTGCCT GCTTGGAGCTGGAAGTGTGGCTGCTGGTGTCATT CAGTCCCCAAGGCACCTGATCAAAGAGAAGAGA GAGACAGCCACTCTGAAGTGCTACCCCATT**CCTA** **GACACGACACG**GTCTATTGGTATCAGCAAGGAC CTGGACAGGACCCTCAGTTCCTGATCAGC**TTCTA** **CGAGAAGATGCAG**AGCGACAAGGGCAGCATCC CCGACAGATTTTCTGCCCAGCAGTTCAGCGACTA CCACAGCGAGCTGAACATGAGCAGCCTGGAACT GGGCGATAGCGCCCTGTACTTC**TGTGCCTCTTCT** **TTCGCACGCCTGGAAGGTCGCGATAATGAACA** **ATTTTTT**GGGCCAGGGACACGGCTCACCGTGCTA Gaagatctgaacaaggtgttcctccagaggtggccgtgttcgagccttctaagg ccgagatcgcccacacacaaaaagccacctcgtgtgcctggccaccggctttt ccccgaccacgtggaactgtcttggtgggtcaacggcaaagaggtgcactccg gcgtgtcaacggatccccagcctctgaaagaacagcctgccctgaacgacagc cggtactgcctgagctccagactgagagtgtccgccaccttctggcagaacccc cggaaccacttcagatgccaggtgcagttttacggcctgagcgagaacgacgag tggacccaggacagagccaagcccgtgacacaaatcgtgtctgccgaagcctg gggaagagccgattgcggcatcaccagcgcctcctatcaccagggcgtgctga gcgccacaatcctgtacgaaatcctgctgggcaaggccaccctgtacgccgtgc tggtgtctgctctggtgctgatggccatggtcaagcggaaggactttggcagcgg c*agagccaaaaggtccgggagcggt*GCGACAAACTTTAGCCTG *TTGAAACAAGCCGGCGACGTTGAAGAGAACCCCGG* *ACCT*ATGGCCTGTCCTGGCTTCCTGTGGGCCCTTG TGATCAGCACTTGCCTGGAATTCAGCATGGCTCA GACAGTCACCCAGTCTCAGCCCGAAATGAGCGTC CAAGAGGCTGAAACCGTGACTCTGTCTTGTACCT ACGAC**ACCTCCGAGAGCGATTACTAC**CTCTTTT GGTATAAGCAACCGCCGTCCAGGCAAATGATCCT CGTGATCCGG**CAAGAAGCTTACAAACAGCAGA** **AT**GCTACCGAAAACCGGTTCTCCGTCAATTTTCA GAAAGCCGCTAAGAGCTTTAGCCTGAAAATCTCC GACTCTCAGCTCGGCGACGCTGCTATGTATTTC**T** **GTGCCTACCGCAAAACTTCTTACGATAAAGTC** **ATTTTT**GGGCCAGGGACAAGCTTATCAGTCATTC CAAacatccagaaccccgaccccgccgtgtaccagctgagggactccaagt ccagcgacaagagcgtgtgtctgtttacggacttcgacagccagaccaacgtga gtcaaagcaaggacagcgacgtctacataacggataagaccgtgctggacatg cggagcatggacttcaagagcaacagcgccgtggcctggtccaacaagagcg acttcgcctgcgccaacgccttcaacaacagcatcatccccgaggacaccttctt ccccagcagcgacgtgccctgcgacgtgaaactggtggagaagtccttcgaga cagacaccaatctgaacttcagaacctgctggtgatcgtgctgcggattctgctg ctgaaagtggccggcttcaatctgctgatgaccctgcggctgtggagcagc	96

TSC-204-A0201 MAGEA1-278-1479 MGTM codon optimized sequence (also known as clone "MAGEA1-1479," "TCR 1479", "1479", TCR expressed by "TSC-204-A02", and TCR expressed by "TSC-204-A0201")	Alpha TRAV20/TRAJ26/MGTM modified TRAC	ATGGAAAAAATGCTCGAGTGCGCCTTCATCGTGC TTTGGCTGCAGCTCGGATGGCTGAGCGGAGAGGA TCAAGTGACACAGTCTCCCGAGGCTCTGAGGCTG CAAGAGGGCGAAAGCAGCTCCCTGAATTGCAGC TACACC**GTGTCTGGCCTGAGGGGC**CTGTTTTGG TACAGACAAGACCCTGGCAAGGGACCCGAGTTC CTGTTCACA**CTGTACTCTGCCGGCGAAGAA**AAA GAGAAAGAGCGCCTGAAAGCAACCCTGACCAAG AAAGAGAGCTTCCTGCACATCACAGCCCCTAAGC CAGAGGACAGCGCTACTTACCTG**TGTGCCGTTT** **CATACGGCCAGAATTTCGTTTTT**GGTCCCGGAA CCAGATTGTCCGTGCTGCCCTacatccagaaccccgaccccg ccgtgtaccagctgagggactccaagtccagcgacaagagcgtgtgtctgtttac ggacttcgacagccagaccaacgtgagtcaaagcaaggacagcgacgtctaca taacggataagaccgtgctggacatgcggagcatggacttcaagagcaacagc gccgtggcctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaac agcatcatccccgaggacaccttcttccccagcagcgacgtgcccctgcgacgtg aaactggtggagaagtccttcgagacagacaccaatctgaacttcagaacctgc tggtgatcgtgctgcggattctgctgctgaaagtggccggcttcaatctgctgatg accctgcggctgtggagcagc	97
	Beta TRBV5-8/TRBJ1-1/MGTM modified TRBC	ATGGGACCCAGGCTCCTCTTCTGGGCACTGCTTT GTCTCCTCGGAACAGGCCCAGTGGAGGCTGGAGT CACACAAAGTCCCACACACCTGATCAAAACGAG AGGACAGCAAGCGACTCTGAGATGCTCTCCTATC **TCTGGGCACACCAGT**GTGTACTGGTACCAACAG GCCCTGGGTCTGGGCCTCCAGTTCCTCCTTTGG**TA** **TGACGAGGGTGAAGAG**AGAAACAGAGGAAACT TCCCTCCTAGATTTTCAGGTCGCCAGTTCCCTAAT TATAGCTCTGAGCTGAATGTGAACGCCTTGGAGC TGGAGGACTCGGCCCTGTATCTC**TGTGCTTCCTC** **ACTTGGGCAATTGAACACAGAGGCATTCTTT**G GACAAGGCACCAGACTCACAGTTGTAGaagatctgaac aaggtgttcctccagaggtggccgtgttcgagccttctaaggccgagatcgccc acacacaaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgt ggaactgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacgga tccccagcctctgaaagaacagcctgccctgaacgacagccggtactgcctgag ctccagactgagagtgtccgccaccttctggcagaacccccggaaccacttcag atgccaggtgcagttttacggcctgagcgagaacgacgagtggacccaggaca gagccaagccccgtgacacaaatcgtgtctgccgaagcctggggaagagccgat tgcggcatcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctg tacgaaatcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctgg tgctgatggccatggtcaagcggaaggactttt	98
	Complete Beta+Alpha ORF-Encoded	ATGGGACCCAGGCTCCTCTTCTGGGCACTGCTTT GTCTCCTCGGAACAGGCCCAGTGGAGGCTGGAGT CACACAAAGTCCCACACACCTGATCAAAACGAG AGGACAGCAAGCGACTCTGAGATGCTCTCCTATC **TCTGGGCACACCAGT**GTGTACTGGTACCAACAG GCCCTGGGTCTGGGCCTCCAGTTCCTCCTTTGG**TA** **TGACGAGGGTGAAGAG**AGAAACAGAGGAAACT TCCCTCCTAGATTTTCAGGTCGCCAGTTCCCTAAT	99

	Protein Sequence	TATAGCTCTGAGCTGAATGTGAACGCCTTGGAGC TGGAGGACTCGGCCCTGTATCTC**TGTGCTTCCTC ACTTGGGCAATTGAACACAGAGGCATTCTTT**G GACAAGGCACCAGACTCACAGTTGTAGaagatctgaac aaggtgttccctccagaggtggccgtgttcgagccttctaaggccgagatcgccc acacacaaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgt ggaactgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacgga tccccagcctctgaaagaacagcctgccctgaacgacagccggtactgcctgag ctccagactgagagtgtccgccaccttctggcagaaccccccggaaccacttcag atgccaggtgcagttttacggcctgagcgagaacgacgagtggacccaggaca gagccaagccccgtgacacaaatcgtgtctgccgaagcctggggaagagccgat tgcggcatcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctg tacgaaatcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctgg tgctgatggccatggtcaagcggaaggactttggcagcggc*agagccaaaag gtccgggagcggtGCGACAAACTTTAGCCTGTTGAAACAA GCCGGCGACGTTGAAGAGAACCCCCGGACCT*ATGGA AAAAATGCTCGAGTGCGCCTTCATCGTGCTTTGG CTGCAGCTCGGATGGCTGAGCGGAGAGGATCAA GTGACACAGTCTCCCGAGGCTCTGAGGCTGCAAG AGGGCGAAAGCAGCTCCCTGAATTGCAGCTACAC C**GTGTCTGGCCTGAGGGGC**CTGTTTTGGTACAG ACAAGACCCTGGCAAGGGACCCGAGTTCCTGTTC ACA**CTGTACTCTGCCGGCGAAGAA**AAAGAGAA AGAGCGCCTGAAAGCAACCCTGACCAAGAAAGA GAGCTTCCTGCACATCACAGCCCCTAAGCCAGAG GACAGCGCTACTTACCTG**TGTGCCGTTTCATAC GGCCAGAATTTCGTTTTT**GGTCCCGGAACCAGA TTGTCCGTGCTGCCCTacatccagaaccccgaccccgccgtgtac cagctgagggactccaagtccagcgacaagagcgtgtgtctgtttacggacttcg acagccagaccaacgtgagtcaaagcaaggacagcgacgtctacataacggat aagaccgtgctggacatgcggagcatggacttcaagagcaacagcgccgtggc ctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaacagcatcat ccccgaggacaccttcttccccagcagcgacgtgcctgcgacgtgaaactggt ggagaagtccttcgagacagacaccaatctgaacttcagaacctgctggtgatc gtgctgcggattctgctgctgaaagtggccggcttcaatctgctgatgaccctgcg gctgtggagcagc	
TSC-204-A0101 MAGEA1-161-458 MGTM codon optimized sequence (also known as	Alpha TRAV21 /TRAJ47/ MGTM modified TRAC	ATGGAAACCCTGCTGGGACTGCTGATCCTGTGGC TGCAGCTTCAGTGGGTGTCCTCTAAGCAAGAAGT GACACAGATCCCTGCCGCACTGTCTGTGCCTGAG GGCGAAAACCTGGTGCTGAACTGCTCCTTCACC**G ACTCCGCCATCTACAAC**CTGCAGTGGTTCAGAC AGGACCCCGGCAAGGGACTGACAAGCCTGCTGC TC**ATTCAGAGCAGCCAGAGAGAG**CAGACCAGC GGCAGACTGAATGCCAGCCTGGATAAGTCCTCCG GCAGAAGCACCCTGTATATCGCCGCTTCTCAGCC AGGCGATAGCGCCACATACCTG**TGCGCTGTGCA ATATGGGAATAAACTCGTTTTC**GGCGCAGGAAC CATTCTGAGAGTCAAGTCCTacatccagaaccccgaccccgc cgtgtaccagctgagggactccaagtccagcgacaagagcgtgtgtctgtttacg gacttcgacagccagaccaacgtgagtcaaagcaaggacagcgacgtctacat	100

clone "MAGEA1-458", "TCR 458", "458", TCR expressed by "TSC-204-A01", TCR expressed by "TSC-204-A01:01", and TCR expressed by "TSC-204-A0101")		aacggataagaccgtgctggacatgcggagcatggacttcaagagcaacagcg ccgtggcctggtccaacaagagcgacttcgcctgcgccaacgccttcaacaaca gcatcatccccgaggacaccttcttccccagcagcgacgtgccctgcgacgtga aactggtggagaagtccttcgagacagacaccaatctgaacttttcagaacctgct ggtgatcgtgctgcggattctgctgctgaaagtggccggcttcaatctgctgatga ccctgcggctgtggagcagc	
	Beta TRBV5-4/TRBJ2-7/MGTM modified TRBC	ATGGGACCCGGCCTTCTGTGTTGGGCCCTGCTTT GCCTTCTCGGAGCTGGCTCTGTGGAAACCGGCGT GACACAGTCTCCTACACATCTGATCAAAACTCGC GGGCAACAAGTGACTCTGCGGTGTAGCTCTCAG**TCCGGCCACAACACA**GTTTCTTGGTATCAGCAAG CTCTCGGCCAGGGGCCACAGTTTATTTTCCAG**TACTACCGCGAGGAAGAG**AACGGCAGAGGCAACT TTCCACCTCGGTTTTCCGGACTGCAGTTTCCCAAC TACTCCTCCGAGCTGAACGTGAACGCCTTGGAGC TGGATGATAGTGCCCTCTACCTC**TGCGCTTCCAG CACAGACATCACCTATGAGCAGTACTTC**GGGC CGGGCACCAGGCTCACGGTCACAGaagatctgaacaaggt gttcctccagaggtggccgtgttcgagccttctaaggccgagatcgcccacaca caaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgtggaac tgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacggatcccc agcctctgaaagaacagcctgccctgaacgacagccggtactgcctgagctcca gactgagagtgtccgccaccttctggcagaaccccccggaaccacttcagatgcc aggtgcagttttacggcctgagcgagaacgacgagtggacccaggacagagcc aagcccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgcgg catcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtacga aatcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgctg atggccatggtcaagcggaaggacttt	101
	Complete Beta+Alpha ORF-Encoded Protein Sequence	ATGGGACCCGGCCTTCTGTGTTGGGCCCTGCTTT GCCTTCTCGGAGCTGGCTCTGTGGAAACCGGCGT GACACAGTCTCCTACACATCTGATCAAAACTCGC GGGCAACAAGTGACTCTGCGGTGTAGCTCTCAG**TCCGGCCACAACACA**GTTTCTTGGTATCAGCAAG CTCTCGGCCAGGGGCCACAGTTTATTTTCCAG**TACTACCGCGAGGAAGAG**AACGGCAGAGGCAACT TTCCACCTCGGTTTTCCGGACTGCAGTTTCCCAAC TACTCCTCCGAGCTGAACGTGAACGCCTTGGAGC TGGATGATAGTGCCCTCTACCTC**TGCGCTTCCAG CACAGACATCACCTATGAGCAGTACTTC**GGGC CGGGCACCAGGCTCACGGTCACAGaagatctgaacaaggt gttcctccagaggtggccgtgttcgagccttctaaggccgagatcgcccacaca caaaaagccaccctcgtgtgcctggccaccggcttttttccccgaccacgtggaac tgtcttggtgggtcaacggcaaagaggtgcactccggcgtgtcaacggatcccc agcctctgaaagaacagcctgccctgaacgacagccggtactgcctgagctcca	102

		gactgagagtgtccgccaccttctggcagaaccccccggaaccacttcagatgcc aggtgcagttttacggcctgagcgagaacgacgagtggacccaggacagagcc aagcccgtgacacaaatcgtgtctgccgaagcctggggaagagccgattgcgg catcaccagcgcctcctatcaccagggcgtgctgagcgccacaatcctgtacga aatcctgctgggcaaggccaccctgtacgccgtgctggtgtctgctctggtgctg atggccatggtcaagcggaaggactttggcagcggc*agagccaaaaggtccg ggagcggtGCGACAAACTTTAGCCTGTTGAAACAAGCC GGCGACGTTGAAGAGAACCCCGGACCT*ATGGAAAC CCTGCTGGGACTGCTGATCCTGTGGCTGCAGCTT CAGTGGGTGTCCTCTAAGCAAGAAGTGACACAG ATCCCTGCCGCACTGTCTGTGCCTGAGGGCGAAA ACCTGGTGCTGAACTGCTCCTTCACC**GACTCCGC CATCTACAAC**CTGCAGTGGTTCAGACAGGACCC CGGCAAGGGACTGACAAGCCTGCTGCTC**ATTCA GAGCAGCCAGAGAGAG**CAGACCAGCGGCAGAC TGAATGCCAGCCTGGATAAGTCCTCCGGCAGAAG CACCCTGTATATCGCCGCTTCTCAGCCAGGCGAT AGCGCCACATACCTG**TGCGCTGTGCAATATGGG AATAAACTCGTTTTC**GGCGCAGGAACCATTCTG AGAGTCAAGTCCTacatccagaaccccgaccccgccgtgtaccagc tgagggactccaagtccagcgacaagagcgtgtgtctgtttacggacttcgacag ccagaccaacgtgagtcaaagcaaggacagcgacgtctacataacggataaga ccgtgctggacatgcggagcatggacttcaagagcaacagcgccgtggcctgg tccaacaagagcgacttcgcctgcgccaacgccttcaacaacagcatcatcccc gaggacaccttcttccccagcagcgacgtgccctgcgacgtgaaactggtggag aagtccttcgagacagacaccaatctgaacttcagaacctgctggtgatcgtgct gcggattctgctgctgaaagtggccggcttcaatctgctgatgaccctgcggctgt ggagcagc	

[0283] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-201-B0702 has the sequence set forth in SEQ ID NO: 103, and further illustrated in FIG. 30.

[0284] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-200-A0201 has the sequence set forth in SEQ ID NO: 104, and further illustrated in FIG. 31.

[0285] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-204-C0702 has the sequence set forth in SEQ ID NO: 105, and further illustrated in FIG. 32.

[0286] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-203-A0201 has the sequence set forth in SEQ ID NO: 106, and further illustrated in FIG. 33.

[0287] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-204-A0201 has the sequence set forth in SEQ ID NO: 107, and further illustrated in FIG. 34.

[0288] In some embodiments, a vector encoded and/or expressed by engineered T cells designated TSC-204-A0101 has the sequence set forth in SEQ ID NO: 108, and further illustrated in FIG. 35.

Vector pNVVD187: TSC-201-B0702 npDNA Transposon: (SEQ ID NO: 103; FIG. 30)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
ATATTCTTTTTTTTCTTATAAAACTTAAAACCTTAGAGGCTATTTAAGTTGCTGAT
TTATATTAATTTTATTGTTCAAACATGAGAGCTTAGTACGTGAAACATGAGAGCT
TAGTACATTAGCCATGAGAGCTTAGTACATTAGCCATGAGGGTTTAGTTCATTAA
ACATGAGAGCTTAGTACATTAAACATGAGAGCTTAGTACATACTATCAACAGGTT
GAACTGCTGATCTGTACAGTAGAATTGGTAAAGAGAGTTGTGTAAAATATTGAGT
TCGCACATCTTGTTGTCTGATTATTGATTTTTGGCGAAACCATTTGATCATATGAC
AAGATGTGTATCTACCTTAACTTAATGATTTTGATAAAAATCATTAGGTACCAAT
TACATTGCTTGCAATTAACCCTTTAACGGTTATAAGGATCTAGATGAGATAGAAA
GATTTGGTTTTCGGATTTGTGTTACATAAGATGCCTAAAATAAAAATTGAGATTC
AATTTTTTTTTAAACTTTTTTTTTAATTGGTGGTAAGAATATTCCCTCTACCTGTTTGA
GAGTAATGAAATTGTAGTATGATTTTTCAACAAACTAAAAAAACAACATAAATCT
CACATAATAACTTTATTTCAATCACACAATTGAATACCAATAGGTTGACAGTACT
TACCAGCCTGCAGG**TGAAAGACCCCACCTGTAGGTTTGGCAAGTTAGCTTAA**
GTAACGCCATTTTGCAAGGCATGGAAAATACATAACTGAGAATAGAGAAGTT
CAGATCAAGGTTAGGAACAGAGAGACAGCAGAATATGGGCCAAACAGGATA
TCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCC
CAGATGCGGTCCCGCCCTCAGCAGTTTCTAGCGAACCATCAGATGTTTCCAG
GGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCA
GTTTGCTTCTTGCTTCTGTTTGTGTGCTTCTGCTCCCTGAGCTCAATAAAAG
AGCCCACAACCCCTCACTTGGTGGGCCAGTCCTCTGATAGACTGTGTCCCCT
GGATACCCGTACGGTACCGCTAGCGCCACC***ATGGGAACCTCTCTGCTGTGCTGGA***
TGGCCCTGTGTCTGCTGGGAGCCGATCATGCCGATACGGGAGTGTCCCAGGATCC
TCGGCACAAGATTACCAAGAGGGGCCAGAACGTGACCTTCCGCTGTGACCCTATCA
GCGAGCACAACCGGCTGTATTGGTACAGACAGACACTCGGCCAGGGGCCTGAATT
TCTCACATACTTCCAGAACGAAGCCCAGCTGGAAAAGTCCCGGCTGCTGAGCGATA
GATTTTCCGCCGAGAGGCCCAAGGGCTCCTTCAGCACTCTGGAAATTCAGCGCACC
GAGCAGGGCGACTCTGCCATGTATCTGTGCGCATCCTCTAAGGGCATTTTTGAGCA
ATATTTTGGGCCGGGCACCAGGCTCACGGTCACAGAAGATCTGAACAAGGTGTTCC
CTCCAGAGGTGGCCGTGTTCGAGCCTTCTAAGGCCGAGATCGCCCACACACAAAAA
GCCACCCTCGTGTGCCTGGCCACCGGCTTTTTCCCCGACCACGTGGAACTGTCTTG
GTGGGTCAACGGCAAAGAGGTGCACTCCGGCGTGTCAACGGATCCCCAGCCTCTG
AAAGAACAGCCTGCCCTGAACGACAGCCGGTACTGCCTGAGCTCCAGACTGAGAG
TGTCCGCCACCTTCTGGCAGAACCCCCGGAACCACTTCAGATGCCAGGTGCAGTTT
TACGGCCTGAGCGAGAACGACGAGTGGACCCAGGACAGAGCCAAGCCCGTGACAC
AAATCGTGTCTGCCGAAGCCTGGGGAAGAGCCGATTGCGGCATCACCAGCGCCTC
CTATCACCAGGGCGTGCTGAGCGCCACAATCCTGTACGAAATCCTGCTGGGCAAG
GCCACCCTGTACGCCGTGCTGGTGTCTGCTCTGGTGCTGATGGCCATGGTCAAGCG

*GAAGGACTTT*GGCAGCGGCAGAGCCAAAAGGTCCGGGAGCGGTGCGACAAACTT
TAGCCTGTTGAAACAAGCCGGCGACGTTGAAGAGAACCCCGGACCTATGAAGAG
AATCCTGGGCGCCCTGCTGGGACTGCTGTCTGCCCAAGTCTGTTGTGTGCG
GGGCATCCAGGTGGAACAGAGCCCTCCAGATCTGATCCTGCAAGAGGGCGC
CAACAGCACCCTGAGATGCAACTTCAGCGACTCCGTGAACAACCTGCAGTG
GTTCCACCAGAATCCTTGGGGCCAGCTGATCAACCTGTTCTACATCCCCAGC
GGCACCAAGCAGAACGGCAGACTGTCTGCTACCACCGTGGCCACCGAGAGA
TACAGCCTGCTGTACATCAGCAGCAGCCAGACCACCGATTCCGGCGTCTACT
TCTGCGCAGTGACTGGTACCGCTTCAAAACTGACATTTGGGACTGGAACAA
GACTTCAGGTCACGCTCGACATCCAGAACCCCGACCCCGCCGTGTACCAGC
TGAGGGACTCCAAGTCCAGCGACAAGAGCGTGTGTCTGTTTACGGACTTCG
ACAGCCAGACCAACGTGAGTCAAAGCAAGGACAGCGACGTCTACATAACGG
ATAAGACCGTGCTGGACATGCGGAGCATGGACTTCAAGAGCAACAGCGCCG
TGGCCTGGTCCAACAAGAGCGACTTCGCCTGCGCCAACGCCTTCAACAACA
GCATCATCCCCGAGGACACCTTCTTCCCCAGCAGCGACGTGCCCTGCGACG
TGAAACTGGTGGAGAAGTCCTTCGAGACAGACACCAATCTGAACTTTCAGAA
CCTGCTGGTGATCGTGCTGCGGATTCTGCTGCTGAAAGTGGCCGGCTTCAA
TCTGCTGATGACCCTGCGGCTGTGGAGCAGCAGGGCTAAGAGGTCCGGCAGC
GGAGCCACCAATTTTTCCCTGCTGAAACAGGCTGGTGACGTGGAAGAAAACCCT
GGCCCC*ATGGCGCTGCCCGTCACCGCGCTGCTGCTGCCCCTGGCGCTGCTGTTACAC*
GCCGCTCGGCCAGAGCTTCCCACCCAGGGCACATTCTCCAACGTGTCCACCAATGTGT
CGGGAGGCGGCGGATCGTCCCAGTTCAGAGTGTCCCCTCTGGACCGCACCTGGAACC
TGGGCGAGACCGTGGAGCTGAAATGTCAGGTCCTGCTGAGCAACCCGACCTCCGGGT
GCAGTTGGCTGTTCCAGCCGCGTGGTGCTGCCGCAAGCCCTACGTTCCTGCTTTACCT
GAGCCAGAACAAGCCCAAGGCGGCCGAGGGCCTGGACACCCAGAGATTCTCCGGCA
AGCGCCTGGGGGACACATTCGTGCTTACTTTGAGCGATTTCCGCAGAGAGAACGAGG
GCTACTATTTCTGTTCGGCGCTGAGCAATTCCATCATGTATTTCAGCCACTTTGTGCCA
GTGTTCCTGCCTGCCAAGCCTACCACAACACCAGCTCCCCGTCCCCCGACTCCGGCG
CCTACCATCGCGAGTCAACCGTTGAGCCTGAGGCCTGAGGCTTGTCGGCCCGCTGCG
GGGGGTGCCGTCCACACCAGGGGCCTCGACTTTGCGTGCGACATCTATATTTGGGCG
CCTCTGGCGGGTACCTGCGGGGTGCTGCTGCTGTCATTGGTGATTACCCTGTACTGCA
ATCACCGCAACCGCCGGCGGGTCTGTAAGTGCCCACGGCCTGTGGTCAAGTCCGGTG
*ACAAACCGTCGCTCTCGGCTCGCTACGTG*CGCGCTAAGCGCAGCGGTTCCGGGGCC
ACCAACTTTTCATTGCTGAAGCAGGCCGGTGATGTGGAGGAGAATCCAGGGCCC
ATGCGCCCCAGGCTTTGGCTCCTTCTTGCTGCTCAGCTCACTGTCTTGCATGGCAA
CTCCGTTCTGCAGCAGACTCCCGCCTACATCAAGGTGCAGACGAACAAGATGGT
GATGCTGTCATGCGAGGCCAAGATCTCTCTTTCAAATATGAGAATTTATTGGCTA
CGACAGCGCCAGGCCCCCTCCAGCGACAGCCACCACGAGTTCCTGGCGCTTTGG
GATTCTGCTAAAGGCACCATCCATGGAGAGGAGGTGGAACAGGAGAAGATAGCT
GTCTTCCGCGACGCATCCCGCTTCATCCTGAACCTGACCAGCGTGAAGCCGGAGG
ACAGCGGCATCTACTTCTGTATGATCGTTGGCTCCCCCGAGCTGACCTTCGGCAA
AGGCACCCAGCTGTCCGTGGTGGACTTCCTGCCCACCACAGCCCAGCCAACCAA
GAAATCCACCCTCAAGAAGCGCGTGTGCCGACTGCCCCGCCCTGAAACCCAGAA
GGGCCCTCTGTGCTCCCCCATCACCCTTGGACTGCTGGTGGCGGGAGTCCTGGTG
CTGCTCGTATCTCTGGGTGTCGCCATCCACCTGTGCTGCCGCCGCCGCCCGCCC
GCCTGAGGTTTATGAAACAGTTTTACAAGTGATAAATCGATGGAAGGGTGGCAT
CCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCCAGTGC
CCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCC
TTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAAGTTGGG
AAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGTGCAGTG

GCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTCTCCTGCC
TCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAATTT
TTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCTCCAACTC
CTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATTACAGGCG
TGAACCACTGCTCCCTTCCCTGTCCTTCTGATTACTAGTGGCTCCGGTGCCCGTCA
GTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGTGGGGAGGGGTCGG
CAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGT
CGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCA
GTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGGTAA
GTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGT
GCCTTGAATTACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAGCTTCGG
GTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGAGCCCCTTCGCCTC
GTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAATCTGGTG
GCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAATTTTT
GATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGCCA
AGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGGGCCCGT
GCGTCCCAGCGCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAGA
ATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGC
CGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCACCAGTTGC
GTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCAAAATGGAG
GACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGGAAAAGGG
CCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTC
CAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGG
GAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTA
GGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGAGTTTGGA
TCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTCCATTTCA
GGTGTCGTGAACTAGTCCAGTGTGGTGGAATTCTGCAGATATCACGGCTAGCGCC
ACCATGGGTCGGGGGCTGCTCAGGGGCCTGTGGCCGCTGCACATCGTCCTGTGGA
CGCGTATCGCCAGCACGATCCCACCGCACGTTCAGAAGTCGGTGAATAACGACA
TGATAGTCACTGACAACAACGGTGCAGTCAAGTTTCCACAACTGTGTAAATTTTG
TGATGTGAGATTTTCCACCTGTGACAACCAGAAATCCTGCATGAGCAACTGCAGC
ATCACCTCCATCTGTGAGAAGCCACAGGAAGTCTGTGTGGCTGTATGGAGAAAG
AATGACGAGAACATAACACTAGAGACAGTTTGCCATGACCCCAAGCTCCCCTAC
CATGACTTTATTCTGGAAGATGCTGCTTCTCCAAAGTGCATTATGAAGGAGAAGA
AAAAGCCTGGTGAGACTTTCTTCATGTGTTCCTGTAGCTCTGATGAGTGCAATGA
CAACATCATCTTCTCAGAAGAATATAACACCAGCAATCCTGACTTGTTGCTAGTC
ATATTTCAAGTGACAGGCATCAGCCTCCTGCCACCACTGGGAGTTGCCATATCTG
TCATCATCATCTTCTACTGCTACCGCGTGAACCGGCAGCAGAAGGCTAGTGGTTC
AGGCGCAACGAATTTCTCTTTGCTGAAGCAGGCTGGGGATGTCGAAGAAAATCC
GGGTCCAATGGTGGGCTCGCTCAACTGCATCGTAGCAGTCTCCCAGAATATGGGC
ATCGGGAAGAACGGTGATTTCCCGTGGCCCCCACTTCGCAACGAGAGCCGTTATT
TCCAAAGAATGACTACAACCTCCTCCGTGGAGGGTAAGCAGAACCTGGTCATCA
TGGGGAAGAAGACCTGGTTCTCTATCCCTGAAAAAAACCGCCCCCTGAAGGGCC
GCATCAACCTGGTGCTGAGCAGGGAACTCAAGGAGCCTCCTCAGGGCGCGCATT
TTCTGAGCCGCTCATTGGATGACGCTCTCAAACTGACCGAACAGCCGGAGCTAGC
CAACAAGGTGGACATGGTGTGGATCGTCGGAGGCTCCTCCGTGTACAAGGAGGC
CATGAATCACCCCGGCCACTTGAAGCTGTTCGTCACCCGGATCATGCAGGACTTC
GAGTCGGACACGTTCTTTCCAGAGATTGACCTGGAGAAGTACAAGCTGCTGCCCG
AGTACCCGGGAGTTCTTAGTGATGTGCAGGAGGAGAAAGGCATCAAGTACAAAT
TTGAGGTGTACGAGAAGAACGACTAACGGTCCGTCCTGACCAATGCTGGAGTTCT

TCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAG
CATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGT
CCAAACTCATCAATGTATCTTATCATGTCTGTATACAGGTTACCTCAGTCTCCTAG
GTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAGAACTTA
CCTTTTTTTCACCACTCTATTGCAAAGATATGTACCGATTTCTCTCGAAGTACAAAA
AACCGCTAGTTTTCAAATTCACCTCAAGACTTTGAAAAAAAATTGAATCTGTCAA
TGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTCAGGTCG
AAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTATTGGTGG
GAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGAGTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. Q tag is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-201-B0702 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD187 (*i.e.*, pNVVD187_TSC-201-B07_TCR-6_MSCV-TCR-6-CD8-EF1a-dnTGFβRII-DHFR as shown in FIG. 30 and SEQ ID NO: 103) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the MAGE-C2-derived peptide RAREFMELL presented on HLA-B*07:02), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector), cell washing to remove MTX, culture expansion, and culture wash, formulation, and cryopreservation.

Vector pNVVD160: TSC-200-A0201 npDNA Transposon: (SEQ ID NO: 104; FIG. 31)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
ATATTCTTTTTTTTCTTATAAAACTTAAAACCTTAGAGGCTATTTAAGTTGCTGAT
TTATATTAATTTTATTGTTCAAACATGAGAGCTTAGTACGTGAAACATGAGAGCT

TAGTACATTAGCCATGAGAGCTTAGTACATTAGCCATGAGGGTTTAGTTCATTAA
ACATGAGAGCTTAGTACATTAAACATGAGAGCTTAGTACATACTATCAACAGGTT
GAACTGCTGATCTGTACAGTAGAATTGGTAAAGAGAGTTGTGTAAAATATTGAGT
TCGCACATCTTGTTGTCTGATTATTGATTTTTGGCGAAACCATTTGATCATATGAC
AAGATGTGTATCTACCTTAACTTAATGATTTTGATAAAAATCATTAGGTACCAAT
TACATTGCTTGCAATTAACCCTTTAACGGTTATAAGGATCTAGATGAGATAGAAA
GATTTGGTTTTCGGATTTGTGTTACATAAGATGCCTAAAATAAAAATTGAGATTC
AATTTTTTTTTAAACTTTTTTTTTAATTGGTGGTAAGAATATTCCCTCTACCTGTTTGA
GAGTAATGAAATTGTAGTATGATTTTTCAACAAACTAAAAAAACAACATAAATCT
CACATAATAACTTTATTTCAATCACACAATTGAATACCAATAGGTTGACAGTACT
TACCAGCCTGCAGG**TGAAAGACCCCACCTGTAGGTTTGGCAAGTTAGCTTAA**
GTAACGCCATTTTGCAAGGCATGGAAAATACATAACTGAGAATAGAGAAGTT
CAGATCAAGGTTAGGAACAGAGAGACAGCAGAATATGGGCCAAACAGGATA
TCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCC
CAGATGCGGTCCCGCCCTCAGCAGTTTCTAGCGAACCATCAGATGTTTCCAG
GGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCA
GTTTGCTTCTTGCTTCTGTTTGTGTGCTTCTGCTCCCTGAGCTCAATAAAAG
AGCCCACAACCCCTCACTTGGTGGGCCAGTCCTCTGATAGACTGTGTCCCCT
GGATACCCGTACGGTACCGCTAGCGCCACC*ATGGATACCTGGCTCGTGTGTTGGG*
CCATCTTTAGCCTGCTGAAGGCCGGACTGACCGAGCCTGAAGTGACCCAGACTCCA
AGCCATCAAGTGACTCAGATGGGGCAAGAAGTCATTCTGCGTTGCGTGCCCATCAG
CAACCACCTGTACTTTTATTGGTATCGCCAGATCCTGGGCCAGAAAGTGGAATTCC
TGGTGTCCTTCTACAACAATGAGATCTCCGAGAAGTCCGAGATCTTCGACGACCAG
TTCTCCGTGGAAAGACCCGACGGCAGCAACTTCACACTGAAGATCCGGTCTACCAA
ACTTGAGGACTCCGCTATGTATTTTTGTGCAATCACAGGTCGCGTTTCATATGAGC
AATATTTCGGGCCGGGCACCAGGCTCACGGTCACAGAAGATCTCAATAAAGTGTTC
CCCCCTGAGGTTGCGGTGTTTGAGCCGTCCAAAGCGGAGATTGCCCACACACAGA
AAGCGACTTTGGTTTGTTTGGCGACAGGCTTTTTCCCTGACCACGTAGAGCTGTCT
TGGTGGGTCAACGGCAAGGAGGTTCACAGCGGTGTGTCAACGGATCCCCAGCCTC
TGAAAGAACAGCCTGCCCTGAACGACAGCCGGTACTGCCTGAGCTCCAGACTGAG
AGTGTCCGCCACCTTCTGGCAGAACCCCCGGAACCACTTCAGATGCCAGGTGCAGT
TTTACGGCCTGAGCGAGAACGACGAGTGGACCCAGGACAGAGCCAAGCCCGTGAC
ACAAATCGTGTCTGCCGAAGCCTGGGGAAGAGCCGATTGCGGCATCACCAGCGCC
TCCTATCACCAGGGCGTGCTGAGCGCCACAATCCTGTACGAAATCCTGCTGGGCAA
GGCCACCCTGTACGCCGTGCTGGTGTCTGCTCTGGTGCTGATGGCCATGGTCAAGC
*GGAAGGACTTT*GGCAGCGGCAGAGCCAAAAGGTCCGGGAGCGGTGCGACAAACT
TTAGCCTGTTGAAACAAGCCGGCGACGTTGAAGAGAACCCCGGACCT**ATGCTGC**
TGATCACCTCCATGCTGGTGCTGTGGATGCAGCTGAGCCAAGTGAACGGCC
AGCAAGTGATGCAGATCCCTCAGTACCAGCACGTGCAAGAAGGCGAGGACT
TCACCACCTACTGCAACAGCAGCACCACACTGAGCAACATCCAGTGGTACAA
GCAGCGGCCTGGCGGACACCCTGTGTTTCTGATCCAGCTGGTCAAGTCCGG
CGAAGTGAAGAAGCAGAAGCGGCTGACCTTCCAGTTCGGCGAGGCCAAGAA
GAACAGCAGCCTGCACATCACCGCCACACAGACCACAGATGTGGGCACCTA
CTTCTGCGCTGGCATCGGTAGCAGCAACACCGGTAAGCTCATCTTTGGGCA
AGGGACAACTTTACAAGTAAAACCAGACATCCAGAACCCCGACCCCGCCGT
GTACCAGCTGAGGGACTCCAAGTCCAGCGACAAGAGCGTGTGTCTGTTTAC
GGACTTCGACAGCCAGACCAACGTGAGTCAAAGCAAGGACAGCGACGTCTA
CATAACGGATAAGACCGTGCTGGACATGCGGAGCATGGACTTCAAGAGCAA
CAGCGCCGTGGCCTGGTCCAACAAGAGCGACTTCGCCTGCGCCAACGCCTT
CAACAACAGCATCATCCCCGAGGACACCTTCTTCCCCAGCAGCGACGTGCC

CTGCGACGTGAAACTGGTGGAGAAGTCCTTCGAGACAGACACCAATCTGAA
CTTTCAGAACCTGCTGGTGATCGTGCTGCGGATTCTGCTGCTGAAAGTGGCC
GGCTTCAATCTGCTGATGACCCTGCGGCTGTGGAGCAGCAGGGCTAAGAGGT
CCGGCAGCGGAGCCACCAATTTTTCCCTGCTGAAACAGGCTGGTGACGTGGAAG
AAAACCCTGGCCCC*ATGGCGCTGCCCGTCACCGCGCTGCTGCTGCCCCTGGCGCTG*
*CTGTTACACGCCGCTCGGCCA*GAGCTTCCCACCCAGGGCACATTCTCCAACGTGTCCA
*CCAATGTGTCG*GGAGGCGGCGGATCGTCCCAGTTCAGAGTGTCCCCTCTGGACCGCA
CCTGGAACCTGGGCGAGACCGTGGAGCTGAAATGTCAGGTCCTGCTGAGCAACCCGA
CCTCCGGGTGCAGTTGGCTGTTCCAGCCGCGTGGTGCTGCCGCAAGCCCTACGTTCC
TGCTTTACCTGAGCCAGAACAAGCCCAAGGCGGCCGAGGGCCTGGACACCCAGAGAT
TCTCCGGCAAGCGCCTGGGGGACACATTCGTGCTTACTTTGAGCGATTTCCGCAGAGA
GAACGAGGGCTACTATTTCTGTTCGGCGCTGAGCAATTCCATCATGTATTTCAGCCACT
TTGTGCCAGTGTTCCTGCCTGCCAAGCCTACCACAACACCAGCTCCCCGTCCCCCGAC
TCCGGCGCCTACCATCGCGAGTCAACCGTTGAGCCTGAGGCCTGAGGCTTGTCGGCC
CGCTGCGGGGGGTGCCGTCCACACCAGGGGCCTCGACTTTGCGTGCGACATCTATAT
TTGGGCGCCTCTGGCGGGTACCTGCGGGGTGCTGCTGCTGTCATTGGTGATTACCCT
GTACTGCAATCACCGCAACCGCCGGCGGGTCTGTAAGTGCCCACGGCCTGTGGTCAA
*GTCCGGTGACAAACCGTCGCTCTCGGCTCGCTACGTG*CGCGCTAAGCGCAGCGGTT
CCGGGGCCACCAACTTTTCATTGCTGAAGCAGGCCGGTGATGTGGAGGAGAATC
CAGGGCCCATGCGCCCCAGGCTTTGGCTCCTTCTTGCTGCTCAGCTCACTGTCTTG
CATGGCAACTCCGTTCTGCAGCAGACTCCCGCCTACATCAAGGTGCAGACGAAC
AAGATGGTGATGCTGTCATGCGAGGCCAAGATCTCTCTTTCAAATATGAGAATTT
ATTGGCTACGACAGCGCCAGGCCCCCTCCAGCGACAGCCACCACGAGTTCCTGG
CGCTTTGGGATTCTGCTAAAGGCACCATCCATGGAGAGGAGGTGGAACAGGAGA
AGATAGCTGTCTTCCGCGACGCATCCCGCTTCATCCTGAACCTGACCAGCGTGAA
GCCGGAGGACAGCGGCATCTACTTCTGTATGATCGTTGGCTCCCCCGAGCTGACC
TTCGGCAAAGGCACCCAGCTGTCCGTGGTGGACTTCCTGCCCACCACAGCCCAGC
CAACCAAGAAATCCACCCTCAAGAAGCGCGTGTGCCGACTGCCCCGCCCTGAAA
CCCAGAAGGGCCCTCTGTGCTCCCCCATCACCCTTGGACTGCTGGTGGCGGGAGT
CCTGGTGCTGCTCGTATCTCTGGGTGTCGCCATCCACCTGTGCTGCCGCCGCCGCC
GCGCCCGCCTGAGGTTTATGAAACAGTTTTACAAGTGATAAATCGATGGAAGGG
TGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCC
AGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAG
GTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAA
GTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGT
GCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTC
TCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAG
CTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCT
CCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATT
ACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTACTAGTGGCTCCGGTG
CCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGTGGGGAG
GGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAA
GTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATAT
AAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACA
CAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCC
CTTGCGTGCCTTGAATTACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAG
CTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGAGCCCCTT
CGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAAT
CTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAA
ATTTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCG

GGCCAAGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGG
GCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCA
CCGAGAATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGC
CTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCAC
CAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCAA
AATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGG
AAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGG
CGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGT
TGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACT
GAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGA
GTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTC
CATTTCAGGTGTCGTGAACTAGTCCAGTGTGGTGGAATTCTGCAGATATCACGGC
TAGCGCCACCATGGGTCGGGGGCTGCTCAGGGGCCTGTGGCCGCTGCACATCGTC
CTGTGGACGCGTATCGCCAGCACGATCCCACCGCACGTTCAGAAGTCGGTGAAT
AACGACATGATAGTCACTGACAACAACGGTGCAGTCAAGTTTCCACAACTGTGT
AAATTTTGTGATGTGAGATTTTCCACCTGTGACAACCAGAAATCCTGCATGAGCA
ACTGCAGCATCACCTCCATCTGTGAGAAGCCACAGGAAGTCTGTGTGGCTGTATG
GAGAAAGAATGACGAGAACATAACACTAGAGACAGTTTGCCATGACCCCAAGCT
CCCCTACCATGACTTTATTCTGGAAGATGCTGCTTCTCCAAAGTGCATTATGAAG
GAGAAGAAAAAGCCTGGTGAGACTTTCTTCATGTGTTCCTGTAGCTCTGATGAGT
GCAATGACAACATCATCTTCTCAGAAGAATATAACACCAGCAATCCTGACTTGTT
GCTAGTCATATTTCAAGTGACAGGCATCAGCCTCCTGCCACCACTGGGAGTTGCC
ATATCTGTCATCATCATCTTCTACTGCTACCGCGTGAACCGGCAGCAGAAGGCTA
GTGGTTCAGGCGCAACGAATTTCTCTTTGCTGAAGCAGGCTGGGGATGTCGAAGA
AAATCCGGGTCCAATGGTGGGCTCGCTCAACTGCATCGTAGCAGTCTCCCAGAAT
ATGGGCATCGGGAAGAACGGTGATTTCCCGTGGCCCCCACTTCGCAACGAGAGC
CGTTATTTCCAAAGAATGACTACAACCTCCTCCGTGGAGGGTAAGCAGAACCTGG
TCATCATGGGGAAGAAGACCTGGTTCTCTATCCCTGAAAAAAACCGCCCCCTGAA
GGGCCGCATCAACCTGGTGCTGAGCAGGGAACTCAAGGAGCCTCCTCAGGGCGC
GCATTTTCTGAGCCGCTCATTGGATGACGCTCTCAAACTGACCGAACAGCCGGAG
CTAGCCAACAAGGTGGACATGGTGTGGATCGTCGGAGGCTCCTCCGTGTACAAG
GAGGCCATGAATCACCCCGGCCACTTGAAGCTGTTCGTCACCCGGATCATGCAGG
ACTTCGAGTCGGACACGTTCTTTCCAGAGATTGACCTGGAGAAGTACAAGCTGCT
GCCCGAGTACCCGGGAGTTCTTAGTGATGTGCAGGAGGAGAAAGGCATCAAGTA
CAAATTTGAGGTGTACGAGAAGAACGACTAACGGTCCGTCCTGACCAATGCTGG
AGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAG
CAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTG
GTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGTATACAGGTTACCTCAGTC
TCCTAGGTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAG
AACTTACCTTTTTTCACCACTCTATTGCAAAGATATGTACCGATTTCTCTCGAAGT
ACAAAAAACCGCTAGTTTTCAAATTCACCTCAAGACTTTGAAAAAAAATTGAATC
TGTCAATGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTC
AGGTCGAAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTAT
TGGTGGGAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGA
GTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. Q tag is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-200-A0201 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD160 (*i.e.*, pNVVD160_TSC-200-A02_TCR-28_MSCV-TCR-28-CD8-EF1a-TGFR-DHFR as shown in FIG. 31 and SEQ ID NO: 104) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the HPV16 E7-derived peptide YMLDLQPET presented on HLA-A*02:01), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector), cell washing to remove MTX, culture expansion, and culture wash, formulation, and cryopreservation.

Vector PNVVD142: TSC-204-C0702 npDNA Transposon: (SEQ ID NO: 105; FIG. 32)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
ATATTCTTTTTTTTCTTATAAAACTTAAAACCTTAGAGGCTATTTAAGTTGCTGAT
TTATATTAATTTTATTGTTCAAACATGAGAGCTTAGTACGTGAAACATGAGAGCT
TAGTACATTAGCCATGAGAGCTTAGTACATTAGCCATGAGGGTTTAGTTCATTAA
ACATGAGAGCTTAGTACATTAAACATGAGAGCTTAGTACATACTATCAACAGGTT
GAACTGCTGATCTGTACAGTAGAATTGGTAAAGAGAGTTGTGTAAAATATTGAGT
TCGCACATCTTGTTGTCTGATTATTGATTTTTGGCGAAACCATTTGATCATATGAC
AAGATGTGTATCTACCTTAACTTAATGATTTTGATAAAAATCATTAGGTACCAAT
TACATTGCTTGCAATTAACCCTTTAACGGTTATAAGGATCTAGATGAGATAGAAA
GATTTGGTTTTCGGATTTGTGTTACATAAGATGCCTAAAATAAAAATTGAGATTC
AATTTTTTTTTAAACTTTTTTTTTAATTGGTGGTAAGAATATTCCCTCTACCTGTTTGA
GAGTAATGAAATTGTAGTATGATTTTTCAACAAACTAAAAAAACAACATAAATCT
CACATAATAACTTTATTTCAATCACACAATTGAATACCAATAGGTTGACAGTACT
TACCAGCCTGCAGG**TGAAAGACCCCACCTGTAGGTTTGGCAAGTTAGCTTAA**
GTAACGCCATTTTGCAAGGCATGGAAAATACATAACTGAGAATAGAGAAGTT
CAGATCAAGGTTAGGAACAGAGAGACAGCAGAATATGGGCCAAACAGGATA
TCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCC
CAGATGCGGTCCCGCCCTCAGCAGTTTCTAGCGAACCATCAGATGTTTCCAG

GGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCA
GTTTGCTTCTTGCTTCTGTTTGTGTGCTTCTGCTCCCTGAGCTCAATAAAAG
AGCCCACAACCCCTCACTTGGTGGGCCAGTCCTCTGATAGACTGTGTCCCCT
GGATACCCGTACGGTACCGCTAGCGCCACC*ATGGGCTCCTGGACCCTCTGCTGTG*
TGTCCCTTTGCATCCTGGTTGCAAAGCACACAGATGCTGGAGTTATCCAGTCACCC
CGGCACGAGGTGACAGAGATGGGACAAGAAGTGACTCTGAGATGTAAACCAATTT
CAGGACATGACTACCTTTTCTGGTACAGACAGACCATGATGCGGGGACTGGAGTTG
CTCATTTACTTCAACAACAACGTTCCTATTGATGATTCAGGGATGCCCGAGGATCG
CTTCTCAGCTAAGATGCCTAATGCATCATTCTCCACTCTGAAGATCCAGCCCTCAGA
ACCCAGGGACTCAGCTGTGTACTTCTGTGCCAGCAGTTTTCTCGGCTGGAATGAAA
AACTGTTCTTTGGCAGTGGAACCCAGCTCTCTGTCTTGGAAGATCTGAACAAGGTG
TTCCCTCCAGAGGTGGCCGTGTTCGAGCCTTCTAAGGCCGAGATCGCCCACACACA
AAAAGCCACCCTCGTGTGCCTGGCCACCGGCTTTTTCCCCGACCACGTGGAACTGT
CTTGGTGGGTCAACGGCAAAGAGGTGCACTCCGGCGTGTCAACGGATCCCCAGCC
TCTGAAAGAACAGCCTGCCCTGAACGACAGCCGGTACTGCCTGAGCTCCAGACTGA
GAGTGTCCGCCACCTTCTGGCAGAACCCCCGGAACCACTTCAGATGCCAGGTGCA
GTTTTACGGCCTGAGCGAGAACGACGAGTGGACCCAGGACAGAGCCAAGCCCGTG
ACACAAATCGTGTCTGCCGAAGCCTGGGGAAGAGCCGATTGCGGCATCACCAGCG
CCTCCTATCACCAGGGCGTGCTGAGCGCCACAATCCTGTACGAAATCCTGCTGGGC
AAGGCCACCCTGTACGCCGTGCTGGTGTCTGCTCTGGTGCTGATGGCCATGGTCAA
*GCGGAAGGACTTT*GGCAGCGGCAGAGCCAAAAGGTCCGGGAGCGGTGCGACAAA
CTTTAGCCTGTTGAAACAAGCCGGCGACGTTGAAGAGAACCCCGGACCT**ATGGT**
CCTGAAATTCTCCGTGTCCATTCTTTGGATTCAGTTGGCATGGGTGAGCACC
CAGCTGCTGGAGCAGAGCCCTCAGTTTCTTAGCATCCAAGAGGGAGAAAAT
CTCACTGTGTACTGCAACTCCTCAAGTGTTTTCTCCAGCCTTCAATGGTACA
GACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTTGTTACTGGTG
GAGAAGTGAAGAAGCTGAAGAGACTTACCTTTCAGTTTGGTGATGCAAGAA
AGGACAGTTCTCTCCACATCACTGCAGCCCAGCCTGGTGATACAGGCCTCTA
CCTCTGTGCAGGAGATGAAAGTATTAGCTATGGAAAGCTGACATTTGGACAA
GGGACCATCTTGACTGTCCATCCAAACATCCAGAACCCCGACCCCGCCGTGT
ACCAGCTGAGGGACTCCAAGTCCAGCGACAAGAGCGTGTGTCTGTTTACGG
ACTTCGACAGCCAGACCAACGTGAGTCAAAGCAAGGACAGCGACGTCTACA
TAACGGATAAGACCGTGCTGGACATGCGGAGCATGGACTTCAAGAGCAACA
GCGCCGTGGCCTGGTCCAACAAGAGCGACTTCGCCTGCGCCAACGCCTTCA
ACAACAGCATCATCCCCGAGGACACCTTCTTCCCCAGCAGCGACGTGCCCT
GCGACGTGAAACTGGTGGAGAAGTCCTTCGAGACAGACACCAATCTGAACT
TTCAGAACCTGCTGGTGATCGTGCTGCGGATTCTGCTGCTGAAAGTGGCCG
GCTTCAATCTGCTGATGACCCTGCGGCTGTGGAGCAGCAGGGCTAAGAGGTC
CGGCAGCGGAGCCACCAATTTTTCCCTGCTGAAACAGGCTGGTGACGTGGAAGA
AAACCCTGGCCCC*ATGGCGCTGCCCGTCACCGCGCTGCTGCTGCCCCTGGCGCTGC*
TGTTACACGCCGCTCGGCCA<u>*GAGCTTCCCACCCAGGGCACATTCTCCAACGTGTCCAC*</u>
<u>*CAATGTGTCG*</u>*GGAGGCGGCGGATCGTCCCAGTTCAGAGTGTCCCCTCTGGACCGCAC*
CTGGAACCTGGGCGAGACCGTGGAGCTGAAATGTCAGGTCCTGCTGAGCAACCCGAC
CTCCGGGTGCAGTTGGCTGTTCCAGCCGCGTGGTGCTGCCGCAAGCCCTACGTTCCT
GCTTTACCTGAGCCAGAACAAGCCCAAGGCGGCCGAGGGCCTGGACACCCAGAGATT
CTCCGGCAAGCGCCTGGGGGACACATTCGTGCTTACTTTGAGCGATTTCCGCAGAGAG
AACGAGGGCTACTATTTCTGTTCGGCGCTGAGCAATTCCATCATGTATTTCAGCCACTT
TGTGCCAGTGTTCCTGCCTGCCAAGCCTACCACAACACCAGCTCCCCGTCCCCCGACT
CCGGCGCCTACCATCGCGAGTCAACCGTTGAGCCTGAGGCCTGAGGCTTGTCGGCCC
GCTGCGGGGGGTGCCGTCCACACCAGGGGCCTCGACTTTGCGTGCGACATCTATATT

TGGGCGCCTCTGGCGGGTACCTGCGGGGTGCTGCTGCTGTCATTGGTGATTACCCTG
TACTGCAATCACCGCAACCGCCGGCGGGTCTGTAAGTGCCCACGGCCTGTGGTCAAG
*TCCGGTGACAAACCGTCGCTCTCGGCTCGCTACGTG*CGCGCTAAGCGCAGCGGTTC
CGGGGCCACCAACTTTTCATTGCTGAAGCAGGCCGGTGATGTGGAGGAGAATCC
AGGGCCCATGCGCCCCAGGCTTTGGCTCCTTCTTGCTGCTCAGCTCACTGTCTTGC
ATGGCAACTCCGTTCTGCAGCAGACTCCCGCCTACATCAAGGTGCAGACGAACA
AGATGGTGATGCTGTCATGCGAGGCCAAGATCTCTCTTTCAAATATGAGAATTTA
TTGGCTACGACAGCGCCAGGCCCCCTCCAGCGACAGCCACCACGAGTTCCTGGC
GCTTTGGGATTCTGCTAAAGGCACCATCCATGGAGAGGAGGTGGAACAGGAGAA
GATAGCTGTCTTCCGCGACGCATCCCGCTTCATCCTGAACCTGACCAGCGTGAAG
CCGGAGGACAGCGGCATCTACTTCTGTATGATCGTTGGCTCCCCCGAGCTGACCT
TCGGCAAAGGCACCCAGCTGTCCGTGGTGGACTTCCTGCCCACCACAGCCCAGCC
AACCAAGAAATCCACCCTCAAGAAGCGCGTGTGCCGACTGCCCCGCCCTGAAAC
CCAGAAGGGCCCTCTGTGCTCCCCCATCACCCTTGGACTGCTGGTGGCGGGAGTC
CTGGTGCTGCTCGTATCTCTGGGTGTCGCCATCCACCTGTGCTGCCGCCGCCGCC
GCGCCCCGCCTGAGGTTTATGAAACAGTTTTACAAGTGATAAATCGATGGAAGGG
TGGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCC
AGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAG
GTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAA
GTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGT
GCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTC
TCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAG
CTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCT
CCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATT
ACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTACTAGTGGCTCCGGTG
CCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGTGGGGAG
GGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAA
GTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATAT
AAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACA
CAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCC
CTTGCGTGCCTTGAATTACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAG
CTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGAGCCCCTT
CGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAAT
CTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAA
ATTTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCG
GGCCAAGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGG
GCCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCA
CCGAGAATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGC
CTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCAC
CAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCAA
AATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGG
AAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGG
CGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGT
TGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACT
GAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGA
GTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTC
CATTTCAGGTGTCGTGAACTAGTCCAGTGTGGTGGAATTCTGCAGATATCACGGC
TAGCGCCACCATGGGTCGGGGGCTGCTCAGGGGCCTGTGGCCGCTGCACATCGTC
CTGTGGACGCGTATCGCCAGCACGATCCCACCGCACGTTCAGAAGTCGGTGAAT
AACGACATGATAGTCACTGACAACAACGGTGCAGTCAAGTTTCCACAACTGTGT

AAATTTTGTGATGTGAGATTTTCCACCTGTGACAACCAGAAATCCTGCATGAGCA
ACTGCAGCATCACCTCCATCTGTGAGAAGCCACAGGAAGTCTGTGTGGCTGTATG
GAGAAAGAATGACGAGAACATAACACTAGAGACAGTTTGCCATGACCCCAAGCT
CCCCTACCATGACTTTATTCTGGAAGATGCTGCTTCTCCAAAGTGCATTATGAAG
GAGAAGAAAAAGCCTGGTGAGACTTTCTTCATGTGTTCCTGTAGCTCTGATGAGT
GCAATGACAACATCATCTTCTCAGAAGAATATAACACCAGCAATCCTGACTTGTT
GCTAGTCATATTTCAAGTGACAGGCATCAGCCTCCTGCCACCACTGGGAGTTGCC
ATATCTGTCATCATCATCTTCTACTGCTACCGCGTGAACCGGCAGCAGAAGGCTA
GTGGTTCAGGCGCAACGAATTTCTCTTTGCTGAAGCAGGCTGGGGATGTCGAAGA
AAATCCGGGTCCAATGGTGGGCTCGCTCAACTGCATCGTAGCAGTCTCCCAGAAT
ATGGGCATCGGGAAGAACGGTGATTTCCCGTGGCCCCCACTTCGCAACGAGAGC
CGTTATTTCCAAAGAATGACTACAACCTCCTCCGTGGAGGGTAAGCAGAACCTGG
TCATCATGGGGAAGAAGACCTGGTTCTCTATCCCTGAAAAAAACCGCCCCCTGAA
GGGCCGCATCAACCTGGTGCTGAGCAGGGAACTCAAGGAGCCTCCTCAGGGCGC
GCATTTTCTGAGCCGCTCATTGGATGACGCTCTCAAACTGACCGAACAGCCGGAG
CTAGCCAACAAGGTGGACATGGTGTGGATCGTCGGAGGCTCCTCCGTGTACAAG
GAGGCCATGAATCACCCCGGCCACTTGAAGCTGTTCGTCACCCGGATCATGCAGG
ACTTCGAGTCGGACACGTTCTTTCCAGAGATTGACCTGGAGAAGTACAAGCTGCT
GCCCGAGTACCCGGGAGTTCTTAGTGATGTGCAGGAGGAGAAAGGCATCAAGTA
CAAATTTGAGGTGTACGAGAAGAACGACTAACGGTCCGTCCTGACCAATGCTGG
AGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAG
CAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTG
GTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGTATACAGGTTACCTCAGTC
TCCTAGGTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAG
AACTTACCTTTTTTCACCACTCTATTGCAAAGATATGTACCGATTTCTCTCGAAGT
ACAAAAAACCGCTAGTTTTCAAATTCACCTCAAGACTTTGAAAAAAAATTGAATC
TGTCAATGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTC
AGGTCGAAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTAT
TGGTGGGAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGA
GTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. Q tag is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-204-C0702 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD142 (*i.e.*, pNVVD142_TSC-204-C07_TCR-41_MSCV-TCR-41-CD8-EF1a-TGFR-DHFR as shown in FIG. 32 and SEQ ID NO: 105) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the MAGE-A1-derived peptide VRFFFPSL presented on HLA-C*07:02), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to

facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector), cell washing to remove MTX, culture expansion, and culture wash, formulation, and cryopreservation.

Vector pNVVD134: TSC-203-A0201 npDNA Transposon: (SEQ ID NO: 106; FIG. 33)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
ATATTCTTTTTTTTCTTATAAAACTTAAAACCTTAGAGGCTATTTAAGTTGCTGAT
TTATATTAATTTTATTGTTCAAACATGAGAGCTTAGTACGTGAAACATGAGAGCT
TAGTACATTAGCCATGAGAGCTTAGTACATTAGCCATGAGGGTTTAGTTCATTAA
ACATGAGAGCTTAGTACATTAAACATGAGAGCTTAGTACATACTATCAACAGGTT
GAACTGCTGATCTGTACAGTAGAATTGGTAAAGAGAGTTGTGTAAAATATTGAGT
TCGCACATCTTGTTGTCTGATTATTGATTTTTGGCGAAACCATTTGATCATATGAC
AAGATGTGTATCTACCTTAACTTAATGATTTTGATAAAAATCATTAGGTACCAAT
TACATTGCTTGCAATTAACCCTTTAACGGTTATAAGGATCTAGATGAGATAGAAA
GATTTGGTTTTCGGATTTGTGTTACATAAGATGCCTAAAATAAAAATTGAGATTC
AATTTTTTTTTAAACTTTTTTTTTAATTGGTGGTAAGAATATTCCCTCTACCTGTTTGA
GAGTAATGAAATTGTAGTATGATTTTTCAACAAACTAAAAAAACAACATAAATCT
CACATAATAACTTTATTTCAATCACACAATTGAATACCAATAGGTTGACAGTACT
TACCAGCCTGCAGG**TGAAAGACCCCACCTGTAGGTTTGGCAAGTTAGCTTAA**
GTAACGCCATTTTGCAAGGCATGGAAAATACATAACTGAGAATAGAGAAGTT
CAGATCAAGGTTAGGAACAGAGAGACAGCAGAATATGGGCCAAACAGGATA
TCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCC
CAGATGCGGTCCCGCCCTCAGCAGTTTCTAGCGAACCATCAGATGTTTCCAG
GGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCA
GTTTGCTTCTTGCTTCTGTTTGTGTGCTTCTGCTCCCTGAGCTCAATAAAAG
AGCCCACAACCCCTCACTTGGTGGGCCAGTCCTCTGATAGACTGTGTCCCCT
GGATACCCGTACGGTACCGCTAGCGCCACC*ATGCTGAGCCCCGACCTGCCTGACA*
GCGCTTGGAATACCAGACTCCTGTGCAGAGTGATGCTGTGCCTGCTTGGAGCTGGA
AGTGTGGCTGCTGGTGTCATTCAGTCCCCAAGGCACCTGATCAAAGAGAAGAGAG
AGACAGCCACTCTGAAGTGCTACCCCATTCCTAGACACGACACGGTCTATTGGTAT
CAGCAAGGACCTGGACAGGACCCTCAGTTCCTGATCAGCTTCTACGAGAAGATGCA
GAGCGACAAGGGCAGCATCCCCGACAGATTTTCTGCCCAGCAGTTCAGCGACTACC
ACAGCGAGCTGAACATGAGCAGCCTGGAACTGGGCGATAGCGCCCTGTACTTCTG
TGCCTCTTCTTTCGCACGCCTGGAAGGTCGCGATAATGAACAATTTTTTGGGCCAG
GGACACGGCTCACCGTGCTAGAAGATCTGAACAAGGTGTTCCCTCCAGAGGTGGC
CGTGTTCGAGCCTTCTAAGGCCGAGATCGCCCACACACAAAAAGCCACCCTCGTGT
GCCTGGCCACCGGCTTTTTCCCCGACCACGTGGAACTGTCTTGGTGGGTCAACGGC

AAAGAGGTGCACTCCGGCGTGTCAACGGATCCCCAGCCTCTGAAAGAACAGCCTG
CCCTGAACGACAGCCGGTACTGCCTGAGCTCCAGACTGAGAGTGTCCGCCACCTTC
TGGCAGAACCCCCCGGAACCACTTCAGATGCCAGGTGCAGTTTTACGGCCTGAGCG
AGAACGACGAGTGGACCCAGGACAGAGCCAAGCCCGTGACACAAATCGTGTCTGC
CGAAGCCTGGGGAAGAGCCGATTGCGGCATCACCAGCGCCTCCTATCACCAGGGC
GTGCTGAGCGCCACAATCCTGTACGAAATCCTGCTGGGCAAGGCCACCCTGTACGC
*CGTGCTGGTGTCTGCTCTGGTGCTGATGGCCATGGTCAAGCGGAAGGACTTT*GGC
AGCGGCAGAGCCAAAAGGTCCGGGAGCGGTGCGACAAACTTTAGCCTGTTGAAA
CAAGCCGGCGACGTTGAAGAGAACCCCGGACCT**ATGGCCTGTCCTGGCTTCCT**
GTGGGCCCTTGTGATCAGCACTTGCCTGGAATTCAGCATGGCTCAGACAGT
CACCCAGTCTCAGCCCGAAATGAGCGTCCAAGAGGCTGAAACCGTGACTCT
GTCTTGTACCTACGACACCTCCGAGAGCGATTACTACCTCTTTTGGTATAAG
CAACCGCCGTCCAGGCAAATGATCCTCGTGATCCGGCAAGAAGCTTACAAA
CAGCAGAATGCTACCGAAAACCGGTTCTCCGTCAATTTTCAGAAAGCCGCTA
AGAGCTTTAGCCTGAAAATCTCCGACTCTCAGCTCGGCGACGCTGCTATGTA
TTTCTGTGCCTACCGCAAAACTTCTTACGATAAAGTCATTTTTGGGCCAGGG
ACAAGCTTATCAGTCATTCCAAACATCCAGAACCCCGACCCCGCCGTGTACC
AGCTGAGGGACTCCAAGTCCAGCGACAAGAGCGTGTGTCTGTTTACGGACT
TCGACAGCCAGACCAACGTGAGTCAAAGCAAGGACAGCGACGTCTACATAA
CGGATAAGACCGTGCTGGACATGCGGAGCATGGACTTCAAGAGCAACAGCG
CCGTGGCCTGGTCCAACAAGAGCGACTTCGCCTGCGCCAACGCCTTCAACA
ACAGCATCATCCCCGAGGACACCTTCTTCCCCAGCAGCGACGTGCCCTGCG
ACGTGAAACTGGTGGAGAAGTCCTTCGAGACAGACACCAATCTGAACTTTCA
GAACCTGCTGGTGATCGTGCTGCGGATTCTGCTGCTGAAAGTGGCCGGCTT
CAATCTGCTGATGACCCTGCGGCTGTGGAGCAGCAGGGCTAAGAGGTCCGGC
AGCGGAGCCACCAATTTTTCCCTGCTGAAACAGGCTGGTGACGTGGAAGAAAAC
CCTGGCCCC*ATGGCGCTGCCCGTCACCGCGCTGCTGCTGCCCCTGGCGCTGCTGTTA*
CACGCCGCTCGGCCA<u>*GAGCTTCCCACCCAGGGCACATTCTCCAACGTGTCCACCAAT*</u>
<u>*GTGTCG*</u>*GGAGGCGGCGGATCGTCCCAGTTCAGAGTGTCCCCTCTGGACCGCACCTGG*
AACCTGGGCGAGACCGTGGAGCTGAAATGTCAGGTCCTGCTGAGCAACCCGACCTCC
GGGTGCAGTTGGCTGTTCCAGCCGCGTGGTGCTGCCGCAAGCCCTACGTTCCTGCTT
TACCTGAGCCAGAACAAGCCCAAGGCGGCCGAGGGCCTGGACACCCAGAGATTCTCC
GGCAAGCGCCTGGGGGACACATTCGTGCTTACTTTGAGCGATTTCCGCAGAGAGAAC
GAGGGCTACTATTTCTGTTCGGCGCTGAGCAATTCCATCATGTATTTCAGCCACTTTGT
GCCAGTGTTCCTGCCTGCCAAGCCTACCACAACACCAGCTCCCCGTCCCCCGACTCC
GGCGCCTACCATCGCGAGTCAACCGTTGAGCCTGAGGCCTGAGGCTTGTCGGCCCGC
TGCGGGGGGTGCCGTCCACACCAGGGGCCTCGACTTTGCGTGCGACATCTATATTTG
GGCGCCTCTGGCGGGTACCTGCGGGGTGCTGCTGCTGTCATTGGTGATTACCCTGTA
CTGCAATCACCGCAACCGCCGGCGGGTCTGTAAGTGCCCACGGCCTGTGGTCAAGTC
*CGGTGACAAACCGTCGCTCTCGGCTCGCTACGTG*CGCGCTAAGCGCAGCGGTTCCG
GGGCCACCAACTTTTCATTGCTGAAGCAGGCCGGTGATGTGGAGGAGAATCCAG
GGCCC<u>ATGCGCCCCAGGCTTTGGCTCCTTCTTGCTGCTCAGCTCACTGTCTTGCAT</u>
<u>GGCAACTCCGTTCTGCAGCAGACTCCCGCCTACATCAAGGTGCAGACGAACAAG</u>
<u>ATGGTGATGCTGTCATGCGAGGCCAAGATCTCTCTTTCAAATATGAGAATTTATT</u>
<u>GGCTACGACAGCGCCAGGCCCCCTCCAGCGACAGCCACCACGAGTTCCTGGCGC</u>
<u>TTTGGGATTCTGCTAAAGGCACCATCCATGGAGAGGAGGTGGAACAGGAGAAGA</u>
<u>TAGCTGTCTTCCGCGACGCATCCCGCTTCATCCTGAACCTGACCAGCGTGAAGCC</u>
<u>GGAGGACAGCGGCATCTACTTCTGTATGATCGTTGGCTCCCCCGAGCTGACCTTC</u>
<u>GGCAAAGGCACCCAGCTGTCCGTGGTGGACTTCCTGCCCACCACAGCCCAGCCA</u>
<u>ACCAAGAAATCCACCCTCAAGAAGCGCGTGTGCCGACTGCCCCGCCCTGAAACC</u>

CAGAAGGGCCCTCTGTGCTCCCCCATCACCCTTGGACTGCTGGTGGCGGGAGTCC
TGGTGCTGCTCGTATCTCTGGGTGTCGCCATCCACCTGTGCTGCCGCCGCCGCCG
CGCCCGCCTGAGGTTTATGAAACAGTTTTACAAGTGATAAATCGATGGAAGGGT
GGCATCCCTGTGACCCCTCCCCAGTGCCTCTCCTGGCCCTGGAAGTTGCCACTCC
AGTGCCCACCAGCCTTGTCCTAATAAAATTAAGTTGCATCATTTTGTCTGACTAG
GTGTCCTTCTATAATATTATGGGGTGGAGGGGGGTGGTATGGAGCAAGGGGCAA
GTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGAACCAAGCTGGAGT
GCAGTGGCACAATCTTGGCTCACTGCAATCTCCGCCTCCTGGGTTCAAGCGATTC
TCCTGCCTCAGCCTCCCGAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAG
CTAATTTTTGTTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCAGGCTGGTCT
CCAACTCCTAATCTCAGGTGATCTACCCACCTTGGCCTCCCAAATTGCTGGGATT
ACAGGCGTGAACCACTGCTCCCTTCCCTGTCCTTCTGATTACTAGTGGCTCCGGTG
CCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGTGGGGAG
GGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAA
GTGATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATAT
AAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACA
CAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCC
CTTGCGTGCCTTGAATTACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAG
CTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGAGCCCCTT
CGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAAT
CTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAA
ATTTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCG
GGCCAAGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGG
GCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCA
CCGAGAATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGC
CTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCAC
CAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCAA
AATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGG
AAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGG
CGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGT
TGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACT
GAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGA
GTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTTTTCTTC
CATTTCAGGTGTCGTGAACTAGTCCAGTGTGGTGGAATTCTGCAGATATCACGGC
TAGCGCCACCATGGGTCGGGGGCTGCTCAGGGGCCTGTGGCCGCTGCACATCGTC
CTGTGGACGCGTATCGCCAGCACGATCCCACCGCACGTTCAGAAGTCGGTGAAT
AACGACATGATAGTCACTGACAACAACGGTGCAGTCAAGTTTCCACAACTGTGT
AAATTTTGTGATGTGAGATTTTCCACCTGTGACAACCAGAAATCCTGCATGAGCA
ACTGCAGCATCACCTCCATCTGTGAGAAGCCACAGGAAGTCTGTGTGGCTGTATG
GAGAAAGAATGACGAGAACATAACACTAGAGACAGTTTGCCATGACCCCAAGCT
CCCCTACCATGACTTTATTCTGGAAGATGCTGCTTCTCCAAAGTGCATTATGAAG
GAGAAGAAAAAGCCTGGTGAGACTTTCTTCATGTGTTCCTGTAGCTCTGATGAGT
GCAATGACAACATCATCTTCTCAGAAGAATATAACACCAGCAATCCTGACTTGTT
GCTAGTCATATTTCAAGTGACAGGCATCAGCCTCCTGCCACCACTGGGAGTTGCC
ATATCTGTCATCATCATCTTCTACTGCTACCGCGTGAACCGGCAGCAGAAGGCTA
GTGGTTCAGGCGCAACGAATTTCTCTTTGCTGAAGCAGGCTGGGGATGTCGAAGA
AAATCCGGGTCCAATGGTGGGCTCGCTCAACTGCATCGTAGCAGTCTCCCAGAAT
ATGGGCATCGGGAAGAACGGTGATTTCCCGTGGCCCCCACTTCGCAACGAGAGC
CGTTATTTCCAAAGAATGACTACAACCTCCTCCGTGGAGGGTAAGCAGAACCTGG
TCATCATGGGGAAGAAGACCTGGTTCTCTATCCCTGAAAAAAACCGCCCCCTGAA

GGGCCGCATCAACCTGGTGCTGAGCAGGGAACTCAAGGAGCCTCCTCAGGGCGC
GCATTTTCTGAGCCGCTCATTGGATGACGCTCTCAAACTGACCGAACAGCCGGAG
CTAGCCAACAAGGTGGACATGGTGTGGATCGTCGGAGGCTCCTCCGTGTACAAG
GAGGCCATGAATCACCCCGGCCACTTGAAGCTGTTCGTCACCCGGATCATGCAGG
ACTTCGAGTCGGACACGTTCTTTCCAGAGATTGACCTGGAGAAGTACAAGCTGCT
GCCCGAGTACCCGGGAGTTCTTAGTGATGTGCAGGAGGAGAAAGGCATCAAGTA
CAAATTTGAGGTGTACGAGAAGAACGACTAACGGTCCGTCCTGACCAATGCTGG
AGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAG
CAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTG
GTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGTATACAGGTTACCTCAGTC
TCCTAGGTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAG
AACTTACCTTTTTTTCACCACTCTATTGCAAAGATATGTACCGATTTCTCTCGAAGT
ACAAAAAACCGCTAGTTTTCAAATTCACCTCAAGACTTTGAAAAAAAATTGAATC
TGTCAATGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTC
AGGTCGAAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTAT
TGGTGGGAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGA
GTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. CD34-enrichment tag (Q tag) is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-203-A0201 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD134 (*i.e.*, pNVVD134_TCR_PRAME_366_MSCV-TCR-CD8-EF1a-TGFR-DHFR as shown in FIG. 33) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the PRAME-derived peptide SLLQHLIGL presented on HLA-A*02:01), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector),

cell washing to remove MTX, culture expansion, and culture wash, formulation, and cryopreservation.

Vector pNVVD136: TSC-204-A0201 npDNA Transposon: (SEQ ID NO: 107; FIG. 34)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
ATATTCTTTTTTTTCTTATAAAACTTAAAACCTTAGAGGCTATTTAAGTTGCTGAT
TTATATTAATTTTATTGTTCAAACATGAGAGCTTAGTACGTGAAACATGAGAGCT
TAGTACATTAGCCATGAGAGCTTAGTACATTAGCCATGAGGGTTTAGTTCATTAA
ACATGAGAGCTTAGTACATTAAACATGAGAGCTTAGTACATACTATCAACAGGTT
GAACTGCTGATCTGTACAGTAGAATTGGTAAAGAGAGTTGTGTAAAATATTGAGT
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AGCCCACAACCCCTCACTTGGTGGGCCAGTCCTCTGATAGACTGTGTCCCCT
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GCCCCGAGTACCCGGGAGTTCTTAGTGATGTGCAGGAGGAGAAAGGCATCAAGTA
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TCCTAGGTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAG
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TGTCAATGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTC
AGGTCGAAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTAT
TGGTGGGAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGA
GTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. CD34-enrichment tag (Q tag) is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-204-A0201 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD136 (*i.e.*, pNVVD136_TSC-204-A02_TCR-1479_MSCV-TCR1479-CD8-EF1a-TGFR-DHFR as shown in FIG. 34) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the MAGE-A1-derived peptide KVLEYVIKV presented on HLA-A*02:01), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector), cell washing to remove MTX, culture expansion, and cryopreservation.

Vector pNVVD236: TSC-204-A0101 npDNA Transposon: (SEQ ID NO: 108; FIG. 35)

GCTAGCTGGCTTGTTGTCCACAACCATTAAACCTTAAAAGCTTTAAAAGCCTTAT
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AGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAG
CAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTG
GTTTGTCCAAACTCATCAATGTATCTTATCATGTCTGTATACAGGTTACCTCAGTC
TCCTAGGTACGTCTTATATCTATGAAAAAACATTCAAAAGCACAACATCTAGAAG
AACTTACCTTTTTTCACCACTCTATTGCAAAGATATGTACCGATTTCTCTCGAAGT
ACAAAAAACCGCTAGTTTTCAAATTCACCTCAAGACTTTGAAAAAAAATTGAATC
TGTCAATGTCAAATAAAATCAGAAACAAATGTCATAATGTTACGTTAATGTTGTC
AGGTCGAAAAATAAAATTGCAAATAGAAATTTTGTTCCTTTTTTATTGGTTTTTAT
TGGTGGGAAAAATATTCCCTCTAACTGCAAAAGGGTTAATTATGTTAGAGGTAGA
GTCGAC

MSCV promoter is in bold. Beta chain is annotated using bold and italic text. Alpha chain is annotated using bold and underlined text. CD34-enrichment tag (Q tag) is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

TSC-204-A0101 TCR-T cells (*e.g.*, helper ($CD4^+$, now $CD8^+/CD4^+$) and cytotoxic ($CD8^+$) T cells) as described in the examples were engineered by transposon/transposase-mediated gene delivery of vector pNVVD236 (*i.e.*, pNVVD236_TSC-204-A01_TCR-458_MSCV-TCR-

458-CD8- EF1a-dnTGFβRII-DHFRdm as shown in Figure 35) (unless otherwise indicated), to express (1) a recombinant TCR (*e.g.*, the recombinant TCR specific to the MAGE-A1-derived peptide EADPTGHSY presented on HLA-A*01:01), (2) recombinant CD8α and CD8β co-receptors to maximize the efficacy of the therapeutic product, (3) a CD34-derived epitope tag fused on the N-terminus of CD8α to facilitate tracking of engineered cells *in vitro* and *in vivo*, (4) a mutated form of dihydrofolate reductase (DHFRdm) protein to facilitate enrichment of engineered cells during the manufacturing process, and (5) a dominant negative type II TGFβ receptor (DN-TGFβRII) to further address tumor microenvironment-mediated immune suppression. Such cells can be manufactured using known techniques and, for the present non-*in vitro* examples, were generated through isolation of peripheral blood mononuclear cells (PBMC) from a fresh apheresis product, delivery of transposase mRNA and vector transposon npDNA by electroporation, T cell activation and culture, engineered cell enrichment via addition of methotrexate (MTX) in culture medium (selective growth advantage of engineered cells conferred by DHFRdm expression from transposon vector), cell washing to remove MTX, culture expansion, and culture wash, formulation, and cryopreservation.

Pharmaceutical Compositions

[0289] In another aspect encompassed by the present invention, pharmaceutical compositions of TSC-201-B0702, TSC-200-A0201, TSC-204-C0702, TSC-203-A0201, TSC-204-A0201, or TSC-204-A0101 include a pharmaceutically acceptable carrier, diluent, or excipient. Methods for producing and formulating engineered TCR T cells are known in the art. Exemplary formulation components and excipients can include, for example, CryoStor®, Plasma-Lyte and HSA (human serum albumin), which can be included to promote product quality and stability during cryopreservation, long-term storage (*e.g.*, under liquid nitrogen), freezing and/or thawing, and/or clinical use.

[0290] In various embodiments, at least 40% of cells of a dose (*e.g.*, a first dose and/or a second dose) of engineered T cells express a marker, optionally wherein the marker is Qtag-CD34 (*e.g.*, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%). In various embodiments, the percentage of cells of a dose

of engineered T cells that express a marker, optionally wherein the marker is Qtag-CD34 of interest, is between 40% and 45%, 40% and 50%, 40% and 55%, 40% and 60%, 40% and 65%, 40% and 70%, 40% and 75%, 40% and 80%, 40% and 85%, 40% and 90%, 40% and 95%, and 40% and 100%. In various embodiments, engineered cells are selected by purification, such as chemical selection.

Treatment of Melanoma, Non-Small Cell Lung Cancer (NSCLC), Head and Neck Cancer, Sarcoma, Thyroid Cancer, Cervical Cancer, Ovarian Cancer, Anal Cancer, Genital Cancer, or Anogenital Cancer

[0291] In an aspect encompassed by the present disclosure, provided herein are methods for treating patients with melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer are eligible.

[0292] For example, in some embodiments, subjects may be treated according to one of the following:

Monotherapy (singleplex):

1. TSC-204-A0201 targeting MAGE-A1 on HLA-A*02:01;
2. TSC-204-C0702 targeting MAGE-A1 on HLA-C*07:02;
3. TSC-200-A0201 targeting HPV16 E7 on HLA-A*02:01;
4. TSC-203-A0201 targeting PRAME on HLA-A*02:01;
5. TSC-204-A0101 targeting MAGE-A1 on HLA-A*01:01;
6. TSC-201-B0702 targeting MAGE-C2 on HLA-B*07:02;

T-Plex Combination (multiplex):

7. TSC-204-A0201 + TSC-204-C0702;
8. TSC-204-A0201 + TSC-200-A0201;
9. TSC-204-A0201 + TSC-203-A0201;
10. TSC-204-A0201 + TSC-204-A0101;
11. TSC-204-A0201 + TSC-201-B0702;
12. TSC-204-C0702 + TSC-200-A0201;
13. TSC-204-C0702 + TSC-203-A0201;
14. TSC-204-C0702 + TSC-204-A0101;
15. TSC-204-C0702 + TSC-201-B0702;

16. TSC-200-A0201 + TSC-203-A0201;
17. TSC-200-A0201 + TSC-204-A0101;
18. TSC-200-A0201 + TSC-201-B0702;
19. TSC-203-A0201 + TSC-204-A0101;
20. TSC-203-A0201 + TSC-201-B0702;
21. TSC-204-A0101 + TSC-201-B0702

[0293] Subjects can be selected according to certain criteria (**FIGS. 22, 25**). In particular, subjects can be screened during standard-of-care or subsequent therapy. Screening includes germline HLA typing and archival tumor testing for antigens and HLA LOH any time during cancer treatment. Subjects must be matched to any TCR administered thereto, to ensure that the subject's tumor cells express both the antigen of a given TCR and the HLA from which that TCR's antigen is presented, to support that the subject will respond to the engineered TCR therapy. Germline HLA analysis can be performed to determine suitability of TCR products, as TCR products are HLA specific. Archival tumor samples can also be evaluated for tumor expression of target antigens by immunohistochemistry (IHC) and loss of HLA heterozygosity (HLA LOH). Multiplex TCR T cell therapy can overcome HLA LOH and solid tumor cell heterogeneity (**FIG. 24**).

[0294] Treatment can involve 1 or 2 doses or rounds of TCR-T cell therapy after lymphodepletion. For subjects meeting inclusion criteria (*e.g.,* expression of a target antigen and presenting HLA targeted by a TCR of the present Example), if disease progresses despite at least a first line standard-of-care therapy regimen (and optionally despite a second line regimen), the subject can undergo one round of leukapheresis to isolate PBMCs for production of engineered T cells for single or multiplex TCR T cell production (**FIG. 22**). The subject can then undergo lymphodepletion prior to administration of TCR T cells, about 25 days vein-to-vein time after leukapheresis (**FIG. 22**). Subjects can also receive fludarabine and/or cyclophosphamide. Subjects can not receive IL-2. For multiple dose trial arms, a second round of therapy will be administered 28 days after the first round of therapy (**FIG. 22**).

[0295] In some embodiments, a subject is administered a single dose of TCR T cells expressing one particular TCR. In some embodiments, a subject is administered two doses of TCR T cells encoding the same one particular TCR. In some embodiments, a subject is administered a single round of TCR T cell therapy that includes two separately administered TCR T cell products or populations, each expressing a particular TCR. In some

embodiments, a subject is administered two rounds of TCR T cell therapy, each round including administration of two separate TCR T cell products or populations, each expressing a particular TCR. In some embodiments, each administration of TCR T cells encoding the same TCR are at the same dosing level. In some embodiments, each administration of TCR T cells encoding the same TCR are at different dosing levels, *e.g.*, where the second dose is at a higher dosing level or where the second dose is at a lower dosing level. In some embodiments, two TCR T cell products or populations administered to a subject on the same day are administered at the same dosing level. In some embodiments, two TCR T cell products or populations administered to a subject on the same day are administered at different dosing levels.

[0296] A dose escalation scheme provides a rapid path to multiplexed TCR-T. Initially, each of the six TCR T cell types of the present disclosure can be administered to subjects at two dose levels: Dosage Level 1 (DL1; 0.5x10^9 engineered T cells) and Dosage Level 2 (DL2; 2x10^9 engineered T cells) (**FIG. 21**). Pairs of T cell products that individually clear DL2 without excessive toxicity can be multiplexed (**FIG. 21**). In some therapeutic regimens, subjects will receive one dose of a T cell product, or of each of two T cell products at a first time point (*e.g.*, sequentially administered), followed by a second dose of the T cell product, or of each of the two T cell products (*e.g.*, sequentially administered), at a second time point (*e.g.*, about 28 days after first time point), for a total of two or four doses, respectively (**FIG. 21**). In multiplexed regimens with two T cell products, i) each of the four doses will be a dose of about 2x10^9 engineered T cells, which regimen is referred to as DL3, or (ii) each of the four doses will be a dose of about 5x10^9 engineered T cells), which regimen is referred to as DL4 (**FIG. 21**). In another regimen, subjects will receive two doses of a single T cell product, where the doses include a first dose of about 4x10^9 or about 1x10^10 engineered T cells at a first time point and a second dose at the same level as the first dose (about 4x10^9 or about 1x10^10 engineered T cells, respectively) at a second time point (*e.g.*, about 28 days after first time point),

[0297] For treatment according to the present disclosure (*e.g.*, by administration of cells expressing a TCR disclosed herein), in some embodiments, inclusion and exclusion criteria can be applied to all subjects. In some embodiments, treatment according to the present disclosure can be limited to subjects having a diagnosis of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer, head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, ovarian cancer, cervical cancer, anal cancer, genital cancer, or anogenital cancer. In some embodiments, treatment

according to the present disclosure can be limited to subjects at least 18 years of age. Treatment according to the present disclosure can be limited to subjects for whom standard of care therapy (*e.g.*, including any relevant targeted therapy or checkpoint inhibitor, such as wherein the targeted therapy or checkpoint inhibitor therapy is relevant for the particular disease afflicting the subject) has failed. In some embodiments, treatment according to the present disclosure can be limited to subjects that encode and/or express (*e.g.*, tumor cells express) at least one HLA of a pMHC complex recognized by a TCR of the present disclosure, where the subject does not display LOH of that HLA in their tumor. In some embodiments, treatment according to the present disclosure can be limited to subjects whose tumor cells express the target antigen recognized by a TCR of the present disclosure, as well as the HLA of the pMHC complex recognized by that TCR. In some embodiments, treatment according to the present disclosure can be limited to subjects whose tumor cells have a reasonable chance of expressing the target antigen recognized by a TCR of the present disclosure, as well as the HLA of the pMHC complex recognized by that TCR.

[0298] In some embodiments, treatment according to the present disclosure can be limited to subjects that demonstrate at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. RECIST v.1.1 is a system for assessing tumor burden that can be used in clinical evaluation of cancer therapeutics. RECIST was initially published in 2000 and updated in 2009, and has been commonly considered in the assessment of treatment outcomes. RECIST v1.1 is available online, *e.g.*, available on the World Wide Web at recist.eortc.org/recist-1-1-2/, which is incorporated herein by reference.

[0299] In some embodiments, treatment according to the present disclosure can be limited to subjects that demonstrate Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1 (*e.g.*, at any time during screening) with adequate organ function. ECOG-PS is framework for measuring how disease impacts a subject's daily living abilities, which can be referred to by physicians and researchers as performance status. ECOG-PS is commonly considered in the study of cancer therapy and is available online, *e.g.*, available on the World Wide Web at ecog-acrin.org/resources/ecog-performance-status/, which is incorporated herein by reference.

[0300] In some embodiments, subjects can be excluded from treatment according to the present disclosure if they demonstrate CNS metastases that are symptomatic or in need of treatment. In some embodiments, subjects can be excluded from treatment according to the present disclosure if they demonstrate carcinomatous meningitis. In some embodiments,

subjects can be excluded from treatment according to the present disclosure if they demonstrate major cardiac pathology or stroke/transient ischemic attack (TIA) (*e.g.*, within 12 months of study enrollment). In some embodiments, subjects can be excluded from treatment according to the present disclosure if they receive systemic corticosteroids (*e.g.*, receive systemic corticosteroids within 7 days of enrollment). In some embodiments, subjects can be excluded from treatment according to the present disclosure if they are concurrently receiving a therapy for which they have not yet met washout requirements. In some embodiments, subjects can be excluded from treatment according to the present disclosure if they demonstrate hypersensitivity to fludarabine, hypersensitivity to cyclophosphamide, or hypersensitivity to other agents (*e.g.*, excipients) that are administered as part of treatment according to the present disclosure. In some embodiments, subjects can be excluded from treatment according to the present disclosure if they encode and/or express (*e.g.*, tumor cells express) an HLA type that may interfere with or reduce efficacy of targeting pMHCs that include another HLA type and are targeted by a TCR of the present disclosure that is to be administered to the subject.

[0301] Similarly, as described above, in some embodiments, subjects can be included from treatment according to the present disclosure and/or excluded from treatment according to the present disclosure based on one or more of the following inclusion criteria or exclusion criteria, respectively:

Inclusion Criteria:

1. At least 18 years;
2. Locally advanced (unresectable) or metastatic solid tumor for which there are no available curative treatment options, after failure of the standard of care systemic therapies for that particular indication;
3. Solid tumors, including but not limited to non-nasopharyngeal head and neck cancer, non-small cell lung cancer, cutaneous melanoma, uveal melanoma, sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer and genital cancers. Other tumor types may be permitted if approved by TScan;
4. Participants must express one of the following HLA types, such as assessed by a qualified genomics assay in screening study TSCAN-003;
   HLA-B*07:02 HLA-A*01:01 HLA-C*07:02 HLA-A*02:01;

5. Tumor must express one or more of the following: MAGE-A1, MAGE-C2, PRAME and HPV16-E7, such as assessed in the last 8 months in, for example, a screening study such as TSCAN-003 (NCT05812027);
6. Eastern Cooperative Oncology Group (ECOG) Performance status 0-1 at screening;
7. Participants must be able to understand and be willing to give informed consent; decision-impaired adults may consent with their legally authorized representative;
8. At least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; and/or
9. Adequate bone marrow and organ function.

Exclusion Criteria:

1. Medical or psychological conditions that would make the participant unsuitable candidate for cell therapy at the discretion of a physician, such as a principal investigator;
2. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, cardiac arrhythmia requiring antiarrhythmic or procedure, or other clinically significant cardiac disease within 12 months of enrollment;
3. History of stroke or transient ischemic attack (TIA) within 12 months of enrollment;
4. Systemic corticosteroid therapy >10 mg of prednisone daily or equivalent within 7 days of enrollment;
5. History of severe hypersensitivity to fludarabine or cyclophosphamide or study product excipients including human serum albumin, Cryostor® (DMSO or Dextran 40), or Plasma-Lyte;
6. Untreated or symptomatic central nervous system (CNS) metastases or cytology proven carcinomatous meningitis;
7. Concurrent receipt of another anti-cancer therapy;
8. Presence of fungal, bacterial, viral, or other infection requiring anti-microbials for management;
9. Tumors that have HLA LOH using a central lab clinical trial assay of HLAs addressed by the monotherapy (singleplex) and/or T-Plex (multiplex) combination TCR-Ts in the protocol and have no available TCR-T options for intact HLAs in the participant's tumor; and/or
10. Participants who regularly require supplemental oxygen.

EXAMPLES

[0302] The present Examples support the use of a TCR of Table 1 in the treatment of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer. The present Examples relate to a Phase I clinical trial relating to administration of TCRs of the present disclosure to human subjects as a multiplexed, enhanced T cell receptor-engineered T cell therapy (TCR-T) for melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer (see also **FIGS. 27-29**).

Example 1

[0303] Cells genetically reprogrammed to express engineered TCRs engage natural mechanisms used by the human body to fight cancer. TCR T cells can target both intra-cellular and extra-cellular protein targets. TCR T cells can also augment endogenous patient T cell repertoires, which are often inadequate to eliminate cancer cells. While first generation T cells have had some success in the elimination of cancer cells, there are challenges relating to tumor heterogeneity, antigen selection, coverage of patients from all genetic background (*e.g.*, all HLA genotypes), duration of response, and T cell persistence. Solid tumors (*e.g.*, melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer) are also difficult to treat due to heterogeneity (**FIGS. 1, 18**). Solid tumors can fail to respond to a TCR T cell therapy, or become resistant to the therapy, if the target tumor cells are missing the HLA required to present TCR target or evolve to reduce expression of that HLA. The loss of HLA genes can render tumors resistant to immunotherapy. HLA loss of heterozygosity (LOH) has been estimated to occur in up to 40% of solid tumors (see, *e.g.*, **FIG. 23**). HLA loss of heterozygosity (LOH) often occurs through loss of one HLA haplotype on chromosome 6 (although cancer cells never lose all of their HLAs). Many TCR T cell therapies targeting single antigens have had limited response rates (30-50%) and/or short duration of response (*e.g.*, 3-4 months), which can be due to factors including tumor target heterogeneity and HLA LOH, an immuno-suppressive tumor microenvironment, and/or poor TCR-T persistence and/or TCR-T exhaustion.

[0304] The present Example includes solutions that improve coverage, response, T cell persistence, and risk of relapse. These solutions include therapies that use multiple populations of TCR T cells each engineered to express a distinct TCR (referred to herein as "multiplexing"), and engineering of the therapeutic T cells to express both (i) CD8α and CD8β and (ii) DN-TGFβRII. Prospective screening for HLA LOH allows for selection of TCR-Ts targeting intact HLAs only. Administration of multiplex TCR-Ts, with targets on HLAs from both haplotypes, may prevent tumor escape due to the emergence of LOH during treatment.

[0305] The present Example recognizes that TCRs targeting one or more of the most common HLAs can contribute to the utility of therapeutic products for treatment of a broad patient population. The present disclosure encompasses multiplexing of TCRs that target antigens that are highly expressed by melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer and presented by a plurality of HLAs. HLA prevalence is shown in **FIG. 2**. In general, availability of a library (or "ImmunoBank") of TCRs that target important tumor antigens in the context of distinct HLAs allows for a therapeutic approach in which a patient HLA-matched TCR, or a multiplexed therapy including two or more patient-HLA matched TCRs, can be customized for treatment of patients with melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer (**FIG. 3**).

[0306] Multiplexing TCR T cell populations provides more effective treatment of heterogenous melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer cell populations. TCR-T cell cytotoxicity can be enhanced by CD8α/β to engage helper T cells and/or by a dominant negative TGFβ receptor (DN-TGFβRII) to enhance T cell expansion/persistence (**FIGS. 4-5**). Expression of CD8α and CD8β coreceptors by TSC-201-B0702 engineered T cells can allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function (**FIGS. 4, 19, 26**). CD4+ T cells engineered to express TCR+CD8α+CD8β

coreceptors had ~100-fold higher cytokine production and cytotoxicity versus CD4+ cells expressing TCR alone or TCR+CD8α (**FIGS. 19, 26**).

[0307] Expression of dominant negative TGFβRII (DN-TGFβRII) can increase persistence of engineered T cells in a subject. TGFβ is a key immune suppressor in hostile tumor microenvironments (**FIG. 5**). However, expression of a DN-TGFβRII by engineered T cells of the present Example renders cells resistant to the suppressive signaling effects of TGFβ (**FIGS. 6-7**), resulting in greater cytokine production and T cell proliferation in the presence of TGFβ as compared to a reference T cell population that does not express dominant negative TGFβRII (**FIG. 8**; see also *J Clin Oncol* (2018) 36: 1128-1239; *Nat Med* (2022) 28: 7240734). Utility of DN-TGFβRII was further confirmed in a mouse model using an engineered TCR T cell of the present disclosure, TSC-204-A0201, as shown in **FIG. 20**. Data shown in **FIG. 20** are from NCG mice implanted with human U266B1 tumors and then randomized for receipt of (1) two doses of TSC-204-A0201 TCR-T cells with DN-TGFBRII, (2) two doses of TSC-204-A0201 TCR-T cells without DN-TGFBRII, (3) untransfected control T cells, or (4) vehicle control (PBS). Tumor volumes were measured twice weekly.

[0308] Antigens targeted by TCRs of the present disclosure (*i.e.*, MAGEC2, HPV16, MAGEA1, and PRAME) have been found to be commonly expressed in solid tumors that include NSCLC, melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), head & neck, cervical, and ovarian solid tumors (**FIG. 9**).

[0309] TCRs were expressed from a vector construct shown in **FIG. 16**, where the sequences encoding the TCRα and TCRβ chains encode the TCR chains of a TCR of Table 1. As shown in **FIG. 16**, a promoter is operably linked with the coding sequence that encodes TCRα and TCRβ chains, as well as CD8α and CD8β. The amino acid sequences of the TCRα and TCRβ chains are separated by a self-cleaving peptide (P2A). CD8α and CD8β coreceptors allow CD4+ helper T cells to participate in target recognition and cytotoxicity, boosting CD8+ T cell function. CD8α and CD8β are likewise separated by a self-cleaving peptide (P2A), and the CD8α polypeptide includes an N-terminal CD34 epitope tag that enables purification of engineered T cells as well as tracking in the subject. A separate promoter is operably linked with and controls expression of DN-TGFβRII. The vector further includes a selection gene. The shown sequences of **FIG. 16** are flanked by transposon Terminal Inverted Repeats (TIRs).

[0310] The present Example encompasses:

i) A TCR referred to as TCR-201-B0702 that targets MAGEC2 antigen RAREFMELL (SEQ ID NO: 1) presented by HLA-B*0702 and includes TCR alpha and beta chains according to SEQ ID NOs: 12 and 18, respectively;

ii) A TCR referred to as TCR-200-A0201 that targets HPV16 antigen YMLDLQPET (SEQ ID NO: 2) presented by HLA-A*0201 and includes TCR alpha and beta chains according to SEQ ID NOs: 25 and 31, respectively;

iii) A TCR referred to as TCR-204-C0702 that targets MAGEA1 antigen VRFFFPSL (SEQ ID NO: 3) presented by HLA-B*0702 and includes TCR alpha and beta chains according to SEQ ID NOs: 38 and 44, respectively;

iv) A TCR referred to as TCR-203-A0201 that targets PRAME antigen SLLQHLIGL (SEQ ID NO: 4) presented by HLA-A*0201 and includes TCR alpha and beta chains according to SEQ ID NOs: 51 and 57, respectively;

v) A TCR referred to as TCR-204-A0201 that targets MAGEA1 antigen KVLEYVIKV (SEQ ID NO: 5) presented by HLA-A*0201 and includes TCR alpha and beta chains according to SEQ ID NOs: 64 and 70, respectively; and

vi) A TCR referred to as TCR-204-A0101 that targets MAGEA1 antigen EADPTGHSY (SEQ ID NO: 6) presented by HLA-A*0101 and includes TCR alpha and beta chains according to SEQ ID NOs: 77 and 83, respectively.

In Vitro and In Vivo Demonstration of TCR Targeting

[0311] The present disclosure includes data showing that TSC-200-A0201 (**FIG. 10**), TSC-204-C0702 (**FIG. 11**), TSC-203-A0201 (**FIG. 12**), and TSC-204-A0201 (**FIG. 13**) eliminate tumor cells. Data demonstrate elimination of tumor cells both *in vitro* in cell cultures and *in vivo* in mouse models of disease. **FIG. 10** shows that TSC-200-A0201 results in a dramatic decline in survival of head & neck tumor cells ***in vitro*** and ***in vivo***. **FIG. 11** shows that TSC-204-C0702 results in a dramatic decline in survival of MAGEA1 positive melanoma tumor cells ***in vitro*** and ***in vivo***. **FIG. 12** shows that TSC-203-A0201 results in a dramatic decline in survival of melanoma tumor cells ***in vitro*** and ***in vivo***. **FIG. 13** shows that TSC-204-A0201 results in a dramatic decline in survival of MAGEA1 positive melanoma tumor cells ***in vitro*** and ***in vivo***.

Preparation and Administration of Multiplexed TCR Products

[0312] As discussed above, the present disclosure recognizes that multiplexing of TCR T cells expressing TCRs of the present disclosure are more effective for treatment of

heterogenous tumors (**FIG. 14**). In the present Example, multiplexed T cell products are prepared from a single apheresis product from the patient (**FIG. 17**). PBMCs from the apheresis product are divided into two pools, each contracted with transposase mRNA and a transposon vector encoding a construct of interest for expression of a distinct TCR. The present Example therefore includes production of two distinct pools of engineered TCR T cells, each expressing a distinct TCR, from a single patient apheresis product.

[0313] During administration to the patient, the two engineered TCR T cell products are administered sequentially. All TCR T cells of the present Example are administered by infusion.

Multiplexing of TCRs

[0314] To demonstrate the advantages of multiplexing, immunodeficient mice were implanted with a mixed solid tumor population including a 50/50 mixture of PRAME-expressing and MAGE-A1 expressing tumor cells. After implantation of the tumor, mice were treated with a TCR of the present Example targeting PRAME, a TCR of the present example targeting MAGEA1, or both, with the following dosages:

Vehicle	No engineered T cells
MAGEA1	20 million T cells engineered to express anti-MAGEA1 TCR
PRAME	20 million T cells engineered to express anti-PRAME TCR
Multiplexed, 10+10	10 million T cells engineered to express anti-MAGEA1 TCR 10 million T cells engineered to express anti-PRAME TCR, respectively
Multiplexed, 20+20	20 million T cells engineered to express anti-MAGEA1 TCR 20 million T cells engineered to express anti-PRAME TCR, respectively

[0315] Results shown in **FIG. 15** demonstrate that treatment with engineered T cells expressing one TCR were effective, while delivery of engineered T cell populations expressing each of two TCRs was still more effective, and moreover, that an increasing the dose of both cell populations led to a greater response. Multiplexed TCR is therefore shown to control *in vivo* heterogenous tumor growth to a greater degree than single therapy.

Selection of Trial Subjects and Administration of TCR T Cells

[0316] Patients with melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-

nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, or anogenital cancer are eligible. Subjects can be selected according to certain criteria (**FIGS. 22, 25**). Subjects are screened as part of a screening protocol during standard-of-care or subsequent therapy. Screening includes germline HLA typing and archival tumor testing for antigens and HLA LOH any time during cancer treatment. Germline HLA analysis is performed to determine suitability of TCR products, as TCR products are HLA specific. Archival tumor samples are also evaluated for tumor expression of target antigens by immunohistochemistry (IHC) and loss of HLA heterozygosity (HLA LOH). Multiplex TCR T cell therapy can overcome HLA LOH and solid tumor cell heterogeneity (**FIG. 24**). At least 40% of cells of the one dose or two doses of T cells comprise engineered T cells expressing a marker, optionally wherein the marker is Qtag-CD34.

[0317] For the present Example, inclusion and exclusion criteria can be applied to all subjects. The present Example can be limited to subjects having a diagnosis of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer, head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, ovarian cancer, cervical cancer, anal cancer, genital cancer, or anogenital cancers. The present Example can be limited to subjects at least 18 years of age. The present Example can be limited to subjects for whom standard of care therapy (*e.g.*, including any relevant targeted therapy or checkpoint inhibitor, such as wherein the targeted therapy or checkpoint inhibitor therapy is relevant for the particular disease afflicting the subject) has failed. The present Example can be limited to subjects whose tumor cells express at least one HLA of a pMHC complex recognized by a TCR of the present disclosure, where the subject does not display LOH of that HLA in their tumor. The present Example can be limited to subjects whose tumor cells express the target antigen recognized by a TCR of the present disclosure, as well as the HLA of the pMHC complex recognized by that TCR. The present Example can be limited to subjects whose tumor cells have a reasonable chance of expressing the target antigen recognized by a TCR of the present disclosure, as well as the HLA of the pMHC complex recognized by that TCR.

[0318] The present Example can be limited to subjects that demonstrate at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. RECIST v.1.1 is a system for assessing tumor burden that can be used in clinical evaluation of cancer therapeutics. RECIST was initially published in 2000 and updated in 2009, and has been commonly considered in the assessment of treatment outcomes. RECIST

v1.1 is available online, *e.g.*, available on the World Wide Web at recist.eortc.org/recist-1-1-2/, which is incorporated herein by reference.

[0319] The present Example can be limited to subjects that demonstrate Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1 (*e.g.*, at any time during screening) with adequate organ function. ECOG-PS is framework for measuring how disease impacts a subject's daily living abilities, which can be referred to by physicians and researchers as performance status. ECOG-PS is commonly considered in the study of cancer therapy and is available online, *e.g.*, available on the World Wide Web at ecog-acrin.org/resources/ecog-performance-status/, which is incorporated herein by reference.

[0320] Subjects can be excluded from this Example if they demonstrate CNS metastases that are symptomatic or in need of treatment. Subjects can be excluded from this Example if they demonstrate carcinomatous meningitis. Subjects can be excluded from this Example if they demonstrate major cardiac pathology or stroke/transient ischemic attack (TIA) (*e.g.*, within 12 months of study enrollment). Subjects can be excluded from this Example if they receive systemic corticosteroids (*e.g.*, receive systemic corticosteroids within 7 days of enrollment). Subjects can be excluded from this Example if they are concurrently receiving a therapy for which they have not yet met washout requirements. Subjects can be excluded from this Example if they demonstrate hypersensitivity to fludarabine, hypersensitivity to cyclophosphamide, or hypersensitivity to other agents (*e.g.*, excipients) that are administered as part of the Example. Subjects can be excluded from this Example if they encode and/or express (*e.g.*, tumor cells express) an HLA type that may interfere with or reduce efficacy of targeting pMHCs that include another HLA type and are targeted by a TCR of the present disclosure that is to be administered to the subject.

[0321] Treatment protocol involves 1-2 doses of TCR-T cell therapy after lymphodepletion. For subjects meeting inclusion criteria (*e.g.*, expression of a target antigen and presenting HLA targeted by a TCR of the present Example), if disease progresses despite at least a first line standard-of-care therapy regimen and any approved checkpoint inhibitor or targeted therapy (*e.g.*, wherein the targeted therapy or checkpoint inhibitor therapy is relevant for the particular disease afflicting the subject), the subject will undergo one round of leukapheresis to isolate PBMCs for production of engineered T cells for single or multiplex TCR T cell production (**FIG. 22**). The subject will then undergo lymphodepletion prior to administration of TCR T cells, about 25 days vein-to-vein time after leukapheresis (**FIG. 22**). Lymphodepletion comprises fludarabine and cyclophosphamide, with cyclophosphamide

administered at a dose of 60 mg/kg x two doses and fludarabine administered at a dose of 30 mg/m^2 x 5 doses, beginning 7 days prior to TCR-T cell administration. Subjects will not receive IL-2. For multiple dose trial arms, a second round of therapy will be administered 28 days after the first round of therapy, without repeat of lymphodepletion (**FIG. 22**).

[0322] A dose escalation scheme provides a rapid path to multiplexed TCR-T. Initially, each of the six TCR T cell types of the present disclosure will be administered to subjects at two dose levels: Dosage Level 1 (DL1; 0.5x10^9 engineered T cells) and Dosage Level 2 (DL2; 2x10^9 engineered T cells) (**FIG. 21**). Pairs of T cell products that individually clear DL2 without excessive toxicity can be multiplexed (**FIG. 21**). In some therapeutic regimens, subjects will receive one dose of a T cell product, or of each of two T cell products at a first time point (*e.g.*, sequentially administered), followed by a second dose of the T cell product, or of each of the two T cell products (*e.g.*, sequentially administered), at a second time point (*e.g.*, about 28 days after first time point), for a total of two or four doses, respectively (**FIG. 21**). In multiplexed regimens with two T cell products, i) each of the four doses will be a dose of about 2x10^9 engineered T cells, which regimen is referred to as DL3 or (ii) each of the four doses will be a dose of about 5x10^9 engineered T cells, which regimen is referred to as DL4 (**FIG. 21**). In another regimen, subjects will receive two doses of a single T cell product, where the doses include a first dose of about 4x10^9 or about 1x10^10 engineered T cells at a first time point and a second dose at the same level as the first dose (about 4x10^9 or about 1x10^10 engineered T cells, respectively) at a second time point (*e.g.*, about 28 days after first time point). Subjects can be hospitalized for observation for 3-7 days following infusion with the T cell product. Subjects can undergo lymphodepletion prior to a dose of an engineered T cell product (*e.g.*, starting on day -7 prior to administration of a dose of engineered T cell product), *e.g.*, prior administration of the first dose an engineered T cell product. For example, subjects can receive fludarabine and/or cyclophosphamide (*e.g.*, 60 mg/kg cyclophosphamide on Days -7 and -6 and 30 mg/m^2 fludarabine on Days -7 to -3.

Results

[0323] In this Example, trial results will be evaluated according to several endpoints (**FIG. 22**). Primary endpoints of interest will include measures of safety (adverse event profiles and dose limiting toxicities). Secondary endpoints will include objective response rate (ORR), progression free survival (PFS), and feasibility. ORR refers to the proportion of patients who achieve complete or partial response and DOR is a measure of how long these responses last. PFS refers to the duration of time that subjects survive without disease

progression regardless of whether or not they have achieved a clinical response. Exploratory endpoints will include persistence of engineered T cells, infiltration of engineered T cells into tumor, and measurement of immune activation markers.

Example 2. Further Confirmatory Characterization of Multiplexed TCR-T cell Therapy to Treat Solid Tumors

[0324] This representative Example further confirms the data and results presented in Example 1 and continue to be based, in part, on the recognition that customized multiplexed TCR-T therapy holds great promise for treating solid tumors by addressing intratumor heterogeneity and loss of heterozygosity (LOH) at the HLA locus.

[0325] Intratumor heterogeneity represents a major challenge to cancer therapies, including TCR-T therapy. Not every cell in a tumor expresses a given tumor-associated protein. Tumor cells lacking the targeted protein will be resistant to a single TCR-T therapy and will inevitably drive relapse. Further, loss of heterozygosity at the human leukocyte antigen (HLA) locus can render cells resistant to a TCR-T therapy restricted to the affected HLA.

[0326] To address these challenges, an ImmunoBank of therapeutic TCRs recognizing different target antigens presented on diverse HLA alleles is being built. FIG. 39A shows an ImmunoBank of therapeutic TCRs recognizing a broad range of tumor antigens, consisting of peptide epitopes derived from tumor-associated protein targets, presented on diverse human leukocyte antigens (HLAs) class I. For example, an ImmunoBank currently contains TCRs targeting epitopes derived from the cancer testis antigens MAGE-A1, PRAME and MAGE-C2 or the oncoprotein HPV E7 and can address multiple HLAs including HLA-A*02:01, HLA-A*01:01, HLA-B*07:02, and HLA-C*07:02.

[0327] Two to three TCRs targeting relevant antigens and intact HLA alleles in patients were selected from the ImmunoBank of TCRs to build customized T-Plex products addressing target and HLA heterogeneity. FIGs. 39B and 39C show that once target and HLA expression are determined in a patient's tumor, TCR-T components are selected from the ImmunoBank to manufacture and administer customized multiplexed TCR-T therapy ("T-Plex") designed to address intratumor heterogeneity and loss of heterozygosity (LOH) at the HLA locus.

[0328] Targets of T-Plex were found co-expressed in solid tumors and were typically presenting intra-tumor heterogeneity (FIGs. 40A-40D). FIG. 40A shows publicly available bulk RNA expression data analyzed for the frequency of co-expression of the targets of the

ImmunoBank across different solid tumor indications (source: TCGA). FIG. 40B shows publicly available single cell RNAseq data analyzed for expression of PRAME, MAGE-A1, MAGE-C2 and MAGE-A4 in cells from melanoma and non-small cell lung cancer specimens positive for these targets (source: Curated Cancer Cell Atlas from the Weizmann Institute). FIG. 40C shows representative images of immunofluorescence analysis of MAGE-A4, MAGE-C2 and PRAME in a melanoma specimen. FIG. 40D shows publicly available single cell RNAseq for HPV16 E7, PRAME, and MAGE-A1 in cervical cancer cells (Li *et al.* (2021) *Mol. Ther. Nucleic Acids* 24:682-694) and head and neck cancer cells (Janjic *et al.* (2022) *Front Immunol.* 13:837842).

[0329] To demonstrate the benefit of T-Plex, both *in vitro* and *in vivo* studies were conducted where mixtures of cancer cell lines served as models of heterogeneous cancers. The efficacy of TCR-T monotherapies or multiplex therapies were evaluated to test whether two therapeutic TCRs in T-Plex products exhibit additive or synergistic activities. Multiple scenarios of T-Plex products were evaluated to target a given antigen on different HLAs, two antigens on a shared HLA, or two antigens presented on distinct HLAs.

[0330] These *in vitro* and *in vivo* studies indicate that singleplex TCR-T cell products only addressed the subset of cells presenting the targeted peptide/MHCs, whereas T-Plex products were consistently able to broaden the cytotoxicity activity by targeting all tumor cells.

[0331] For example, FIGs. 41A-41D show a proof-of-concept (POC) study which demonstrates that T-Plex addresses intra-tumor heterogeneity *in vitro*. FIG. 41A shows that two target cell lines were combined to simulate a heterogeneous tumor. For tracking purposes, targets were pre-labeled with lentiviral dye NucLight™ Red (NLR) or NucLight™ Green (NLR; IncuCyte®), or CellTrace™ CFSE or Violet (Flow Cytometry). FIG. 41B shows that the efficacy of the T-Plex products against the mixtures of target cells was monitored by either IncuCyte®-based or Flow Cytometry-based cytotoxicity assays. IncuCyte® enabled tracking the changes in target cell density as assessed by the expression of fluorescent protein NLR or NLG over time. Flow Cytometry enabled endpoint (48 or 72 hours) viability measurements of target cells as assessed by 7-AAD live/dead cell-impermeant dye. FIG. 41C shows that target cell combinations to create heterogeneous targets were based on target antigen and HLA expression. FIG. 41D shows that percentage killing of each tumor cell subset was determined by taking the area under the curve (AUC) calculated from each culture condition and normalized to the relevant UTF condition (IncuCyte®) or by normalizing the dead cell count for each culture condition to the relevant

UTF condition (flow cytometry). These data clearly show that when facing a heterogeneous target cell population, a Singleplex component is sub-optimal as it only targets a subset of the heterogeneous target cells expressing relevant antigens and HLAs. Combining TCR-T cell components from the ImmunoBank into a customized T-Plex product achieves broad cytotoxic activity against heterogenous cancers.

[0332] FIGs. 42A-42D further show a POC study that demonstrates that T-Plex addresses intro-tumor heterogeneity *in vivo*. FIG. 42A shows that U266B1 cancer cells (MAGE-A1+, HLA-A*02:01+, HLA-C*07:02+) were engineered by CRISPR knockout to create two versions of the cell line where only one of the two HLAs of interest is intact (knocking out HLA-A*02:01 or HLA-C*07:02). Each target cell subset was labeled with distinct fluorescent dyes (GFP or BFP, respectively) to be tracked in downstream flow cytometry readouts prior to being mixed at a 1:1 ratio to create a tumor model with intratumor heterogeneity and implanted in NCG mice. The efficacy of the MAGE-A1-targeting TSC-204-A0201, or TSC-204-C0702 as Singleplex products (5E6 or 10E6 total T cell injected), or T-Plex (TSC-204-A0201+TSC-204-C0702; 10E6 or 20E6 total TCR-T cell injected) was tested. FIG. 42B shows that tumors were dissected and photographed to estimate efficacy based on tumor volume. FIG. 42C shows that the tumors were dissociated to analyze their cell composition by flow cytometry. FIG. 42D shows the change in proportion of the subset of target tumor cells (*i.e.*, BFP+/GFP+) following Singleplex and different T-Plex doses of TCR-T cell treatment.

[0333] While each TCR-T component was selectively targeting its relevant target cancer subset, synergistic anti-tumor activity between the two components of T-Plex was also evident, as demonstrated in the studies described below. For example, a "bystander" cytotoxic activity was often observed when the viability of cancer cell was affected by the T cell-mediated killing of a neighbor cancer cell. Further, the target-dependent activity of a TCR-T component within T-Plex could support the function of the other TCR-T component against the tumor. This phenomenon was largely cytokine-mediated and included the target-independent expansion of the second TCR-T component.

[0334] For example, FIGs. 43A-43D show that T-Plex presented additive and synergistic activities. FIG. 43A shows the experimental design schematic. Coculture of T-Plex components was performed in trans-well settings to evaluate the effect of the activity of the TCR-T cells in the top well on the performance of the TCR-T cell in the bottom well. FIG. 43B shows that the activity of TSC-204-C0702 against A101D in the top well supported the target-dependent function of TSC-201-B0702 against SK-MEL-5 in the bottom well.

TSC-204-C0702 activity influenced the viability of the SK-MEL-5 cells and promoted their surface expression of HLA-B*07:02, similarly to IFN-γ treatment. FIG. 43C shows the activity of TSC-204-C0702 against A101D in the top well promoted the target-dependent activation of TSC-201-B0702 (CD69 surface expression) and supported T cell proliferation in the bottom well. FIG. 43D shows that the activity of TSC-204-C0702 against A101D in the top well resulted in enhanced target-dependent secretion of IFN-γ and granzyme-B by TSC-201-B0702 in the bottom well.

[0335] The data illustrated in this Example further confirm that multiplexed TCR-T mimics the natural polyclonal T cell response to cancer and addresses solid tumor heterogeneity. As the ImmunoBank grows, more customized T-Plex products can be built to overcome multiple intratumor heterogeneity scenarios with respect to cancer-associated proteins and/or HLA expression to address each individual patients' needs.

[0336] Moreover, patients have been dosed with various, representative TCRs and data from patients indicate dose-dependent TCR-T cell expansion in an antigen-driven manner (FIG. 44).

OTHER EMBODIMENTS

[0337] It will be appreciated that the scope of the present disclosure is to be defined by that which may be understood from the disclosure and claims rather than by the specific embodiments that have been presented by way of example. Elements described with respect to one aspect or embodiment of the present disclosure are also contemplated with respect to other aspects or embodiments of the present disclosure. Moreover, recitation of claim elements in connection with a particular independent claim support recitation of such elements in connection with other independent claims. Throughout the disclosure and claims, where compositions or methods are described as having, including, or comprising specific elements, compositions that consist essentially of, consist of, or do not comprise the recited elements are likewise hereby disclosed. All references cited herein are hereby incorporated by reference.

CLAIMS

What is claimed is:

1. A method of treating a malignancy selected from the group consisting of melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer in an adult human subject, the treatment comprising infusing one dose of one engineered T cell type (single-plex), two doses of one engineered T cell type (single-plex), or two doses of each of two engineered T cell types (multi-plex), wherein engineered T cell types are selected from the group consisting of:

1) T cells engineered to express a TCR that binds MAGE-C2 peptide (RAREFMELL) when presented by HLA-B*07:02, if the cancer cells express MAGE-C2 and present MAGE-C2 peptide (RAREFMELL) by HLA-B*07:02 (TSC-201-B0702),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, a CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 9, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 13, a CDR2 comprising the amino acid sequence of SEQ ID NO: 14, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 15,

2) T cells engineered to express a TCR that binds HPV16 $E7_{11-19}$ peptide (YMLDLQPET) when presented by HLA-A*02:01, if the cancer cells express HPV16 E7 and present HPV16 $E7_{11-19}$ peptide (YMLDLQPET) by HLA-A*02:01 (TSC-200-A0201),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 20, a CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 22, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 26, a CDR2 comprising the amino acid sequence of SEQ ID NO: 27, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 28,

3) T cells engineered to express a TCR that binds MAGE-A1 peptide (VRFFFPSL) when presented by HLA-C*07:02, if the cancer cells express MAGE-A1 and present MAGE-A1 peptide (VRFFFPSL) by HLA-C*07:02 (TSC-204-C0702),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a CDR2 comprising the amino acid sequence of SEQ ID NO: 34, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 35, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a CDR2 comprising the amino acid sequence of SEQ ID NO: 40, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 41,

4) T cells engineered to express a TCR that binds $PRAME_{425-433}$ peptide (SLLQHLIGL) when presented by HLA-A*02:01, if the cancer cells express PRAME and present $PRAME_{425-433}$ peptide (SLLQHLIGL) by HLA-A*02:01 (TSC-203-A0201),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a CDR2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 48, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a CDR2 comprising the amino acid sequence of SEQ ID NO: 53, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 54,

5) T cells engineered to express a TCR that binds MAGE-$A1_{278-286}$ peptide (KVLEYVIKV) when presented by HLA-A*02:01, if the cancer cells express MAGE-A1 and present MAGE-$A1_{278-286}$ peptide (KVLEYVIKV) by HLA-A*02:01 (TSC-204-A0201),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, a CDR2 comprising the amino acid sequence of SEQ ID NO: 60, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 61, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, a CDR2 comprising the amino acid sequence of SEQ ID NO: 66, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 67, and/or

6) T cells engineered to express a TCR that binds $MAGEA1_{161-169}$ peptide (EADPTGHSY) when presented by HLA-A*01:01, if the cancer cells express MAGE-A1 and present $MAGEA1_{161-169}$ peptide (EADPTGHSY) by HLA-A*01:01 (TSC-204-A0101),

wherein the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 72, a CDR2 comprising the amino acid sequence of SEQ ID NO: 73, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 74, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 78, a CDR2 comprising the amino acid sequence of SEQ ID NO: 79, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 80,

and

wherein (i) single-plexing with one engineered cell type is selected from the group consisting of one dose of about 0.5x10^9 engineered T cells and one dose of about 2x10^9 engineered T cells, (ii) single-plexing with one engineered cell type is selected from the group consisting of two doses of about 4x10^9 engineered T cells per dose and two doses of about 10x10^9 engineered T cells per dose, or (iii) multi-plexing with two engineered cell types is selected from the group consisting of two doses of about 2x10^9 engineered T cells of each of two engineered T cell types per dose and two doses of about 5x10^9 engineered T cells of each of two engineered T cell types per dose.

2. The method of claim 1, wherein

1) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

4) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

5) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

6) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

3. The method of claim 1 or 2, wherein

1) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 42;
4) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 55;
5) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 68; and/or
6) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 81.

4. The method of any one of claims 1-3, wherein
1) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 18;
2) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 31;
3) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 44;
4) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 57;
5) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or
6) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

5. The method of claim 4, wherein

1) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 18;
2) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 31;
3) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 44;
4) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 57;
5) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 70; and/or
6) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 83.

6. The method of any one of claims 1-5, wherein at least 40% of cells of the one dose or two doses of T cells comprise engineered T cells expressing a marker, optionally wherein the marker is Qtag-CD34.

7. The method of any one of claims 1-6, wherein the method comprises infusing one dose of one engineered T cell type (single-plex).

8. The method of claim 7, wherein the one dose of one engineered T cell type (single-plex) comprises about 0.5x10^9 engineered T cells.

9. The method of claim 7, wherein the one dose of one engineered T cell type (single-plex) comprises about 2x10^9 engineered T cells.

10. The method of claim any one of claims 1-6, wherein the method comprises infusing two doses of one engineered T cell type (single-plex).

11. The method of claim 10, wherein each of the two doses of one engineered T cell type comprises about 4x10^9 engineered T cells per dose.

12. The method of claim 10, wherein each of the two doses of one engineered T cell type comprises about 10x10^9 engineered T cells.

13. The method of claim any one of claims 1-6, wherein the method comprises infusing two doses of each of two engineered T cell types (multi-plex).

14. The method of claim 13, wherein each of the two doses of each of the two engineered T cell types comprises about 2x10^9 engineered T cells per dose.

15. The method of claim 13, wherein each of the two doses of each of the two engineered T cell types comprises about 5x10^9 engineered T cells per dose.

16. The method of any one of claims 1-15, wherein the subject having received the first dose of the one engineered T cell type further receives the second dose of the one engineered T cell type if a serious adverse event does not occur as a result of the first dose.

17. The method of any one of claims 1-15, wherein a subject having received the first dose of each of the two engineered T cell types further receives the second dose of each of the two engineered T cell types if a serious adverse event does not occur as a result of the first dose.

18. The method of any one of claims 1-17, wherein the first dose of the first T cell type and the first dose of the second T cell type are administered to the subject on the same day, optionally wherein the administration of the T cell types is sequential.

19. The method of any one of claims 1-18, wherein the second dose of the first T cell type and the second dose of the second T cell type are administered to the subject on the same day, optionally wherein the administration of the T cell types is sequential.

20. The method of any one of claims 1-19, wherein the T cells used to produce the cells of the engineered T cell type are derived from the subject by leukapheresis.

21. The method of any one of claims 1-20 wherein the subject is screened by germline DNA sequencing for the presence of an HLA that presents the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type.

22. The method of any one of claims 1-21, wherein the subject is screened by tumor cell DNA sequencing and/or immunohistochemistry for the presence of an HLA that presents the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type.

23. The method of any one of claims 1-22, wherein the subject is screened by tumor cell DNA sequencing and/or immunohistochemistry for the presence of the peptide bound by each of the one or two engineered T cell types prior at administration of the T cell type.

24. The method of any one of claims 1-23, wherein the subject undergoes lymphodepletion prior to administration of the first dose of the one engineered T cell type or of either of the two engineered T cell types.

25. The method of any one of claims 1-24, wherein the subject receives fludarabine and/or cyclophosphamide,

optionally wherein the subject receives 60 mg/kg cyclophosphamide on days -7 and -6 and 30 mg/m^2 fludarabine on days -7 to -3.

26. The method of any one of claims 1-25, wherein the first dose of the one engineered T cell type or of both of the two engineered T cell types is administered about 25 days after leukapheresis.

27. The method of any one of claims 1-26, wherein the second dose of the one engineered T cell type or of each of the two engineered T cell types is administered to the subject about 28 days after the first dose.

28. The method of any one of claims 1-27, wherein the treatment eliminates tumor cells and/or inhibits tumor growth and/or disease progression.

29. The method of any one of claims 1-28, wherein the treatment causes a complete response and/or a decrease in the likelihood of relapse.

30. The method of any one of claims 1-29, wherein the cells of the one engineered T cell type and/or of each of the two engineered T cell types express CD8α, CD8β, DN-TGFβRII, and/or a selectable protein marker, optionally wherein the selectable protein marker is DHFR and further optionally wherein the CD8α, CD8β, and/or the selectable protein marker is fused to a CD34 enrichment tag.

31. The method of claim 30, wherein cells are enriched using the CD34 enrichment tag.

32. The method of any one of claims 1-31, wherein the cells of the one engineered T cell type and/or of each of the two engineered T cell types comprise a vector encoding the TCR, optionally wherein the vector is a cloning vector, expression vector, or viral vector.

33. The method of claim 32, wherein the vector further comprises a nucleic acid sequence encoding CD8α, CD8β, DN-TGFβRII, and/or a selectable protein marker, optionally wherein the selectable protein marker is dihydrofolate reductase (DHFR).

34. The method of claim 33, wherein the nucleic acid sequence encoding CD8α, CD8β, DN-TGFβRII, and/or the selectable protein marker is operably linked to a nucleic acid encoding a tag.

35. The method of claim 33 or 34, wherein the nucleic acid encoding a tag is at the 5' upstream of the nucleic acid sequence encoding CD8 α, CD8β, and/or the selectable protein marker such that the tag is fused to the N-terminus of CD8α, CD8β, and/or the selectable protein marker.

36. The method of any one of claims 33-35, wherein the tag is a CD34 enrichment tag.

37. The method of any one of claims 33-36, wherein the nucleic acid encoding the binding protein, the nucleic acid sequence encoding TCRα, TCRβ, CD8α, CD8β, and/or the

selectable protein marker are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide.

38. The method of claim 37, wherein the self-cleaving peptide is P2A, E2A, F2A or T2A.

39. A method of assessing the efficacy of a therapy for a malignancy selected from melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer, the method comprising:

a) determining the presence or level of reactivity between T cells obtained from the subject and at least one immunogenic peptide or at least one stable MHC-peptide complex in which an HLA protein presents the immunogenic peptide, in a first sample obtained from the subject prior to providing at least a portion of the therapy, and

b) determining the presence or level of reactivity between the at least one immunogenic peptide, or the at least one stable MHC-peptide complex, and T cells obtained from the subject present in a second sample obtained from the subject following provision of the therapy,

wherein cells of the malignancy express the immunogenic peptide and the HLA protein,

wherein the presence or a higher level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the malignancy, and/or wherein the absence or a reduced level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is not efficacious for treating the malignancy, wherein:

1) the immunogenic peptide is MAGE-C2 peptide (RAREFMELL), the HLA protein is HLA-B*07:02, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, a CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 9, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 13, a CDR2 comprising the amino acid

sequence of SEQ ID NO: 14, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 15,

2) the immunogenic peptide is HPV16 $E7_{11-19}$ peptide (YMLDLQPET), the HLA protein is HLA-A*02:01, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 20, a CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 22, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 26, a CDR2 comprising the amino acid sequence of SEQ ID NO: 27, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 28,

3) the immunogenic peptide is MAGE-A1 peptide (VRFFFPSL), the HLA protein is HLA-C*07:02, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a CDR2 comprising the amino acid sequence of SEQ ID NO: 34, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 35, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a CDR2 comprising the amino acid sequence of SEQ ID NO: 40, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 41,

4) the immunogenic peptide is $PRAME_{425-433}$ peptide (SLLQHLIGL), the HLA protein is HLA-A*02:01, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a CDR2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 48, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a CDR2 comprising the amino acid sequence of SEQ ID NO: 53, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 54,

5) the immunogenic peptide is $MAGE\text{-}A1_{278-286}$ peptide (KVLEYVIKV), the HLA protein is HLA-A*02:01, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, a CDR2 comprising the amino acid sequence of SEQ ID NO: 60, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 61, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, a CDR2 comprising the amino acid sequence of SEQ ID NO: 66, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 67, and

6) the immunogenic peptide is $MAGEA1_{161-169}$ peptide (EADPTGHSY), the HLA protein is HLA-A*01:01, and the TCR comprises:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 72, a CDR2 comprising the amino acid sequence of SEQ ID NO: 73, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 74, and/or

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 78, a CDR2 comprising the amino acid sequence of SEQ ID NO: 79, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 80.

40. The method of claim 39, wherein

1) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

4) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable

domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

5) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

6) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

41. The method of claim 39 or 40, wherein

1) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 42;

4) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 55;

5) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 68; and/or

6) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 81.

42. The method of any one of claims 39-41, wherein

1) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 18;
2) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 31;
3) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 44;
4) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 57;
5) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or
6) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

43. The method of claim 42, wherein
1) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 18;
2) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 31;
3) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 44;
4) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 57;
5) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 70; and/or
6) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 83.

44. The method of any one of claims 39-43, wherein the level of reactivity is indicated by a) the presence of binding and/or b) T cell activation and/or effector function, optionally wherein the T cell activation or effector function is T cell proliferation, killing, or cytokine release.

45. The method of any one of claims 39-44, wherein the binding, activation, and/or effector function is detected using fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay.

46. The method of any one of claims 39-45, wherein the level of reactivity is indicated by an inhibition of tumor cell growth.

47. The method of claim 46, wherein a reduction in tumor cell growth between the first sample and the second sample is an indication that the therapy is efficacious for treating the malignancy.

48. The method of any one of claims 39-47, wherein the level of reactivity is indicated by a decrease in tumor cell number or tumor cell survival.

49. The method of claim 48, wherein a reduction in tumor cell number or tumor cell survival between the first sample and the second sample is an indication that the therapy is efficacious for treating the malignancy.

50. A method of assessing the efficacy of a therapy for a malignancy selected from melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer (NSCLC), head and neck cancer (*e.g.*, non-nasopharyngeal head and neck cancer), sarcoma, thyroid cancer, cervical cancer, ovarian cancer, anal cancer, genital cancer, and anogenital cancer, the method comprising:

a) determining the presence or level of cells and/or cancer cells expressing an immunogenic peptide or at least one stable MHC-peptide complex in which an HLA protein presents the immunogenic peptide, in a first sample obtained from the subject prior to providing at least a portion of the therapy, and

b) determining the presence or level of cells and/or cancer cells expressing an immunogenic peptide, or the at least one stable MHC-peptide complex, in a second sample obtained from the subject following provision of the therapy,

wherein cells of the malignancy express the immunogenic peptide and the HLA protein,

wherein the presence or a lower level in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the malignancy, and/or wherein the a higher level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is not efficacious for treating the malignancy,

optionally wherein:

1) the immunogenic peptide is MAGE-C2 peptide (RAREFMELL), the HLA protein is HLA-B*07:02, and the therapy comprises infusing one dose or two doses of one engineered T cell type or two engineered T cell types according to the present disclosure each comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, a CDR2 comprising the amino acid sequence of SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 9, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 13, a CDR2 comprising the amino acid sequence of SEQ ID NO: 14, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 15,

2) the immunogenic peptide is HPV16 $E7_{11-19}$ peptide (YMLDLQPET), the HLA protein is HLA-A*02:01, and the therapy comprises infusing one dose or two doses of an engineered T cell type according to the present disclosure comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 20, a CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 22, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 26, a CDR2 comprising the amino acid sequence of SEQ ID NO: 27, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 28,

3) the immunogenic peptide is MAGE-A1 peptide (VRFFFPSL), the HLA protein is HLA-C*07:02, and the therapy comprises infusing one dose or two doses of an engineered T cell type according to the present disclosure comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a CDR2 comprising the amino acid sequence of SEQ ID NO: 34, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 35, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a CDR2 comprising the amino acid sequence of SEQ ID NO: 40, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 41,

4) the immunogenic peptide is $PRAME_{425-433}$ peptide (SLLQHLIGL), the HLA protein is HLA-A*02:01, and the therapy comprises infusing one dose or two doses of an engineered T cell type according to the present disclosure comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a CDR2 comprising the amino acid sequence of SEQ ID NO: 47, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 48, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a CDR2 comprising the amino acid sequence of SEQ ID NO: 53, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 54,

5) the immunogenic peptide is $MAGE\text{-}A1_{278-286}$ peptide (KVLEYVIKV), the HLA protein is HLA-A*02:01, the therapy comprises infusing one dose or two doses of an engineered T cell type according to the present disclosure comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, a CDR2 comprising the amino acid sequence of SEQ ID NO: 60, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 61, and

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, a CDR2 comprising the amino acid

sequence of SEQ ID NO: 66, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 67, and

6) the immunogenic peptide is MAGEA1$_{161-169}$ peptide (EADPTGHSY), the HLA protein is HLA-A*01:01, and the therapy comprises infusing one dose or two doses of an engineered T cell type according to the present disclosure comprising a TCR comprising:

a TCR alpha chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 72, a CDR2 comprising the amino acid sequence of SEQ ID NO: 73, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 74, and/or

a TCR beta chain variable domain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 78, a CDR2 comprising the amino acid sequence of SEQ ID NO: 79, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 80.

51. The method of claim 50, wherein

1) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 23 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 42;

4) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 55;

5) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 62 and/or the TCR beta chain variable

domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 68; and/or

6) the TCR alpha chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises an amino acid sequence having at least 90% identity with SEQ ID NO: 81.

52. The method of claim 50 or 51, wherein

1) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 10 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 16;

2) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 23and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 29;

3) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 36 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 42;

4) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 49 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 55;

5) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 62 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 68; and/or

6) the TCR alpha chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 75 and/or the TCR beta chain variable domain sequence comprises the amino acid sequence of SEQ ID NO: 81.

53. The method of any one of claims 50-52, wherein

1) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 12, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 18;

2) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 25, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 31;

3) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 38, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 44;
4) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 51, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 57;
5) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 64, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 70; and/or
6) the TCR comprises a TCR alpha chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 77, and/or a TCR beta chain comprising an amino acid sequence having at least 90% identity with SEQ ID NO: 83.

54. The method of claim 53, wherein
1) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 12, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 18;
2) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 25, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 31;
3) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 38, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 44;
4) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 51, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 57;
5) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 64, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 70; and/or
6) the TCR alpha chain comprises the amino acid sequence of SEQ ID NO: 77, and/or the TCR beta chain comprises the amino acid sequence of SEQ ID NO: 83.

55. The method of any one of claims 1-54, wherein the T cells comprise CD8+ T cells and CD4+ T cells.

56. The method of any one of claims 1-38, wherein the subject meets the following criteria ("inclusion criteria"):
1) diagnosed as having a solid tumor,

2) tumor cells express an HLA that presents the peptide bound by each of the one or two engineered T cell types;

3) does not display LOH of an HLA that presents the peptide bound by one or both of the one or two engineered T cell types;

4) tumor cells express the peptide bound by each of the one or two engineered T cell types;

5) at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;

6) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1;

7) at least 18 years of age;

8) locally advanced (unresectable) or metastatic solid tumor for which there are no available curative treatment options, after failure of the standard of care systemic therapies for that particular indication;

9) express one of the following HLA types: HLA-B*07:02, HLA-A*01:01 HLA-C*07:02, or HLA-A*02:01, optionally wherein expression is assessed by a genomics assay (*e.g.*, as in screening study TSCAN-003);

10) tumor cells express one or more of the following: MAGE-A1, MAGE-C2, PRAME and HPV16-E7, optionally as assessed in the last 8 months in screening study TSCAN-003 (NCT05812027);

11) able to understand and be willing to give informed consent; decision-impaired adults may consent with their legally authorized representative; and/or

12) adequate bone marrow and organ function.

57. The method of claim 56, wherein the solid tumor is melanoma (*e.g.*, cutaneous melanoma, uveal melanoma, or advanced melanoma), non-small cell lung cancer, head and neck cancer (*e.g.*, non-nasopharyngeal), sarcoma, thyroid cancer, ovarian cancer, cervical cancer, anal cancer, genital cancer, or anogenital cancer.

58. The method of claim 56 or 57, wherein the solid tumor has not been adequately treated and/or cured by a standard of care therapy.

59. The method of claim 58, wherein the standard of care therapy is a targeted therapy or a checkpoint inhibitor therapy, optionally wherein the targeted therapy or checkpoint inhibitor therapy is relevant for the particular disease afflicting the subject.

60. The method of any one of claims 1-38 and 56-59, wherein the subject meets the following criteria ("exclusion criteria"):

1) does not demonstrate CNS metastases that are symptomatic or in need of treatment;

2) does not demonstrate carcinomatous meningitis;

3) has not demonstrated major cardiac pathology or stroke/transient ischemic attack (TIA);

4) has not received systemic corticosteroids;

5) is not concurrently receiving a cancer therapy for which they have not yet met washout requirements;

6) has not demonstrated hypersensitivity to fludarabine or cyclophosphamide;

7) does not encode and/or express an HLA type that inhibits binding of one or both of the one or two engineered T cell types with peptide;

8) medical or psychological conditions that would make the participant unsuitable candidate for cell therapy, optionally wherein the suitability is at the discretion of a physician;

9) history of myocardial infarction, cardiac angioplasty or stenting, unstable angina, cardiac arrhythmia requiring antiarrhythmic or procedure, or other clinically significant cardiac disease within 12 months of enrollment;

10) history of stroke or transient ischemic attack (TIA) within 12 months of enrollment;

11) systemic corticosteroid therapy >10 mg of prednisone daily or equivalent within 7 days of enrollment;

12) history of severe hypersensitivity to fludarabine or cyclophosphamide or study product excipients including human serum albumin (HSA), Cryostor® (DMSO or Dextran 40), or Plasma-Lyte;

13) untreated or symptomatic central nervous system (CNS) metastases or cytology proven carcinomatous meningitis;

14) concurrent receipt of another anti-cancer therapy;

15) presence of fungal, bacterial, viral, or other infection requiring anti-microbials for management;

16) tumors that have HLA LOH using a central lab clinical trial assay of HLAs addressed by the monotherapy (singleplex) and/or T-Plex (multiplex) combination TCR-Ts in the protocol and have no available TCR-T options for intact HLAs in the participant's tumor; and/or

17) regularly require supplemental oxygen.