

HUMAN T CELL RECEPTORS AND USES THEREOF

TECHNICAL FIELD

The present invention relates to the field of immunotherapy for the treatment of cancer, in particular, to adoptive T cell therapy or T cell receptor (TCR) gene therapy or TCR fusion protein therapy.

BACKGROUND OF THE INVENTION

T cells form part of the adaptive immune response. T cells develop in the thymus and are equipped with a unique T cell receptor (TCR) that recognizes peptides derived from cellular or extra-cellular antigens and presented by major histocompatibility complex (MHC) molecules. There are two types of T cells: CD8 T cells, which bind to peptides presented on MHC class I (MHC-I), and CD4 T cells, which bind to peptides presented on MHC class II (MHC-II) peptides. CD8 T cells are equipped with the capacity to induce cytotoxicity in target cells upon specific TCR binding to a peptide presented on MHC-I, leading to the elimination of target cells. CD4 T cells primarily play a role in supporting CD8 T cell function and other function of other immune cells.

Conventional CD8 T cells express a TCR that comprises a TCR α and a TCR β chain on the cell surface. The T cell comprises a C'-terminal constant region and a N'-terminal variable region comprising frame region (FR) 1 to 4, interspersed with complementarity determining regions (CDRs) 1, 2 and 3 in the following sequence: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. The CDRs are the main contact point of binding to peptides presented on MHC-I. The specific binding of a TCR to a given MHC-I allele or a group of related MHC-I alleles is called MHC-restriction (Murphy and Weaver Casey; Sidney et al., 2008).

The diversity of the TCR is accomplished by assembling of variable (V), diversity (D) and joining (J) gene allele for the TCR β chain and a V and J gene for the TCR α chain during T cell development. Additional diversity is generated with the additional insertion of nucleotides between the V-D and DJ gene during T cell development, generating a unique TCR in each developing T cell.

T cells recognize peptides derived from pathogens or from cancer cells and are therefore a crucial component of the immune response to infection and cancer. The ability of T cells to

specifically bind to and kill tumor cells has been recognized more than 30 years ago (Topalian et al., J Immunother 12, 203–206 (1992)). Various strategies employing T cells for immunotherapy have been explored (Ellis et al., 2021; Garber, 2018; Rosenberg and Restifo, 2015). The extraction, expansion and re-infusion of tumor-infiltrated T cells has been used successfully as a therapy. However, this procedure is complicated and only applicable for a limited range of cancers. An alternative strategy is the expression of synthetic, exogenous tumor-specific TCRs on T cells from patients or healthy donors. The TCR-engineered T cells made to recognize tumor cells are expanded and adoptively transferred into patients (Shafer et al., 2022). Alternatively, TCRs can be used in other forms for therapeutic application, for example in the form of bi-specific molecules (Strobel, 2022).

The Epstein-Barr virus (a γ herpes virus that stays dormant (latent) for a long period in memory B cells; hereinafter may be abbreviated as EBV) is involved in many malignancies, for example, Burkitt's lymphoma, Hodgkin's disease (HD) and nasopharyngeal carcinoma (NPC), as well as post-transplant lymphoproliferative disorder. In latent infections, viral protein expression is suppressed. All EBV-positive malignant cells exhibit one of the following three latency types. These types are distinguished from each other by the EBV antigen expression patterns. In latency type I, only the EBV nuclear antigen (EBNA) 1 is expressed; in latency type II, latent membrane protein (LMP) 1 and 2 are expressed along with EBNA1; in latency type III, all EBV latent proteins are expressed, meaning EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3, leader protein (LP), LMP1 and LMP2. (US Patent Application No. 20090305324, incorporated here by reference).

Some EBV proteins are known viral oncogenic proteins that can drive the development of cancer and other diseases, causing a high global burden of EBV-driven malignancies, such as nasopharyngeal carcinomas (NPC), gastric carcinoma, Burkitt's lymphoma, Hodgkin's disease, Non-Hodgkin's lymphoma, NK/T cell lymphoma, etc... (Khan and Hashim, Infect Agent Cancer 9 (2014); Thompson and Kurzrock, 2004; US Patent Application No. 20090305324, incorporated here by reference). In addition, chronic EBV infection is a potentially life-threatening condition in immune-suppressed individuals such as patients undergoing transplantation, as is the case for post-transplant lymphoproliferative disorder. Moreover, chronic or recurrent EBV infection has been linked to several autoimmune disorders, such as systemic lupus erythematosus (SLE), Sjögren's syndrome, multiple sclerosis, and other diseases (Houen and Trier, *Front. Immunol.* Jan 2021, Vol. 11, art. 587380).

The immunogenicity of peptides derived from oncogenic EBV proteins makes them very promising targets for T cell mediated therapy in all these EBV-driven diseases. Clinical trials expanding and re-infusing EBV-protein-targeting T cells showed promising results (Bollard et al., 2014; Cho et al., 2015). EBV peptides presented by MHC-I and therefore targetable by CD8⁺ T cells including BRLF1 peptide YVLDHLIVV (SEQ ID 105) and LMP2 peptides CLGGLLTMV (SEQ ID 106) and FLYALALLL (SEQ ID 107) have been reported in the literature. There is thus an increasing interest in using immunotherapy for EBV-associated diseases, disorders and conditions.

Splicing of pre-mRNA by spliceosomes is a cellular process that removes non-coding introns in transcripts and produces alternative splice forms of proteins. Splicing Factor 3B subunit 1 (SF3B1) and other splicing factors have been reported to be mutated in several types of cancers including uveal melanoma (Bigot et al., 2021; Nguyen et al., 2020). Mutated splice-factor-induced peptides are a promising target for TCR-mediated cancer therapy because of the tumor-specific expression of such peptides, and because of the potential increased immunogenicity. Mutated splice factor-induced peptides, including peptide RLPGVLPRA (SEQ ID NO:147) have been reported in the literature (Bigot et al., 2021). The therapeutic value of TCR-based approaches targeting these peptides, however, is not known. The current invention proposes TCR sequences that can be used for the treatment of diseases associated with mutated forms of protein mitogen-activated protein kinase 8 interacting protein 2 (MAPK8IP2), or other splicing factors including SUGP1 and SF3B1.

About 9% of the human genome consists of genetic information from human endogenous retroviruses (HERVs) that was incorporated into germline as humans evolved (Jansz and Faulkner, 2021). HERV-K is a group of HERVs with relatively intact open reading frames, making the expression of HERV-K proteins more likely compared to other HERVs (Gao et al., 2021). Since expression of human endogenous retrovirus group K (HERV-K) proteins is preferentially seen in cancer cells, T cell receptor-mediated therapy against HERV-K T cell epitopes, including FLQFKTWWI (SEQ ID NO:148), is an attractive strategy for the treatment of cancer that has not yet been tested clinically.

Adoptive cell therapy (ACT) using chimeric antigen receptor (CAR)-engineered T-cells has been shown to induce durable remissions in subjects with refractory B-lymphoid cancers. Results are however comparatively modest when CAR-engineered T-cells are directed against solid malignancies. Thus, alternative strategies to redirect T-cell specificity and cytolytic function are necessary to ameliorate ACT as a therapeutic regimen against solid

tumors, and other cancers. Unlike CARs, T-cell receptors (TCRs) may recognize epitopes derived from any subcellular compartment, such as the membrane, cytoplasm, and nucleus. Furthermore, TCRs efficiently respond to epitope densities many fold smaller than required to activate CAR-signaling. Clinical trials demonstrate that TCR-based ACT mediate

5 regression of solid malignancies, including immune-checkpoint refractory tumors (Chandran and Klebanoff, Immunol. Rev. 290:127-147 (2019)).

Results from clinical trials demonstrated the potential of TCR-based therapies (Shafer et al., 2022). However, the number of clinically validated TCRs is very limited and TCR restriction is almost exclusively to the MHC-I allele Human Leukocyte Antigen (HLA)-A*02:01

10 (Upadhaya et al., 2020). Individuals who do not express the HLA-A*02 allele cannot benefit from these therapies and TCRs restricted to other alleles need to be developed for therapy.

Large datasets with TCR sequences have been published from bulk TCR sequencing experiments, but these datasets often only contain the TCR β CDR3 sequence, lacking the information of the paired TCR α chain sequence, which is required for the expression of a full

15 TCR.

Accordingly, the provision of new TCRs with improved properties, e.g., antigen specificity, binding properties, stability, expression levels and the like would represent a significant advance in the art.

SUMMARY OF THE INVENTION

20 In various embodiments, the present disclosure is directed to compositions and methods for editing the genome of a human T cell such that it expresses a novel T Cell Receptor (TCR). The inventors have discovered that a heterologous TCR can be inserted into the genome of a T cell. The methods and compositions provided herein can be used to produce a human T cell with a heterologous TCR having a desired antigen specificity.

25 In various embodiments, the present invention further provides cells expressing these TCRs, nucleic acids encoding the TCRs, and methods of engineering T cells to express the novel TCRs. Also provided is a method of performing adoptive cell transfer on a subject in need of such therapy to prevent, treat or ameliorate a disease state of the subject

In various embodiments, the isolated TCRs comprise a TCR α chain variable domain and a

30 TCR β chain variable domain that binds to Epstein Barr Virus (EBV)-derived antigenic peptides when presented by a major histocompatibility complex (MHC) molecule. In various

embodiments, the isolated TCRs comprise a TCR α chain variable domain and a TCR β chain variable domain that binds to mutant splice-factor-induced peptide of MAPK8IP2 when presented by a major histocompatibility complex (MHC) molecule. In some embodiments, the isolated TCRs comprise a TCR α chain variable domain and a TCR β chain variable domain that binds to human endogenous retrovirus K (HERV-K) gag protein peptide when presented by a major histocompatibility complex (MHC) molecule. The TCR α and TCR β chains each comprises three complementarity determining regions (CDR1, CDR2, and CDR3) of amino acid sequence sharing at least about 95% sequence identity with an amino acid sequence selected from Table 3.

In some embodiments, the present invention provides methods of using TCR-expressing cells for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering an EBV-associated condition, disease, disorder, or pathology, e.g., cancer. The present invention further provides TCR as part of a fusion construct, whereby the fusion construct consists of a TCR and a single-chain fragment that binds to a molecule specifically expressed on T cells, including but not limited to CD3 for the treatment of cancer.

Other objects and embodiments of the invention will be apparent from the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

For a further understanding of the various described implementations, reference should be made to the detailed description below, in conjunction with the following drawings in which like reference numerals refer to corresponding parts throughout the figures.

FIG. 1 shows the antigen-specific binding of Jurkat reporter cells transduced with TCR receptors. Antigen presenting cells (APC) expressing HLA-A*02:01 were incubated with EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105) at a range between 0.000005 and 50 μ M. Successfully bound Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

FIG. 2 shows the antigen-specific binding of Jurkat reporter cells transduced with TCR receptor A0015. A) APC expressing HLA-A*02:01 were incubated with an EBV LMP2A-derived antigenic peptide pool (Miltenyi PepTivator 130-093-615: LMP2A, Premium grade, human) at a range between 0.00006 and 1 nM. B) APC expressing HLA-A*02:01 were incubated with an EBV LMP2A-derived peptide MGSLEMVPM (SEQ ID NO:146) at a range

between 0.00005 and 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

FIG. 3 shows the antigen-specific binding of Jurkat reporter cells transduced with TCR receptor A0099. A) Peripheral blood mononuclear cells (PBMCs) expressing HLA-A alleles 02:01 and 03:01 and HLA-B alleles 07:02 and 35:01 were used as APC and incubated with an EBV-derived peptide pool (Mitenyi PepTivator EBV Consensus) with a concentration range between 0.000001 nM and 1 nM. The binding was tested at three different ratios of transfected Jurkat cells:PBMCs. B) PBMCs expressing HLA-A alleles 01:01 and 11:01 and HLA-B alleles 08:01 and 35:01 and HLA-C alleles 04:01 and 07:01 were used as APC and incubated with EBV protein BZLF1-derived peptide EPLPQGQLTAY (SEQ ID NO:145) at a range of 0.000005 to 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

FIG. 4 shows the EBV LMP2-specific binding of Jurkat reporter cells transduced with TCR receptors. APC expressing HLA-A*02:01 were incubated with EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106) at a range between 0.000005 and 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

FIG. 5 shows the EBV LMP2- antigen-specific binding of Jurkat reporter cells transduced with TCR receptors. APC expressing HLA-A*02:01 were incubated with EBV LMP2-derived antigenic peptide FLYALALLL (SEQ ID NO: 107) at a range between 0.000005 and 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

FIG. 6A and **FIG. 6B** show the sequences logo for the possible CDR3 α sequences (C-A-T-X¹-G-X²-S-G-Y-S-T-L-T-F (SEQ ID NO:181)), and CDR3 β sequences (C-A-S-X³-X⁴-Q-G-G-(S)-X⁵-X⁶-G-Y-T-F (SEQ ID NO:182)), respectively, binding to a HLA-A*02-restricted EBV LMP2-derived antigenic peptide of amino acid sequence FLYALALLL (SEQ ID 107), whereby: X¹ is E or A; X² is D, G, N or S, or any of the following amino acids with related properties: E, A, Q or T; X³ is S or T, or any of the following amino acids with related properties: N or Q; X⁴ is K, R or T, or any of the following amino acids with related properties: H, S; X⁵ is G or A; X⁶ is Y or S, or any of the following amino acids with related properties: F, W, H or T.

FIG. 7A and **FIG. 7B** show the sequences logo for the possible CDR3 α sequences (C-A-X¹-X²-G-A-G-S-Y-Q-L-T-F (SEQ ID NO:183)), and CDR3 β sequences (C-A-S-S-X³-E-G-Q-A-S-S-Y-E-Q-Y-F (SEQ ID NO:184)), respectively, binding to a HLA-A*02-restricted EBV LMP2-derived antigenic peptide of amino acid sequence CLGGLTMTV (SEQ ID NO:106),
 5 whereby: X¹ is G or V, or any of the following amino acids with related properties: A, I or L; X² is A or S, or any of the following amino acids with related properties: G or T; X³ is L or A, or any of the following amino acids with related properties: I, V or G.

FIG. 8 shows splice variant peptide RLPGVLPRA-specific binding of Jurkat reporter cells transduced with TCRs. APC expressing HLA-A*02:01 were incubated with MAPK8IP2
 10 splice variant-derived peptide RLPGVLPRA (SEQ ID NO:147) at a range between 0.000005 and 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

TCR_A0130 and TCR_A0131 were expressed successfully and recognized peptide RLPGVLPRA presented on HLA-A*02:01-expressing APC.

FIG. 9 shows the sequence logo for possible CDR3 α sequence (C-A-F-M-X¹-X²-D-S-X³-X⁴-Y-X⁵-X⁶-I-X⁷ (SEQ ID NO:185)), binding to an HLA-A*02-restricted mutant splice factor-induced splice variant MAPK8IP2-derived antigenic peptide of amino acid sequence RLPGVLPRA (SEQ ID NO:147), whereby X¹ is L or I or E, or any of the following amino acids with related properties: V or D. X² is P or I or A, or any of the following amino acids
 20 with related properties: V, L or G. X³ is G or N, or any of the following amino acids with related properties: Q, A, C or S. X⁴ is T or no AA at this position, or S as an amino acid with related properties. X⁵ is K or Q, or any of the following amino acids with related properties: R, H or N. X⁶ is L or Y, or any of the following amino acids with related properties: I, V, F, W or H. X⁷ is F or W.

FIG. 10 shows the HERV-K-specific binding of Jurkat reporter cells transduced with TCRs. APC expressing HLA-A*02:01 were incubated with peptide FLQFKTWWI (SEQ ID NO:148) at a range between 0.000005 and 50 μ M. Successfully binding Jurkat reporter cells are activated via the TCR and generate a luciferase signal that can be quantified.

TCR_A0100 was expressed successfully and recognized peptide FLQFKTWWI presented on
 30 HLA-A*02:01-expressing APC.

FIG. 11 shows that TCR A0100 is functional when transduced into primary T cells and exposed to cognate peptide antigen pulsed onto target cells. Production of the cytokine IFN γ

was used as a readout to measure the effector function of T cells transduced with TCR A0194, which is TCR A0100 containing modified mouse constant regions.

FIG. 12A-F show that T cells transduced with TCR A0194 effectively kills cancer cells expressing endogenous levels of the target HERV-K antigen. Cancer cell line 92.1, which expresses HERV-K gag and the HLA allele HLA-A*02 (A, D, E), was used to measure cytotoxicity at 12 h (A, B), 24 h (C, D), and 48 h (E, F). As a control for HLA-specific killing of target cells, HERV-K gag-expressing but HLA-A*02-negative cell line MEL202 was used (B, D, F).

FIG. 13A-B show the effector functions of TCR-transduced primary T cells. Three TCRs targeting a mutant splice factor-induced peptide of MAPK8IP2, known to be shared across patients with multiple types of cancer, were successfully isolated from a renal cell carcinoma patient. The TCRs are A0130 modified with mouse constant regions, A0191 (black circles), A0131 modified with mouse constant regions, A0192 (up triangles), and A0132 modified with mouse constant regions, A0193 (down triangles). Data shows the reactivity of TCR-expressing primary T cells to peptide-pulsed HLA-A*02-positive cells (A). The supernatant of the experiment in A was used to quantify IFN γ by ELISA (B). The negative control consisted of non-transduced cells (empty circles).

DETAILED DESCRIPTION

I. INTRODUCTION

T cells are the most actively studied cell type in the growing field of adoptive cellular therapeutics. T cells interact specifically with the target of their T cell receptor (TCR), enabling highly specific responses with minimal side effects. These potentially highly effective and specific responses can be engineered towards novel antigens and targets by inserting a new receptor with the desired specificity into a T cell. However, development of entirely new types of receptors is time consuming, expensive, and fails to take advantage of the fact that, through development of the endogenous T cell repertoire, the body naturally produces TCRs that bind almost any possible antigenic target. The ability to obtain human T cells and replace their endogenous TCR with a TCR having a desired antigen specificity could be transformative in the development and application of adoptive T cell therapies.

In various embodiments, the present invention provides human T cell receptors (TCRs) binding to EBV-derived antigenic peptides, and nucleic acids encoding the TCRs of the invention. In various embodiments, the present invention also provides human T cell receptors (TCRs) binding to tumor-derived or tumor-associated peptides, such as mutant
5 splice-factor-induced peptide of MAPK8IP2 and peptide from HERV-K gag protein. Also provided is a method of transducing a human T cell with a nucleic acid encoding a T cell receptor such that the T cell integrates the nucleic acid into its genome and expresses the encoded TCR. In some embodiments, the invention provides a host cell with the nucleic acid integrated into the host cell genome, and such a T cell expressing the TCR. The instant
10 invention further provides methods of preventing, treating or ameliorating a disease in a subject by administering to a subject in need thereof a cell of the invention. t

II. DEFINITIONS

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology,
15 recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Current Protocols in Molecular Biology (Frederick M. AUSUBEL, 2000, Wiley and son Inc, Library of Congress, USA); Molecular Cloning: A Laboratory Manual, Third Edition, (Sambrook et al, 2001, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press); Oligonucleotide Synthesis (M. J. Gait ed.,
20 1984; Mullis et al. U.S. Pat. No. 4,683,195); Nucleic Acid Hybridization (B. D. Harries & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Culture Of Animal Cells (R. I. Freshney, Alan R. Liss, Inc., 1987); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the series, Methods In ENZYMOLOGY (J. Abelson and M. Simon, eds.-in-chief, Academic
25 Press, Inc., New York), specifically, Vols. 154 and 155 (Wu et al. eds.) and Vol. 185, "Gene Expression Technology" (D. Goeddel, ed.); Gene Transfer Vectors For Mammalian Cells (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook Of Experimental Immunology, Volumes I-IV (D. M. Weir and C. C.
30 Blackwell, eds., 1986); and Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

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

- 5 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, 10 Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

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

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

- The terms "about" or "consisting essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of 20 ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, in some embodiments, "about" or "consisting essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "consisting essentially of" can mean a range of up to 10% (i.e., $\pm 10\%$).

- 25 The term "T cell receptor" (TCR), as used herein, refers to a heteromeric cell-surface receptor capable of specifically interacting with a target antigen. As used herein, "TCR" includes but is not limited to naturally occurring and non-naturally occurring TCRs; full-length TCRs and antigen binding portions thereof, chimeric TCRs; TCR fusion constructs; and synthetic TCRs. In human, TCRs are expressed on the surface of T cells, and they are responsible for T 30 cell recognition and targeting of antigen presenting cells. Antigen presenting cells (APC) display fragments of foreign or self proteins (antigens) complexed with the major histocompatibility complex (MHC; also referred to herein as complexed with an HLA

molecule, e.g., an HLA class 1 molecule). A TCR recognizes and binds to the antigen:HLA complex and recruits CD3 (expressed by T cells), activating the TCR. The activated TCR initiates downstream signaling and an immune response, including the destruction of the APC.

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

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

The term CDR3 used herein describes the CDR3 region including the fixed C'-terminal amino acid C (cysteine) and N'-terminal amino acid F (phenylalanine) or W(Tryptophan), or the respective nucleotide sequence coding for these amino acids. The CDR3 including
25 C'terminal C and N'-terminal F/W, or the respective codons, is also termed "Junction" in the field.

Where not expressly stated, and unless the context indicates otherwise, the term "TCR" also includes an antigen-binding fragment or an antigen-binding portion of any TCR disclosed herein, and includes a monovalent and a divalent fragment or portion, and a single chain
30 TCR. The term "TCR" is not limited to naturally occurring TCRs bound to the surface of a T cell. As used herein, the term "TCR" further refers to a TCR described herein that is expressed on the surface of a cell other than a T cell (e.g., a cell that naturally expresses or

that is modified to express CD3, as described herein), or a TCR described herein that is free from a cell membrane (e.g., an isolated TCR or a soluble TCR).

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

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

"Antigen-derived", for example "EBV-derived", refers to an immunogenic peptide/epitope being a portion of the antigen/polypeptide from which it has been processed. For example, an antigen is processed in the cell by the proteasome or immunoproteasome and the resulting antigen-derived peptides are presented on the MHC class I or MHC class II complex.

"Administering" refers to the physical introduction of an agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes

of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as in vivo electroporation. In some embodiments, the formulation is administered via a non-parenteral route, e.g., orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

"Parenteral" administration of composition of the invention includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, or infusion techniques.

As used herein, "treating" or "treatment" refers to an approach for obtaining beneficial or desired results, including and preferably clinical results. Treatment can refer to either the amelioration of symptoms of the disease or condition, or the delaying of the progression of the disease or condition.

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

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

A "cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor.

In some embodiments, the engineered cells have an anti-tumor effect, and methods of the present invention can be used to reduce the tumor size of a tumor. The particular cancer can be responsive to chemo- or radiation therapy or the cancer can be refractory. A refractory cancer refers to a cancer that is not amenable to surgical intervention, and the cancer is either initially unresponsive to chemo- or radiation therapy or the cancer becomes unresponsive over time.

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

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

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

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

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

As used herein, an "engineered immune cell" refers to an immune cell that has been genetically modified as compared to a naturally-occurring immune cell. The term "genetically engineered" or "engineered" refers to a method of modifying the genome of a

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

As used herein, a "substantially purified" cell is a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other
10 cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some embodiments, the cells are cultured in vitro. In other embodiments, the cells are not cultured in vitro.

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

The term "immunotherapy" or "cellular immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response.

25 Examples of immunotherapy include, but are not limited to, T cell therapies, antibody therapy, fusion protein therapy. T cell therapy can include adoptive T cell therapy, tumor-infiltrating lymphocyte (TIL) immunotherapy, autologous cell therapy, engineered autologous cell therapy (eACT), and allogeneic T cell transplantation. (see, e.g., June, C. H., ed., 2001, In: Cancer Chemotherapy and Biotherapy: Principles and Practice, Lippincott
30 Williams & Wilkins, Baltimore; Vonderheide et al., 2003, Immun. Research 27: 1-15).

Cells used in immunotherapy described herein can come from any source known in the art. For example, T cells can be differentiated in vitro from a hematopoietic stem cell population,

or T cells can be obtained from a subject. T cells can be obtained from, e.g., peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In addition, the T cells can be derived from one or more T cell lines available in the art. T cells can also be obtained

5 from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as FICOLL.TM. separation and/or apheresis. Additional methods of isolating T cells for a T cell therapy are disclosed in U.S. Patent Publication No.

2013/0287748, which is herein incorporated by references in its entirety. An immunotherapy can also comprise administering a modified cell to a subject, wherein the modified cell

10 expresses CD3 and a TCR disclosed herein. In some embodiments, the modified cell is not a T cell.

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

15 The term "HLA," as used herein, refers to the human leukocyte antigen. HLA genes encode the major histocompatibility complex (MHC) proteins in humans. MHC proteins are expressed on the surface of cells and are involved in activation of the immune response. HLA class I genes encode MHC class I molecules, which are expressed on the surface of cells in complex with peptide fragments (antigens) of self or non-self proteins. T cells expressing

20 TCR and CD3 recognize the antigen:MHC class I complex and initiate an immune response to target and destroy antigen presenting cells displaying non-self proteins.

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

25 herein.

The MHC Class I molecule comprises two protein chains: the alpha chain and the β 2-microglobulin (β 2m) chain. Human β 2m is encoded by the B2M gene. The amino acid sequence of β 2m is set forth in SEQ ID NO: (Table 1). The alpha chain of the MHC Class I molecule is encoded by the HLA gene complex. The HLA complex is located within the

30 6p21.3 region on the short arm of human chromosome 6 and contains more than 220 genes of diverse function. The HLA gene are highly variant, with over 20,000 HLA alleles and related alleles, including over 15,000 HLA Class I alleles, known in the art, encoding thousands of

HLA proteins, including over 10,000 HLA Class I proteins (see, e.g., hla.alleles.org, last visited Feb. 27, 2019). There are at least three genes in the HLA complex that encode an MHC Class I alpha chain protein: HLA-A, HLA-B, and HLA-C. In addition, HLA-E, HLA-F, and HLA-G encode proteins that associate with the MHC Class I molecule.

5 **Table 1. Amino Acid Sequence of Human β 2m SEQ ID NO:144**

SEQ ID NO:	Human Beta-2-globuline (β 2m)
144	MSRSVALAVLALLSLSGLEAIQRTPKIQVYSRHPAENGKSNFLNCYVSGFH PSDIEVDLLKNGERIEKVEHSDLSFSKDWSFYLLYYTEFTPTEKDEYACRV NHVTLSQPKIVKWDRDM

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

As used herein, the term "nucleic acid" refers to a polymer comprising multiple nucleotide monomers (e.g., ribonucleotide monomers or deoxyribonucleotide monomers). "Nucleic acid" includes, for example, genomic DNA, cDNA, RNA, and DNA-RNA hybrid molecules. Nucleic acid molecules can be naturally occurring, recombinant, or synthetic. In addition, nucleic acid molecules can be single- stranded, double-stranded or triple- stranded. In some

embodiments, nucleic acid molecules can be modified. In the case of a double-stranded polymer, "nucleic acid" can refer to either or both strands of the molecule.

The term "nucleotide sequence," in reference to a nucleic acid, refers to a contiguous series of nucleotides that are joined by covalent linkages, such as phosphorus linkages (*e.g.*, phosphodiester, alkyl and aryl-phosphonate, phosphorothioate, phosphotriester bonds), and/or non-phosphorus linkages (*e.g.*, peptide and/or sulfamate bonds). In certain embodiments, the nucleotide sequence encoding, *e.g.*, a target-binding molecule linked to a localizing domain is a heterologous sequence (*e.g.*, a gene that is of a different species or cell type origin).

The terms "nucleotide" and "nucleotide monomer" refer to naturally occurring ribonucleotide or deoxyribonucleotide monomers, as well as non-naturally occurring derivatives and analogs thereof. Accordingly, nucleotides can include, for example, nucleotides comprising naturally occurring bases (*e.g.*, adenosine, thymidine, guanosine, cytidine, uridine, inosine, deoxyadenosine, deoxythymidine, deoxyguanosine, or deoxycytidine) and nucleotides comprising modified bases known in the art.

As will be appreciated by those of skill in the art, in some aspects, the nucleic acid further comprises a plasmid sequence. The plasmid sequence can include, for example, one or more operatively linked sequences selected from the group consisting of a promoter sequence, a selection marker sequence, and a locus -targeting sequence.

The term "sequence identity" means that two nucleotide or amino acid sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least, *e.g.*, at least about 70% sequence identity, at least about 80% sequence identity, at least about 85% sequence identity, at least about 90% sequence identity, at least 95% sequence identity, at least about 99% sequence identity, or more. For sequence comparison, typically one sequence acts as a reference sequence (*e.g.*, parent sequence), to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 48:443 (1970), by the

search for similarity method of Pearson & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al. 2000, 5 Current Protocols in Molecular Biology). One example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al, J. Mol. Biol. 215:403 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (publicly accessible through the National Institutes of Health NCBI internet 10 server). Typically, default program parameters can be used to perform the sequence comparison, although customized parameters can also be used. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89: 10915 (1989)).

15 As used herein, the term "operably linked" may refer to a juxtaposition or arrangement of specified elements that allows them to perform in concert to bring about an effect. For example, a promoter may be operably linked to a coding sequence if it controls the transcription of the coding sequence.

"Expression vector" refers to a vector comprising a recombinant polynucleotide comprising 20 expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, such as cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., Sendai viruses, lentiviruses, retroviruses, adenoviruses, and 25 adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "isolated" refers to a composition, compound, substance, or molecule altered by the hand of man from the natural state. For example, a composition or substance that occurs in nature is isolated if it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living animal is not 30 isolated, but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is isolated, as the term is employed herein.

"Encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (i.e., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or an RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

A "vector" is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, Sendai viral vectors, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "promoter" as used herein is defined as a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory

sequence may, for example, be one which expresses the gene product in a tissue specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

A "lentivirus" as used herein refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses. Vectors derived from lentiviruses offer the means to achieve significant levels of gene transfer in vivo.

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof. An exemplary "peptide" of a length of normally between 8 and 12 amino acids, presented on

MHC-I, represents the molecular structure recognized by a TCR. A “peptide” can be interchangeably called a “T cell epitope” or “epitope”.

As used herein, the term "conservative sequence modifications" is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into a TCR of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain.

Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the TCR can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for the ability to bind antigens using recognized functional assays.

The phrase "antigenic specificity," as used herein, means that the TCR can specifically bind to and immunologically recognize an antigen. Exemplary antigens include, but are not limited to EBV antigens, e.g., BRLF1, or LMP2, and mutant splice factor-induced peptide of MAPK8IP2, or HERV-K gag protein.

The term “antigen-presenting cell”, as used herein, designates cells having the capability to present processed antigenic moiety fragments via MHC class I or MHC class II molecules. Most cell types including cancer cells can express MHC class I molecules and present fragments via MHC class I molecules, while MHC class II molecules are expressed on professional antigen presenting cells. Professional antigen-presenting cells may be a B-cell, a monocyte, or a dendritic cell. The antigen presenting cells may be synthetic, or be isolated from peripheral blood mononuclear cells (PBMCs). Artificial APCs are a type of cell line that expresses an HLA molecule of interest for testing of TCR binding. The HLA protein can be endogenously expressed, or the artificial APCs can be engineered to express the HLA

molecule of interest. Artificial APCs expressing the HLA allele of interest can be loaded with peptides such that the binding of a TCR to a peptide:HLA class I complex can be tested.

In the context of the present invention, by "EBV-associated disease, disorder or condition" is meant any clinical pathology resulting from infection by an Epstein Barr virus. To this end,

5 EBV-associated disease, disorder or condition can mean any disease caused, directly or indirectly, by EBV as well as diseases which predispose a patient to infection by EBV. Examples of diseases falling into the former category include infectious mononucleosis, nasopharyngeal carcinoma, and Burkitt's lymphoma. Diseases in the latter category (i.e., those which place the patient at risk of EBV infection) include acquired immune deficiency
10 syndrome and, generally, any condition that causes a state of immunosuppression or decreased function of the immune system such as patients who receive organ transplants and certain cancer therapies. In one particular embodiment, the EBV-associated disease, disorder or condition suitably is or comprises multiple sclerosis.

The term "transfected" or "transformed" or "transduced" as used herein refers to a process by
15 which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

By the term "specifically binds," as used herein with respect to a T cell receptor, is meant a T
20 cell receptor which recognizes a specific antigen complexed with an MHC molecule, but does not substantially recognize or bind other antigen:MHC complexes in a sample.

By the term "stimulation," is meant a primary response induced by binding of a stimulatory molecule (e.g., a TCR/CD3 complex) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex.
25 Stimulation can mediate altered expression of certain molecules, such as downregulation of TGF-beta, and/or reorganization of cytoskeletal structures, and the like.

A "stimulatory molecule," as the term is used herein, means a molecule on a T cell that specifically binds with a cognate stimulatory ligand present on an antigen presenting cell.

Throughout this specification and the claims which follow, unless the context requires
30 otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. When used herein,

the term "comprising" can be substituted with the term "containing" or "including" or sometimes when used herein with the term "having".

When used herein "consisting of" excludes any element, step, or ingredient not specified in the claim element. When used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

It should be understood that this invention is not limited to the particular methodology, protocols, material, reagents, and substances, etc., described herein and as such can vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

In various embodiments, the invention includes one or more of the features defined hereinabove.

III. DETAILED DESCRIPTION OF THE EMBODIMENTS

In various embodiments, the present invention provides human T cell receptors (TCRs) binding to EBV-derived antigenic peptides, and nucleic acids encoding the TCRs of the invention. In various embodiments, the present invention also provides human T cell receptors (TCRs) binding to tumor-derived or tumor-associated peptides, such as mutant splice-factor-induced peptide of MAPK8IP2 and peptide from HERV-K gag protein. Also provided is a method of transfecting a human T cell with a nucleic acid encoding a T cell receptor such that the T cell integrates the nucleic acid into its genome and expresses the encoded TCR. In some embodiments, the invention provides a host cell with the nucleic acid integrated into the host cell genome, and such a T cell expressing the TCR. The instant

invention further provides methods of preventing, treating or ameliorating a disease in a subject by administering to a subject in need thereof a cell of the invention.

A. Adoptive cell transfer

In some embodiments, the engineered TCRs described herein are used in T-cell-based ACT.

- 5 In some embodiments, the engineered TCRs described herein are exogenously expressed on T-cells through genetic engineering methods including, but not limited to, lentiviral transduction, or messenger ribonucleic acid (mRNA) transfection, of nucleic acids encoding for the TCR sequences described herein. In some embodiments, the TCRs used for ACT comprise a TCR sequence fused with a T-cell binding domain, including but not limited to a
10 single-chain fragment binding to CD3. In some embodiments, the TCRs are used in T-cell based ACT in combination with one or more therapeutic agents, e.g., immune modulating agents, including but not limited to cytokines, TLR agonists, RIG-I like receptor (RLR) agonists.

- Adoptive cell transfer (ACT) is an immunotherapy involving administration of immune cells
15 with direct anti-cancer activity to a subject in need thereof. The advantages of ACT over other immunotherapies are multiple. Firstly, the antitumor T-cells can be grown in vitro in large numbers, then selected for high-avidity recognition of the desired tumor antigen, as well as effector functions. Secondly, in vitro activation circumvents the presence of inhibitory factors found in vivo. Thirdly, ACT allows for manipulation of the host before cell transfer to
20 provide a favorable microenvironment supporting antitumor activity (Rosenberg and Restifo, Science 348(6230):62-68 (2015)).

- ACT using naturally occurring tumor-reactive T-cells achieves durable, complete regressions in patients with melanoma, as well as other common epithelial cancers (Rosenberg and Restifo, Science 348(6230):62-68 (2015)). In some embodiments, TCR-expressing T-cells
25 are used for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering from cancer, including an EBV-associated cancer.

- In other embodiments, ACT is used in combination with immune modulating agents, selected from the group of cytokines, TLR agonist, RIG-I like receptor (RLR) agonists, immune checkpoint inhibitors, chemotherapeutic agents, antibodies, radiotherapy and a combination
30 thereof.

B. CDRs

Complementarity determining regions (CDRs) are regions of high variability present in the variable domain of TCRs, CARs, single chain fragments and antibodies. These highly variable CDRs are interspaced by relatively constant sequences termed framework regions (FR). In the case of TCRs, the 3 CDR regions of the TCR α chain variable domain are paired with the 3 CDRs of the TCR β chain variable domain. Together, the 6 CDRs form the antigen binding site of the TCR, thus conferring onto each TCR its specificity (Schroeder and Cavacini, J Allergy Clin Immunol 125(202):S41-S52 (2010); Bhati et al., Protein Science 23:260-272 (2014)).

- 10 In some embodiments, the isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain that binds to Epstein Barr Virus (EBV)-derived antigenic peptides when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprises three complementarity determining regions (CDR1, CDR2, and CDR3), each comprising an amino acid sequence sharing at least about 95% sequence identity with an amino acid sequence selected from Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR1 amino acid sequences share at least about 95% sequence identity with an amino acid sequence selected from: SEQ ID NOS:1; 2; 3; 4; 5; 6; 136; 149; 25; 26; 27; 28; 29; 30; 31; 32; 154, and 155, and combinations thereof, as set forth in Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR2 amino acid sequences share at least about 95% sequence identity with the TCR α chain and the TCR β chain CDR2 amino acid sequences selected from: SEQ ID NOS:7; 8; 9; 10; 11; 12; 13; 137; 150; 33; 34; 35; 36; 37; 38; 39; 40; 41; 156; 157; and 158, and combinations thereof, as set forth in Table 3.

- 25 In some embodiments, the TCR α chain comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with a member selected from SEQ ID NOS:15; 16; 17; 18; 19; 20; 21; 22; 23; 24; and 138; in combination with the TCR β chain as set forth in Table 3, which comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with a member selected from SEQ ID NOS:43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; and 139. In some embodiments, the TCR comprises a variable domain comprising the TCR α chain CDR3 and TCR β chain CDR3 of polypeptide SEQ ID pairs selected from the group consisting of: SEQ ID NOS:15 and 43; SEQ ID NOS:16 and 44; SEQ ID NOS:15 and 45; SEQ ID NOS:17 and 46; SEQ ID NOS:18 and 47; SEQ ID NOS:19 and 48; SEQ ID NOS:20 and 49; SEQ ID NOS:21 and 50; SEQ ID NOS:22 and 50;

SEQ ID NOS:21 and 51; SEQ ID NOS:23 and 52; SEQ ID NOS:23 and 53; SEQ ID NOS:24 and 54; and SEQ ID NOS:138 and 139.

In some embodiments, the isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain that binds to Mutant splice factor-induced peptide of MAPK8IP2-derived antigenic peptide when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprises three complementarity determining regions (CDR1, CDR2, and CDR3), each comprising an amino acid sequence sharing at least about 95% sequence identity with an amino acid sequence selected from Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR1 amino acid sequences share at least about 95% sequence identity with an amino acid sequence selected from: SEQ ID NOS:31, 32, 149, 154 165, and combinations thereof, as set forth in Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR2 amino acid sequences share at least about 95% sequence identity with the TCR α chain and the TCR β chain CDR2 amino acid sequences selected from: SEQ ID NOS:40, 150, 156, and 157, and combinations thereof, as set forth in Table 3.

In some embodiments, the TCR α chain comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with a member selected from SEQ ID NOS:14, 151, and 152; in combination with the TCR β chain, which comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with a member selected from SEQ ID NOS:42, 159, and 160. In some embodiments, the TCR comprises a variable domain comprising the TCR α chain CDR3 and TCR β chain CDR3 of polypeptide SEQ ID pairs selected from the group consisting of: SEQ ID NOS:14 and 42; SEQ ID NOS:151 and 159; and SEQ ID NOS:152 and 160.

In some embodiments, the isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain that binds to HERV-K gag protein-derived antigenic peptide when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprises three complementarity determining regions (CDR1, CDR2, and CDR3), each comprising an amino acid sequence sharing at least about 95% sequence identity with an amino acid sequence selected from Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR1 amino acid sequences share at least about 95% sequence identity with an amino acid sequence selected from: SEQ ID NOS:4, and 155, as set forth in Table 3. In some embodiments, the TCR α chain and the TCR β chain CDR2 amino acid sequences share at least about 95% sequence identity with the TCR α chain and the TCR β

chain CDR2 amino acid sequences selected from: SEQ ID NOS:10, and 158, as set forth in Table 3.

5 In some embodiments, the TCR α chain comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with SEQ ID NO:153, in combination with the TCR β chain, which comprises a complementary determining region CDR3 sharing at least about 95% sequence identity with SEQ ID NO:161. In some embodiments, the TCR comprises a variable domain comprising the TCR α chain CDR3 and TCR β chain CDR3 of polypeptide SEQ ID pair SEQ ID NO:153 and 161.

10 An exemplary known TCR, peptide used for isolation of TCRs, and target antigen are set forth in Kamga et al., 2019, as follows: TCR_A0001, for target antigen BRLF1, specific for peptide YVLDHLIVV (SEQ ID NO:105).

Table 2. Listing of exemplary TCRs, peptide used for isolation of TCRs, and target antigen

TCR NO	TCR ID	Peptide	Target antigen	Reference
1	TCR_A0001	YVLDHLIVV (SEQ ID NO:105)	EBV BRLF1	Reported in Kamga et al 2019
2	TCR_A0002	YVLDHLIVV (SEQ ID NO:105)	EBV BRLF1	TCR α CDR3 as reported in Kamga et al.
3	TCR_A0003	YVLDHLIVV (SEQ ID NO:105)	EBV BRLF1	
4	TCR_A0004	YVLDHLIVV (SEQ ID NO:105)	EBV BRLF1	TCR α CDR3 as reported in Kamga et al.
5	TCR_A0005	YVLDHLIVV (SEQ ID NO:105)	EBV BRLF1	
6	TCR_A0015	Peptide pool/ MGSLEMVPM (SEQ ID NO: 146)	EBV LMP2	
7	TCR_A0061	CLGGLTMV (SEQ ID NO:106)	EBV-LMP2	
8	TCR_A0062	FLYALALL (SEQ ID NO:107)	EBV LMP2	
9	TCR_A0064	CLGGLTMV (SEQ ID NO:106)	EBV-LMP2	
10	TCR_A0065	CLGGLTMV (SEQ ID NO:106)	EBV-LMP2	
11	TCR_A0066	CLGGLTMV (SEQ ID NO:106)	EBV-LMP2	
12	TCR_A0068	FLYALALL (SEQ ID NO:107)	EBV LMP2	
13	TCR_A0069	FLYALALL (SEQ ID NO:107)	EBV LMP2	
14	TCR_A0070	FLYALALL (SEQ ID NO:107)	EBV LMP2	
15	TCR_A0099	Peptide pool/ EPLPQGQLTAY (SEQ ID NO: 145)	EBV/BZLF1	
16	TCR_A0130	RLPGVLPRA (SEQ ID NO:147)	Mutant splice factor- induced peptide of MAPK8IP2	
17	TCR_A0131	RLPGVLPRA (SEQ ID NO:147)	Mutant splice factor-	

			induced peptide of MAPK8IP2	
18	TCR_A0100	FLQFKTWWI (SEQ ID NO:148)	HERV-K gag protein	
19	TCR_0132	RLPGVLPRA (SEQ ID NO:147)	Mutant splice factor-induced peptide of MAPK8IP2	

Table 3. Amino acid sequences of CDR1, 2 and 3 regions of TCR α and TCR β

TCR ID	SEQ ID	CDR1 α	SEQ ID	CDR2 α	SEQ ID	CDR3 α	SEQ ID	CDR1 β	SEQ ID	CDR2 β	SEQ ID	CDR3 β
TCR_A0002	1	YGGT VN	7	YFSGDPLV	15	CAVKDTDKLIF	26	LGHDT	34	YNNKEL	43	CASSPDFNEQFF
TCR_A0003	1	YGGT VN	7	YFSGDPLV	16	CAGGAAGNKLTF	27	SGHAT	35	FQNNGV	44	CASSSPLGGFAGANVLT
TCR_A0004	1	YGGT VN	7	YFSGDPLV	15	CAVKDTDKLIF	25	KGHDR	33	SFDVKD	45	CATSDFISDTQYF
TCR_A0005	2	TSDQ SYG	8	QGSYDEQ N	17	CAMREGGNFNKFY F	28	SQVT M	36	ANQGSE A	46	CSVGGTSGTLPANEQ FF
TCR_A0015	3	SSVS VY	9	YLSGSTLV	18	CAVSALSYNQGGK LIF	29	SGHNS	37	FNNNVP	47	CASSWTGNEQYF
TCR_A0061	4	DSAIY N	10	IQSSQRE	19	CAVLMSDNYQLIW	30	WSHS Y	38	SAAADI	48	CASSSDGMNTEAFF
TCR_A0062	5	TSIN N	11	IRSNERE	20	CATEGSSGYSTLTF	31	MNHE Y	39	SVGAGI	49	CASSKQGGGYGYTF
TCR_A0064	6	TTLS N	12	LVKSGEV	21	CAGAGAGSYQLTF	32	SGHRS	40	YFSETQ	50	CASSLEGQASSYEQYF
TCR_A0065	6	TTLS N	12	LVKSGEV	22	CAVSGAGSYQLTF	32	SGHRS	40	YFSETQ	50	CASSLEGQASSYEQYF
TCR_A0066	6	TTLS N	12	LVKSGEV	21	CAGAGAGSYQLTF	32	SGHRS	40	YFSETQ	51	CASSAEGQASSYEQYF
TCR_A0068	5	TSIN N	13	IRSNERE	23	CATEGSSGYSTLTF	31	MNHE Y	41	SVGAGI	52	CASSRQGGSGSGYTF
TCR_A0069	5	TSIN N	13	IRSNERE	23	CATEGDSGYSTLTF	31	MNHE Y	41	SVGAGI	53	CASSTQGGAYGYTF
TCR_A0070	5	TSIN N	13	IRSNERE	24	CATAGNSGYSTLTF	31	MNHE Y	41	SVGAGI	54	CASPTQGGNEAFF
TCR_A0099	136	SSNF YA	137	MTLNGDE SSNFYA	138	CAVNAGGTSYGKLT	27	SGHAT	35	FQNNGV	139	CASSSDWTANNEQFF
TCR_A0130	149	TSEN NYY	150	QEAYKQQ N	151	CAFMIIPDSNYQLI W	154	LGHNA	156	YNFKEQ	159	CASSQVGTSGRGGEL FF
TCR_A0131	165	TSEN NYY	150	QEAYKQQ N	152	CAFMLIDSGTYKYIF	31	MNHE Y	157	SMNVEV	160	CASSLGQGTETQYF
TCR_A0100	4	DSAIY N	10	IQSSQRE	153	CAVGGNNDMRF	155	PRHDT	158	FYEKM	161	CASSLINTEAFF
TCR_A0132	149	TSEN NYY	150	QEAYKQQ N	14	CAFMEADSNYQLI W	32	SGHRS	40	YFSETQ	42	CASKGRRGPDYNSPL HF

Known exemplary amino acid sequences of CDR1, 2 and 3 regions of TCR α and TCR β are set forth in Kanga et al., 2019, as follows: TCR_A0001 CDR α 1: YGGTVN (SEQ ID NO:1); CDR2 α : YFSGDPLV (SEQ ID NO:7); CDR3 α : CAVKDTDKLIF (SEQ ID NO:15); CDR1 β : KGHDR (SEQ ID NO:25); CDR2 β : SFDVKD (SEQ ID NO:33); and CDR3 β :CATSDWDDSTGELFF (SEQ ID NO:192).

C. TCRs

The T cell receptor (TCR) is composed of two chains ($\alpha\beta$ or $\gamma\delta$) that pair on the surface of the T cell to form a heterodimeric receptor. The $\alpha\beta$ TCR is expressed on most T cells in the body and is known to be involved in the recognition of MHC-restricted antigens. The molecular genetics, structure, and biochemistry of $\alpha\beta$ TCRs have now been studied thoroughly. Each α and β chain is composed of two domains: Constant domains (C) that anchor the protein in the

cell membrane and that associate with invariant subunits of the CD3 signaling apparatus, and Variable domains (V) that confer antigen recognition through six loops, called complementarity determining regions (CDR). The V domains of each chain have three CDRs. These CDRs interact with a complex between an antigenic peptide bound to a protein encoded by the major histocompatibility complex (pMHC) (Davis and Bjorkman (1988) *Nature*, 334, 395-402; Davis et al. (1998) *Annu Rev Immunol*, 16, 523-544; Murphy (2012), xix, 868 p.).

Provided herein are novel synthetic TCRs comprising the TCR α and TCR β amino acid sequences listed in Table 4, or nucleotide sequences listed in Table 5, or optimized nucleotide sequences listed in Table 6, below. Provided herein are also synthetic TCRs comprising TCR α and TCR β human variable regions and mouse constant regions, in order to improve the expression of the TCR, and in order to use the mouse constant region for the tracking of transfected human T cells with an anti-mouse antibody. Provided are human/mouse hybrid TCRs comprising mouse TCR α and TCR β constant region amino acid sequences listed in Table 7. In some embodiments, the TCRs bind to EBV-derived antigenic peptides mixes. In some embodiments, the TCRs bind to EBV-derived antigenic single peptides. In some embodiments, the TCRs bind to the EBV BRLF1-derived antigenic peptide with the sequence from SEQ ID NO:105. In some embodiments, the TCRs bind to the EBV LMP2-derived antigenic peptide with the sequence from SEQ ID NO:106. In some embodiments, the TCRs bind to the EBV LMP2-derived antigenic peptide with the sequence from SEQ ID NO:107. In some embodiments, the TCR binds to BRLF1. In some embodiments, the TCR binds to LMP2. In some embodiments, the TCR binds to BZLF1. In some embodiments, the TCR binds to BMLF1, BALF2, BMRF1, BNRF1, BLLF1, BXLF2, EBNA1, EBNA2, EBNA3, EBNA4, EBNA6, or LMP1. In some embodiments, the TCR binds to a mutant splice factor-induced peptide of MAPK8IP2. In some embodiments, the TCR binds to a peptide from HERV-K gag protein.

In some embodiments, the TCRs comprise a TCR α peptide chain sharing at least about 80%, about 85%, about 90%, or about 95% amino acid sequence identity with a member selected from SEQ ID NOS:55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 140; 162, 163 and 164 in combination with: a TCR β peptide chain sharing at least about 80%, about 85%, about 90%, or about 95% amino acid sequence identity with a member selected from SEQ ID NOS: 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 91; 141; 166; 167; and 168. In some embodiments, the TCRs comprise a variable domain comprising a TCR α chain and TCR β chain of

polypeptide SEQ ID pairs selected from the group consisting of: SEQ ID NOS: 55 and 67; SEQ ID NOS: 56 and 68; SEQ ID NOS:55 and 69; SEQ ID NOS:57 and 70; SEQ ID NOS:58 and 71; SEQ ID NOS:59 and 72; SEQ ID NOS:60 and 73; SEQ ID NOS:61 and 74; SEQ ID NOS:62 and 74; SEQ ID NOS:61 and 75; SEQ ID NOS:63 and 76; SEQ ID NOS:64 and 77; SEQ ID NOS:65 and 78; SEQ ID NOS:140 and 141; SEQ ID NOS:162 and 166; SEQ ID NOS:163 and 167; SEQ ID NOS:164 and 168; and SEQ ID NOS: 66 and 91.

In some embodiments, the TCRs comprise a TCR α chain variable domain encoded by a nucleic acid sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 142; 169; 170; 171; 108; 109; 110; 111; 112; 113; 114; 115; 116; 117; 118; 119; 120; 134; 175; 176; 177; 186; and 188 in combination with a TCR β chain encoded by a nucleic acid sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:92; 93; 94; 95; 96; 97; 98; 99; 100; 101; 102; 103; 104; 143; 172; 173; 174; 121; 122; 123; 124; 125; 126; 127; 128; 129; 130; 131; 132; 133; 135; 178; 179; 180, 187 and 189, as set forth in Table 5 and Table 6. In some embodiments, the TCRs comprise TCR α chain and TCR β chain of nucleotide SEQ ID pairs selected from the group consisting of: SEQ ID NOS:79 and 92; SEQ ID NOS:80 and 93; SEQ ID NOS:79 and 94; SEQ ID NOS:81 and 95; SEQ ID NOS:82 and 96; SEQ ID NOS:83 and 97; SEQ ID NOS:84 and 98; SEQ ID NOS:85 and 99; SEQ ID NOS:86 and 100; SEQ ID NOS:87 and 101; SEQ ID NOS:88 and 102; SEQ ID NOS:89 and 103; SEQ ID NOS:90 and 104; SEQ ID NOS:142 and 143; SEQ ID NOS:169 and 172; SEQ ID NOS: 170 and 173; SEQ ID NOS: 171 and 174; SEQ ID NOS:108 and 121; SEQ ID NOS:109 and 122; SEQ ID NOS:110 and 123; SEQ ID NOS:111 and 124; SEQ ID NOS:112 and 125; SEQ ID NOS:113 and 126; SEQ ID NOS:114 and 127; SEQ ID NOS:115 and 128; SEQ ID NOS:116 and 129; SEQ ID NOS:117 and 130; SEQ ID NOS:118 and 131; SEQ ID NOS:119 and 132; SEQ ID NOS:120 and 133; SEQ ID NOS:134 and 135; SEQ ID NOS:175 and 178; SEQ ID NOS:176 and 179; SEQ ID NOS: 177 and 180; SEQ ID NOS:186 and 187 and SEQ ID NOS: 188 and 189.

In some embodiments, the TCRs comprise the TCR α chain and the TCR β chain complete amino acid sequences share at least about 80%, about 85%, about 90%, or about 95% sequence identity with the sequence combinations set forth in Table 4. In some embodiments, the TCRs comprise the TCR α chain and the TCR β chain complete nucleotide sequences share at least about 80%, about 85%, about 90%, or about 95% sequence identity with the sequence combinations set forth in Table 5 and Table 6.

Table 4. Amino acid sequences of the TCR α and TCR β variable regions. The CDR3 region is underlined.

TCR ID	TCR α variable region	TCR β variable region
TCR_A0002	AQSVSQHNHHVILSEAA SELE GCNYSYGGTVNLFWYVQYPG QHLQ LL LYFSGDPLVKGIKGF EA EIKSKFSNLRKPSVQWS DTAEYFC AVK DT DKL IFGTGTRLQVFP (SEQ ID NO:55)	DTAVSQTPKYLV TQ MGNDKSIKCEQNLGHDTMYWYKQDS KKFLKIMFSYNNKELIINETV PN RFSPKSPDKAHLNLHINSLEL GDSAVYFC ASS PD FNE QFFGPGTRLTVL (SEQ ID NO:67)
TCR_A0003	AQSVSQHNHHVILSEAA SELE GCNYSYGGTVNLFWYVQYPG QHLQ LL LYFSGDPLVKGIKGF EA EIKSKFSNLRKPSVQWS DTAEYFCAGGAAGNKLTFGGGTRVLVKP (SEQ ID NO:56)	EAGVAQSPRYKIEKRQSVAFWCNPISGHATLYWYQQILGQ GPKLLIQFQNGVVDSDQLPKDRFSAERLKGVDSTLKIQPA KLEDSAVYLC ASS SP LG GFAGANVLTFGAGSRLTVL (SEQ ID NO:68)
TCR_A0004	AQSVSQHNHHVILSEAA SELE GCNYSYGGTVNLFWYVQYPG QHLQ LL LYFSGDPLVKGIKGF EA EIKSKFSNLRKPSVQWS DTAEYFC AVK DT DKL IFGTGTRLQVFP (SEQ ID NO:55)	DADVTQTPRNRIKTGKRIMLECSQTKGHDRMYWYRQDP GLGLRLIYYSFDVKDINKGEISDGYSVSRQAQAKFSLSESAIP NQATALYFC ATS DFISDTQYFGPGTRLTVL (SEQ ID NO:69)
TCR_A0005	AQKITQTQPGMFVQKEAVTLDCTYDSDQSYGLFWYKQPS SGEMIFLIYQGSYDEQNATEGRYSLNFKARKSANLVISASQL GDSAMYFC AM REGGNFNK FY FGSGTKLNVKP (SEQ ID NO:57)	SAVISQKPSRDIQCRGTSLTICQCVDSQVTMMFWYRQPG QSLTLIATANQGSEATYESGFVIDKFPISRNLTFTSTLVSNM SPEDSSIIY CS VGGTSGTL PANE QFFGPGTRLTVL (SEQ ID NO:70)
TCR_A0015	AQSVTQLDSQVPFEEAPVELRCNYSYSSVYLFWYVQYPN QGLQ LL LYLSGSTLVKINGFEAEFNKSQTSFHLRKPSPVHISD TAEYFC AV SALSYNQGGKLI F FGQGTLSVKP (SEQ ID NO:58)	DAGVIQSPRHEVTEMGQEVTLRCKPISGHNSLFWYRQTM MRGLELLIYFNNVPIDDSGMPEDRFSAKMPNASFSTLKIQ PSEPRDSAVYFC ASS WTGNEQYFGPGTRLTVT (SEQ ID NO:71)
TCR_A0061	KQEV TQ IPAA SV PEGENLV NC SFTSDAIYNLQWFRQDPGK GLTSL LL IYSSQREQTSGRLNASL DK SGRSTLYIAASQPGDSA TYL CA VLMDSNYQLI W GAGTKLIKP (SEQ ID NO:59)	DAGITQSPRYKITETGRQVTLMCHQTWSHSYMFYRQDL GHGLRLIYSSAAADITDKGEVDPGYVVSRSKTENFPLTLESAT RSQTSVYFC ASS SDGMNTEAFFGQGTRLTVV (SEQ ID NO:72)
TCR_A0062	SQQGEEDPQALSIQEGENATMNCYSYKTSINN LQ WYRQNSG RGLVHLILIRSNEREKHSGRRLVTLDTSKSS LL ITASRAADTA SYFCATEGSSGYSTLT FG KGTMLLVSP (SEQ ID NO:60)	NAGVTQTPKFQVLKTGQSM TL QCAQDMNHEYMSWYRQ DPGMGLRLIHYSVGAGITDQGEV PN GYNVSRTTDFPLRL LSAAPSQTSVYFC ASS KQGGGYGTYFGSGTRLTVV (SEQ ID NO:73)
TCR_A0064	GQQVMQIPQYQHVQEGEDFTTYCNSST LS NIQWYKQRP GHPVFLIQLVKS GE VKKQKRLTFQGEAKNSSLHITATQTTD VGTYFC AG AGAGSYQLT FG KGTKLSVIP (SEQ ID NO:61)	KAGVTQTPRYLIKTRGQV TL SCSPISGHRSVSWYQQTPGQ GLQFLFEYFSETQRNKG NF GRFSGRQFSNSRSEMN V STLE LGDSALYL CASS LEGQASSYEYQYFGPGTRLTVT (SEQ ID NO:74)
TCR_A0065	GQQVMQIPQYQHVQEGEDFTTYCNSST LS NIQWYKQRP GHPVFLIQLVKS GE VKKQKRLTFQGEAKNSSLHITATQTTD VGTYFC AV SGAGSYQLT FG KGTKLSVIP (SEQ ID NO:62)	KAGVTQTPRYLIKTRGQV TL SCSPISGHRSVSWYQQTPGQ GLQFLFEYFSETQRNKG NF GRFSGRQFSNSRSEMN V STLE LGDSALYL CASS LEGQASSYEYQYFGPGTRLTVT (SEQ ID NO:74)
TCR_A0066	GQQVMQIPQYQHVQEGEDFTTYCNSST LS NIQWYKQRP GHPVFLIQLVKS GE VKKQKRLTFQGEAKNSSLHITATQTTD VGTYFC AG AGAGSYQLT FG KGTKLSVIP (SEQ ID NO:61)	KAGVTQTPRYLIKTRGQV TL SCSPISGHRSVSWYQQTPGQ GLQFLFEYFSETQRNKG NF GRFSGRQFSNSRSEMN V STLE LGDSALYL CASS AEGQASSYEYQYFGPGTRLTVT (SEQ ID NO:75)
TCR_A0068	SQQGEEDPQALSIQEGENATMNCYSYKTSINN LQ WYRQNSG RGLVHLILIRSNEREKHSGRRLVTLDTSKSS LL ITASRAADTA SYFCATEGSSGYSTLT FG KGTMLLVSP (SEQ ID NO:63)	NAGVTQTPKFQVLKTGQSM TL QCAQDMNHEYMSWYRQ DPGMGLRLIHYSVGAGITDQGEV PN GYNVSRTTDFPLRL LSAAPSQTSVYFC ASS RQGGSGSYT FG SGTRLTVV (SEQ ID NO:76)
TCR_A0069	SQQGEEDPQALSIQEGENATMNCYSYKTSINN LQ WYRQNSG RGLVHLILIRSNEREKHSGRRLVTLDTSKSS LL ITASRAADTA SYFCATEGDSGYSTLT FG KGTMLLVSP (SEQ ID NO:64)	NAGVTQTPKFQVLKTGQSM TL QCAQDMNHEYMSWYRQ DPGMGLRLIHYSVGAGITDQGEV PN GYNVSRTTDFPLRL LSAAPSQTSVYFC AST TQGGAYGYT FG SGTRLTVV (SEQ ID NO:77)
TCR_A0070	SQQGEEDPQALSIQEGENATMNCYSYKTSINN LQ WYRQNSG RGLVHLILIRSNEREKHSGRRLVTLDTSKSS LL ITASRAADTA SYFCATAGNSGYSTLT FG KGTMLLVSP (SEQ ID NO:65)	NAGVTQTPKFQVLKTGQSM TL QCAQDMNHEYMSWYRQ DPGMGLRLIHYSVGAGITDQGEV PN GYNVSRTTDFPLRL LSAAPSQTSVYFC AST PQGGNEAFFGQGTRLTVV (SEQ ID NO:78)
TCR_A0099	ILNVEQSPQSLHVQEGDSTNFTCSFPSSNFYALHWYRWETA KSPEALFVMTLNGDEKKGRISATLNTKEGYSYLYIKGSQPED SATYL CA VNAGGTSYGLT FG QGQGTILT V HP (SEQ ID NO:140)	EAGVAQSPRYKIEKRQSVAFWCNPISGHATLYWYQQILGQ GPKLLIQFQNGVVDSDQLPKDRFSAERLKGVDSTLKIQPA KLEDSAVYLC ASS SDWTANNEQFFGPGTRLTVL (SEQ ID NO:141)
TCR_A0130	AQTVTQSQPEMSVQEAETVLTCTYDTS ES NYLFWYKQPP SRQMILVIRQEAYKQ Q NATENRFSVNFQKA AK SFSLKISDSQ LGDTAM Y FC AF MIPDSNYQLI W GAGTKLIKP (SEQ ID NO:162)	ETGVTQTPRHLVGMGMTN KK SLKCEQHLGH N AMYWYKQS AKKPLELMFYVNFKEQTENN SV PSRFSPECN SS HLFLHLHT LQPEDSALYL CASS QVGTSGRGELFFEGGSRLTVL (SEQ ID NO:166)
TCR_A0131	AQTVTQSQPEMSVQEAETVLTCTYDTS ES NYLFWYKQPP SRQMILVIRQEAYKQ Q NATENRFSVNFQKA AK SFSLKISDSQ LGDTAM Y FC AF MLIDSGTYK Y IFGTGTRLKVL (SEQ ID NO:163)	EAQVTQNPRLITVTGK KL TVTCSQNMNHEYMSWYRQDP GLGLRQIY SM NNEVTDKGDVPEGYK VS RKEKRNFLILESP SPNQTSLYFC ASS LQGQGTETQYFGPGTRL LL V (SEQ ID NO:167)

TCR_A0100	KQEVTPQAALSVPEGENLVNCSFTDSAIYNLQWFRQDPGK GLTSLLIQSSQREQTSGRNLNASLDKSSGRSTLYIAASQPGDSA TYLCAVGGNNNDMRFGAGTRLTVP (SEQ ID NO:164)	AAGVIQSPRHLIKEKRETATLCYPIPRHDTVYVYQQGPGQ DPQFLISFYEQMQSDKGSIPDRFSAQQFSDYHSELNMSSEL GDSALYFCASSLINTAEFFGQGTTLTV (SEQ ID NO:168)
TCR_A0132	AQTVTQSQPEMSVQEAETVLTSCYDTSESNNYLFYWKQPP SRQMILVIRQEAYKQQNATENRFSVNFQKAASFSLKISDSQ LGDAMYFCAFMEADSNYQLIWGAGTKLIKP (SEQ ID NO:66)	KAGVTQTPRYLIKTRGQQVTLSCSPISGHRVSWYQQTPGQ GLQFLFEYFSETQRNKGFPGRFSGRQFSNSRSEMNVTLE LGDSALYLCASKGRRGPDYNSPLHFGNGTRTLTV (SEQ ID NO:91)

Exemplary known TCR α and TCR β variable regions amino acid sequences are set forth in Kamga et al., 2019, as follows: TCR_A0001: TCR α variable region:

QSVSQHNHHVILSEAASLELGCNYSYGGTVNLFWYVQYPGQHLQLLLKYFSGDPLV
KGIKGFEAEFIKSKFSFNLRKPSVQWSDTAEYFCAVKDTDKLIFGTGTRLQVFP (SEQ
ID NO:55); TCR β variable region:

DADVTQTPRNRITKTGKRIMLECSQTKGHDRMYWYRQDPGLGLRLIYYSFDVKDIN
KGEISDGYSVSRQAQAKFSLSLESAIPNQATALYFCATSDWDDSTGELFFGEGSRLTVL
(SEQ ID NO:193). The CDR3 region is underlined.

In some embodiments, the TCR α chain variable domain nucleotide sequence is selected from the group consisting of SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:142, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:186. In some embodiments, the TCR α chain variable domain nucleotide sequence shares at least about 80%, or 85%, or 90%, or 95% sequence identity with a member selected from: SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:142, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:186, as listed in Table 5.

In some embodiments, the TCR β chain variable region nucleotide sequence is selected from the group consisting of SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:143, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, and SEQ ID NO: 187. In some embodiments, the TCR β chain variable region nucleotide sequence is at least 80%, or 85%, or 90%, or 95%, or 99% identical to SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:143, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, and SEQ ID NO: 187 as listed in Table 5.

Table 5. Nucleotide sequences of the TCR α and TCR β variable regions. The CDR3 region is underlined.

TCR ID	TCR α variable region	TCR β variable region
TCR_A0002	GCCCAGTCTGTGAGCCAGCATAA CCACCACGTAATTCTCTCTGAAGC AGCCTCACTGGAGTTGGGATGCA ACTATTCCTATGGTGGAAGTGTTA ATCTCTTCTGGTATGTCCAGTACC CTGGTCAACACCTTCAGCTTCTCC TCAAGTACTTTTCAGGGGATCCAC TGGTTAAAGGCATCAAGGGCTTT GAGGCTGAATTTATAAAGAGTAA ATTCTCCTTTAATCTGAGGAAACC CTCTGTGCAGTGGAGTGACACAG CTGAGTACTTCT <u>GTGCCGTGAAGG</u> <u>ACACCGACAAGCTCATCTTTGGG</u> ACTGGGACCAGATTACAAGTCTTT CCA (SEQ ID NO:79)	GACACAGCTGTTTCCCAGACTCCA AAATACCTGGTCACACAGATGGG AAACGACAAGTCCATTAAATGTG AACAAAATCTGGGCCATGATACT ATGTATTGGTATAAACAGGACTCT AAGAAATTTCTGAAGATAATGTTT AGCTACAATAATAAGGAGCTCAT TATAAATGAAACAGTTCCAAATC GCTTCTCACCTAAATCTCCAGACA AAGCTCACTTAAATCTTCACATCA ATTCCCTGGAGCTTGGTGACTCTG CTGTGTATTTCTGTGCCAGCAGCC <u>CAGACTTCAATGAGCAGTTCTTCG</u> GGCCAGGGACACGGCTCACCGTG CTA (SEQ ID NO:92)
TCR_A0003	GCCCAGTCTGTGAGCCAGCATAA CCACCACGTAATTCTCTCTGAAGC AGCCTCACTGGAGTTGGGATGCA ACTATTCCTATGGTGGAAGTGTTA ATCTCTTCTGGTATGTCCAGTACC CTGGTCAACACCTTCAGCTTCTCC TCAAGTACTTTTCAGGGGATCCAC TGGTTAAAGGCATCAAGGGCTTT GAGGCTGAATTTATAAAGAGTAA ATTCTCCTTTAATCTGAGGAAACC CTCTGTGCAGTGGAGTGACACAG CTGAGTACTTCT <u>GTGCCGGGGGA</u> <u>GCTGCAGGCAACAAGCTAACTTT</u> <u>TGGAGGAGGAACCAGGGTGCTAG</u> TTAAACCA (SEQ ID NO:80)	GAAGCTGGAGTTGCCCAGTCTCC CAGATATAAGATTATAGAGAAAA GGCAGAGTGTGGCTTTTTTGGTGCA ATCCTATATCTGGCCATGCTACCC TTTACTGGTACCAGCAGATCCTGG GACAGGGCCCAAAGCTTCTGATT CAGTTTCAGAATAACGGTGTAGT GGATGATTACAGTTGCCTAAGG ATCGATTTTCTGCAGAGAGGCTCA AAGGAGTAGACTCCACTCTCAAG ATCCAACCTGCAAAGCTTGAGGA CTCGGCCGTGTATCTCTGTGCCAG <u>CAGTTCACCATTGGGGGGGTTTCG</u> <u>CGGGGGCCAACGTCCTGACTTTC</u> GGGGCCGGCAGCAGGCTGACCGT GCTG (SEQ ID NO:93)
TCR_A0004	GCCCAGTCTGTGAGCCAGCATAA CCACCACGTAATTCTCTCTGAAGC AGCCTCACTGGAGTTGGGATGCA ACTATTCCTATGGTGGAAGTGTTA ATCTCTTCTGGTATGTCCAGTACC CTGGTCAACACCTTCAGCTTCTCC TCAAGTACTTTTCAGGGGATCCAC TGGTTAAAGGCATCAAGGGCTTT GAGGCTGAATTTATAAAGAGTAA ATTCTCCTTTAATCTGAGGAAACC CTCTGTGCAGTGGAGTGACACAG CTGAGTACTTCT <u>GTGCCGTGAAGG</u> <u>ACACCGACAAGCTCATCTTTGGG</u> ACTGGGACCAGATTACAAGTCTTT CCA	GATGCTGATGTTACCCAGACCCC AAGGAATAGGATCACAAAGACAG GAAAGAGGATTATGCTGGAATGT TCTCAGACTAAGGGTCATGATAG AATGTACTGGTATCGACAAGACC CAGGACTGGGCCTACGGTTGATC TATTACTCCTTTGATGTCAAAGAT ATAAACAAAGGAGAGATCTCTGA TGGATACAGTGTCTCTCGACAGG CACAGGCTAAATTCTCCCTGTCCC TAGAGTCTGCCATCCCCAACCAG ACAGCTCTTTACTTCTGTGCCACC <u>AGTGATTTTCATCTCAGATACGCAG</u> <u>TATTTTGGCCCAGGCACCCGGCTG</u> ACAGTGCTC

	(SEQ ID NO:79)	(SEQ ID NO:94)
TCR_A0005	GCCCAGAAGATAACTCAAACCCA ACCAGGAATGTTCTGTCAGGAAA AGGAGGCTGTGACTCTGGACTGC ACATATGACACCAGTGATCAAAG TTATGGTCTATTCTGGTACAAGCA GCCCAGCAGTGGGGAAATGATTT TTCTTATTTATCAGGGGTCTTATG ACGAGCAAAATGCAACAGAAGGT CGCTACTCATTGAATTTCCAGAAG GCAAGAAAATCCGCCAACCTTGT CATCTCCGCTTCACAACTGGGGG ACTCAGCAATGTATTTCTGTGCAA <u>TGAGAGAGGGCGGGAACTTCAAC</u> <u>AAATTTTACTTTGGATCTGGGACC</u> AAACTCAATGTAAAACCA (SEQ ID NO:81)	AGTGCTGTCATCTCTCAAAAGCCA AGCAGGGATATCTGTCAACGTGG AACCTCCCTGACGATCCAGTGTCA AGTCGATAGCCAAGTCACCATGA TGTTCTGGTACCGTCAGCAACCTG GACAGAGCCTGACACTGATCGCA ACTGCAAATCAGGGCTCTGAGGC CACATATGAGAGTGGATTTGTCAT TGACAAGTTTCCCATCAGCCGCCC AAACCTAACATTCTCAACTCTGAC TGTGAGCAACATGAGCCCTGAAG ACAGCAGCATATATCTCTGACG <u>GTTGGTGGGACTAGCGGGACTCT</u> <u>CCCTGCCAATGAGCAGTTCTTCGG</u> GCCAGGGACACGGCTCACCGTGC TA (SEQ ID NO:95)
TCR_A0015	GCCCAGTCTGTGACCCAGCTTGAC AGCCAAGTCCCTGTCTTTGAAGA AGCCCCTGTGGAGCTGAGGTGCA ACTACTCATCGTCTGTTTCAGTGT ATCTCTTCTGGTATGTGCAATACC CCAACCAAGGACTCCAGCTTCTCC TGAAGTATTTATCAGGATCCACCC TGGTTAAAGGCATCAACGGTTTGT AGGCTGAATTTAACAAGAGTCAA ACTTCCTTCCACTTGAGGAAACCC TCAGTCCATATAAGCGACACGGC TGAGTACTTCTGTGCTGTGAGTGC <u>CCTTTCTTATAACCAGGGAGGAA</u> <u>AGCTTATCTTCGGACAGGGAACG</u> GAGTTATCTGTGAAACCC (SEQ ID NO:82)	GATGCTGGAGTTATCCAGTCACCC CGCCATGAGGTGACAGAGATGGG ACAAGAAGTGACTCTGAGATGTA AACCAATTTCAGGCCACAACCTCC CTTTTCTGGTACAGACAGACCATG ATGCGGGGACTGGAGTTGCTCAT TACTTTAACAACAACGTTCCGAT AGATGATTTCAGGGATGCCCCGAGG ATCGATTCTCAGCTAAGATGCCTA ATGCATCATTCTCCACTCTGAAGA TCCAGCCCTCAGAACCCAGGGAC TCAGCTGTGTACTTCTGTGCCAGC <u>AGCTGGACAGGGAACGAGCAGTA</u> <u>CTTCGGGCCGGGCACCAGGCTCA</u> CGGTCACA (SEQ ID NO:96)
TCR_A0061	AAACAGGAGGTGACACAGATTCC TGCAGCTCTGAGTGTCACAGAAG GAGAAAACCTGGTTCTCAACTGC AGTTTCACTGATAGCGCTATTTAC AACCTCCAGTGGTTTAGGCAGGA CCCTGGGAAAGGTCTCACATCTCT GTTGCTTATTCAGTCAAGTCAGAG AGAGCAAACAAGTGGAAGACTTA ATGCCTCGCTGGATAAATCATCA GGACGTAGTACTTTATACATTGCA GCTTCTCAGCCTGGTGACTCAGCC ACCTACCTCTGTGCTGTCCTTATG <u>GATAGCAACTATCAGTTAATCTG</u> <u>GGGCGCTGGGACCAAGCTAATTA</u> TAAAGCCA (SEQ ID NO:83)	GATGCTGGAATCACCCAGAGCCC AAGATACAAGATCACAGAGACAG GAAGGCAGGTGACCTTGATGTGT CACCAGACTTGGAGCCACAGCTA TATGTTCTGGTATCGACAAGACCT GGGACATGGGCTGAGGCTGATCT ATTACTCAGCAGCTGCTGATATTA CAGATAAAGGAGAAGTCCCCGAT GGCTATGTTGTCTCCAGATCCAAG ACAGAGAATTTCCCCCTCACTCTG GAGTCAGCTACCCGCTCCCAGAC ATCTGTGTATTTCTGCGCCAGCAG <u>CTCGGACGGGATGAACACTGAAG</u> <u>CTTTCTTTGGACAAGGCACCAGAC</u> TCACAGTTGTA (SEQ ID NO:97)
TCR_A0062	AGTCAACAGGGAGAAGAGGATCC TCAGGCCTTGAGCATCCAGGAGG GTGAAAATGCCACCATGAACTGC AGTTACAAAACCTAGTATAAACAA	AATGCTGGTGTCACTCAGACCCC AAAATTCCAGGTCTGAAGACAG GACAGAGCATGACACTGCAGTGT GCCAGGATATGAACCATGAATA

	TTTACAGTGGTATAGACAAAATTC AGGTAGAGGCCTTGTCCACCTAA TTTTAATACGTTCAAATGAAAGA GAGAAACACAGTGGAAGATTAAG AGTCACGCTTGACACTTCCAAGA AAAGCAGTTCCTTGTGATCACGG CTTCCCGGGCAGCAGACACTGCTT CTTACTTCTGTGCTACGGAGGGCT <u>CTTCAGGATACAGCACCTCACCT</u> <u>TTGGGAAGGGGACTATGCTTCTA</u> GTCTCTCCA (SEQ ID NO:84)	CATGTCCTGGTATCGACAAGACC CAGGCATGGGGCTGAGGCTGATT CATTACTCAGTTGGTGCTGGTATC ACTGACCAAGGAGAAGTCCCCAA TGGCTACAATGTCTCCAGATCAAC CACAGAGGATTTCCCGCTCAGGC TGCTGTCGGCTGCTCCCTCCCAGA CATCTGTGTACTTCTGTGCCAGCA <u>GTAAACAGGGAGGGGGCTATGGC</u> <u>TACACCTTCGGTTCGGGGACCAG</u> GTTAACCGTTGTA (SEQ ID NO:98)
TCR_A0064	GGACAACAGGTAATGCAAATTCC TCAGTACCAGCATGTACAAGAAG GAGAGGACTTCACCACGTACTGC AATTCCTCAACTACTTTAAGCAAT ATACAGTGGTATAAGCAAAGGCC TGGTGGACATCCCGTTTTTTTGAT ACAGTTAGTGAAGAGTGGAGAAG TGAAGAAGCAGAAAAGACTGACA TTTCAGTTTGGAGAAGCAAAAAA GAACAGCTCCCTGCACATCACAG CCACCCAGACTACAGATGTAGGA ACCTACTTCTGTGCAGGAGCTGG <u>GGCTGGGAGTTACCAACTCACTTT</u> <u>CGGGAAGGGGACCAAACCTCTCGG</u> TCATACCA (SEQ ID NO:85)	AAGGCTGGAGTCACTCAAACCTCC AAGATATCTGATCAAAACGAGAG GACAGCAAGTGACACTGAGCTGC TCCCCTATCTCTGGGCATAGGAGT GTATCCTGGTACCAACAGACCCC AGGACAGGGCCTTCAGTTCCTCTT TGAATACTTCAGTGAGACACAGA GAAACAAAGGAAACTTCCCTGGT CGATTCTCAGGGCGCCAGTTCTCT AACTCTCGCTCTGAGATGAATGTG AGCACCTTGGAGCTGGGGGACTC GGCCCTTTATCTTTGCGCCAGCAG <u>CCTCGAGGGACAGGCGAGCTCCT</u> <u>ACGAGCAGTACTTCGGGCCGGGC</u> ACCAGGCTCACGGTCACA (SEQ ID NO:99)
TCR_A0065	GGACAACAGGTAATGCAAATTCC TCAGTACCAGCATGTACAAGAAG GAGAAGACTTCACCACGTACTGC AATTCCTCAACTACTTTAAGCAAT ATACAGTGGTATAAGCAAAGGCC TGGTGGACATCCCGTTTTTTTGAT ACAGTTAGTGAAGAGTGGAGAAG TGAAGAAGCAGAAAAGACTGACA TTTCAGTTTGGAGAAGCAAAAAA GAACAGCTCCCTGCACATCACAG CCACCCAGACTACAGATGTAGGA ACCTACTTCTGTGCAGTCTCTGGG GCTGGGAGTTACCAACTCACTTTC GGGAAGGGGACCAAACCTCTCGGT CATACCA (SEQ ID NO:86)	AAGGCTGGAGTCACTCAAACCTCC AAGATATCTGATCAAAACGAGAG GACAGCAAGTGACACTGAGCTGC TCCCCTATCTCTGGGCATAGGAGT GTATCCTGGTACCAACAGACCCC AGGACAGGGCCTTCAGTTCCTCTT TGAATACTTCAGTGAGACACAGA GAAACAAAGGAAACTTCCCTGGT CGATTCTCAGGGCGCCAGTTCTCT AACTCTCGCTCTGAGATGAATGTG AGCACCTTGGAGCTGGGGGACTC GGCCCTTTATCTTTGCGCCAGCAG <u>CTTGAGAGGGCAGGCCTCCTCCT</u> <u>ACGAGCAGTACTTCGGGCCGGGC</u> ACCAGGCTCACGGTCACA (SEQ ID NO:100)
TCR_A0066	GGACAACAGGTAATGCAAATTCC TCAGTACCAGCATGTACAAGAAG GAGAGGACTTCACCACGTACTGC AATTCCTCAACTACTTTAAGCAAT ATACAGTGGTATAAGCAAAGGCC TGGTGGACATCCCGTTTTTTTGAT ACAGTTAGTGAAGAGTGGAGAAG TGAAGAAGCAGAAAAGACTGACA TTTCAGTTTGGAGAAGCAAAAAA GAACAGCTCCCTGCACATCACAG	AAGGCTGGAGTCACTCAAACCTCC AAGATATCTGATCAAAACGAGAG GACAGCAAGTGACACTGAGCTGC TCCCCTATCTCTGGGCATAGGAGT GTATCCTGGTACCAACAGACCCC AGGACAGGGCCTTCAGTTCCTCTT TGAATACTTCAGTGAGACACAGA GAAACAAAGGAAACTTCCCTGGT CGATTCTCAGGGCGCCAGTTCTCT AACTCTCGCTCTGAGATGAATGTG

	CCACCCAGACTACAGATGTAGGA ACCTACTTCTGTGCAGGGGCTGG <u>GGCTGGGAGTTACCAACTCACTTT</u> <u>CGGGAAGGGGACCAAACCTCTCGG</u> TCATACCA (SEQ ID NO:87)	AGCACCTTGGAGCTGGGGGACTC GGCCCTTTATCTTTGCGCCAGCAG <u>CGCGGAGGGACAGGCTTCCTCCT</u> <u>ACGAGCAGTACTTCGGGGCCGGGC</u> ACCAGGCTCACGGTCACA (SEQ ID NO:101)
TCR_A0068	AGTCAACAGGGAGAAGAGGATCC TCAGGCCTTGAGCATCCAGGAGG GTGAAAATGCCACCATGAACTGC AGTTACAAAAC TAGTATAAACAA TTTACAGTGGTATAGACAAAATTC AGGTAGAGGCCTTGTCACCTAA TTTTAATACGTTCAAATGAAAGA GAGAAACACAGTGGAAGATTAAG AGTCACGCTTGACACTTCCAAGA AAAGCAGTTCCTTGTTGATCACGG CTTCCCGGGCAGCAGACACTGCTT CTTACTTCT <u>GTGCTACTGAGGGCG</u> <u>GTTCAGGATACAGCACCTCACCT</u> <u>TTGGGAAGGGGACTATGCTTCTA</u> GTCTCTCCA (SEQ ID NO:88)	AATGCTGGTGTCACTCAGACCCC AAAATTCCAGGTCCTGAAGACAG GACAGAGCATGACACTGCAGTGT GCCCAGGATATGAACCATGAATA CATGTCCTGGTATCGACAAGACC CAGGCATGGGGCTGAGGCTGATT CATTACTCAGTTGGTGCTGGTATC ACTGACCAAGGAGAAGTCCCCAA TGGCTACAATGTCTCCAGATCAAC CACAGAGGATTTCCCGCTCAGGC TGCTGTCGGCTGCTCCCTCCCAGA CATCTGTGTACTTCT <u>GTGCCAGCA</u> <u>GTGACAAGGGGGTTCCGGGAGT</u> <u>GGCTACACCTTCGGTTCGGGGAC</u> CAGGTAAACCGTTGTA (SEQ ID NO:102)
TCR_A0069	AGTCAACAGGGAGAAGAGGATCC TCAGGCCTTGAGCATCCAGGAGG GTGAAAATGCCACCATGAACTGC AGTTACAAAAC TAGTATAAACAA TTTACAGTGGTATAGACAAAATTC AGGTAGAGGCCTTGTCACCTAA TTTTAATACGTTCAAATGAAAGA GAGAAACACAGTGGAAGATTAAG AGTCACGCTTGACACTTCCAAGA AAAGCAGTTCCTTGTTGATCACGG CTTCCCGGGCAGCAGACACTGCTT CTTACTTCT <u>GTGCTACGGAGGGGG</u> <u>ATTCAGGATACAGCACCTCACCT</u> <u>TTGGGAAGGGGACTATGCTTCTA</u> GTCTCTCCA (SEQ ID NO:89)	AATGCTGGTGTCACTCAGACCCC AAAATTCCAGGTCCTGAAGACAG GACAGAGCATGACACTGCAGTGT GCCCAGGATATGAACCATGAATA CATGTCCTGGTATCGACAAGACC CAGGCATGGGGCTGAGGCTGATT CATTACTCAGTTGGTGCTGGTATC ACTGACCAAGGAGAAGTCCCCAA TGGCTACAATGTCTCCAGATCAAC CACAGAGGATTTCCCGCTCAGGC TGCTGTCGGCTGCTCCCTCCCAGA CATCTGTGTACTTCT <u>GTGCCAGCA</u> <u>CCACCCAGGGGGGGGCCTATGGC</u> <u>TACACCTTCGGTTCGGGGACCAG</u> GTAAACCGTTGTA (SEQ ID NO:103)
TCR_A0070	AGTCAACAGGGAGAAGAGGATCC TCAGGCCTTGAGCATCCAGGAGG GTGAAAATGCCACCATGAACTGC AGTTACAAAAC TAGTATAAACAA TTTACAGTGGTATAGACAAAATTC AGGTAGAGGCCTTGTCACCTAA TTTTAATACGTTCAAATGAAAGA GAGAAACACAGTGGAAGATTAAG AGTCACGCTTGACACTTCCAAGA AAAGCAGTTCCTTGTTGATCACGG CTTCCCGGGCAGCAGACACTGCTT CTTACTTCT <u>GTGCTACGGCCGGTA</u> <u>ATTCAGGATACAGCACCTCACCT</u> <u>TTGGGAAGGGGACTATGCTTCTA</u> GTCTCTCCA (SEQ ID NO:90)	AATGCTGGTGTCACTCAGACCCC AAAATTCCAGGTCCTGAAGACAG GACAGAGCATGACACTGCAGTGT GCCCAGGATATGAACCATGAATA CATGTCCTGGTATCGACAAGACC CAGGCATGGGGCTGAGGCTGATT CATTACTCAGTTGGTGCTGGTATC ACTGACCAAGGAGAAGTCCCCAA TGGCTACAATGTCTCCAGATCAAC CACAGAGGATTTCCCGCTCAGGC TGCTGTCGGCTGCTCCCTCCCAGA CATCTGTGTACTTCT <u>GTGCCAGCA</u> <u>CCCCCAGGGGGGCAACGAAGCT</u> <u>TTCTTTGGACAAGGCACCAGACTC</u> ACAGTTGTA (SEQ ID NO:104)

TCR_A0099	ATACTGAACGTGGAACAAAGTCC TCAGTCACTGCATGTTCAAGGAGG GAGACAGCACCAATTTACCTGC AGCTTCCCTTCCAGCAATTTTAT GCCTTACACTGGTACAGATGGGA AACTGCAAAAAGCCCCGAGGCCT TGTGTGTAATGACTTTAAATGGGG ATGAAAAGAAGAAAGGACGAAT AAGTGCCACTCTTAATACCAAGG AGGGTTACAGCTATTTGTACATCA AAGGATCCCAGCCTGAAGACTCA <u>GCCACATACCTCTGTGCCGTTAAT</u> <u>GCTGGTGGTACTAGCTATGGA</u> <u>GCTGACATTTGGACAAGGGACCA</u> TCTTGACTGTCCATCCA (SEQ ID NO:142)	GAAGCTGGAGTTGCCCAGTCTCC CAGATATAAGATTATAGAGAAAA GGCAGAGTGTGGCTTTTTTGGTGCA ATCCTATATCTGGCCATGCTACCC TTTACTGGTACCAGCAGATCCTGG GACAGGGGCCAAAGCTTCTGATT CAGTTTCAGAATAACGGTGTAGT GGATGATTACAGTTGCCTAAGG ATCGATTTTCTGCAGAGAGGCTCA AAGGAGTAGACTCCACTCTCAAG ATCCAACCTGCAAAGCTTGAGGA CTCGGCCGTGTATCTCTGTGCCAG <u>CAGCTCCGATTGGACAGCGAACA</u> <u>ATGAGCAGTTCTTCGGGCCAGGG</u> ACACGGCTCACCGTGCTA (SEQ ID NO:143)
TCR_A0130	GCCCAGACAGTCACTCAGTCTCA ACCAGAGATGTCTGTGCAGGAGG CAGAGACTGTGACCCTGAGTTGC ACATATGACACCAGTGAGAGTAA TTATTATTTGTTCTGGTACAAACA GCCTCCCAGCAGGCAGATGATTC TCGTTATTCGCCAAGAAGCTTATA AGCAACAGAATGCAACGGAGAAT CGTTTCTCTGTGAACTTCCAGAAA GCAGCCAAATCCTTCAGTCTCAA GATCTCAGACTCACAGCTGGGGG ACACTGCGATGTATTTCTGTGCTT TCATGATACCGGATAGCAACTAT CAGTTAATCTGGGGCGCTGGGAC CAAGCTAATTATAAAGCCA (SEQ ID NO:169)	GAAACGGGAGTTACGCAGACACC AAGACACCTGGTCATGGGAATGA CAAATAAGAAGTCTTTGAAATGT GAACAACATCTGGGGCATAACGC TATGTATTGGTACAAGCAAAGTG CTAAGAAGCCACTGGAGCTCATG TTTGTCTACAACCTTTAAAGAACAG ACTGAAAACAACAGTGTGCCAAG TCGCTTCTCACCTGAATGCCCCAA CAGCTCTCACTTATTCCTTCACCT ACACACCCTGCAGCCAGAAGACT CGGCCCTGTATCTCTGTGCCAGCA GCCAAGTTGGGACTAGCGGGAGG GGCGGGGAGCTGTTTTTTGGAGA AGGCTCTAGGCTGACCGTACTG (SEQ ID NO:172)
TCR_A0131	GCCCAGACAGTCACTCAGTCTCA ACCAGAGATGTCTGTGCAGGAGG CAGAGACTGTGACCCTGAGTTGC ACATATGACACCAGTGAGAATAA TTATTATTTGTTCTGGTACAAGCA GCCTCCCAGCAGGCAGATGATTC TCGTTATTCGCCAAGAAGCTTATA AGCAACAGAATGCAACGGAGAAT CGTTTCTCTGTGAACTTCCAGAAA GCAGCCAAATCCTTCAGTCTCAA GATCTCAGACTCACAGCTGGGGG ACACTGCGATGTATTTCTGTGCTT TCATGTTAATAGACTCAGGAACCT ACAAATACATCTTTGGAACAGGC ACCAGGCTGAAGGTTTTAGCA (SEQ ID NO:170)	GAAGCCCAAGTGACCCAGAACCC AAGATACCTCATCACAGTGAAGT GAAAGAAGTTAACAGTGAAGTGT TCTCAGAATATGAACCATGAGTA TATGTCCTGGTATCGACAAGACCC AGGGCTGGGCTTAAGGCAGATCT ACTATTCAATGAATGTTGAGGTG ACTGATAAGGGAGATGTTCTCTGA AGGGTACAAAGTCTCTCGAAAAG AGAAGAGGAATTTCCCCCTGATC CTGGAGTCGCCAGCCCCAACCA GACCTCTCTGTACTTCTGTGCCAG CAGTCTTGGACAGGGAACAGAGA CCCAGTACTTCGGGCCAGGCACG CGGCTCCTGGTGCTC (SEQ ID NO:173)
TCR_A0100	AAACAGGAGGTGACACAGATTCC TGCAGCTCTGAGTGTCCAGAAAG GAGAAAACCTTGGTTCTCAACTGC AGTTTCACTGATAGCGCTATTTAC AACCTCCAGTGGTTTAGGCAGGA CCCTGGGAAAGGTCTCACATCTCT	GAAACGGGAGTTACGCAGACACC AAGACACCTGGTCATGGGAATGA CAAATAAGAAGTCTTTGAAATGT GAACAACATCTGGGGCATAACGC TATGTATTGGTACAAGCAAAGTG CTAAGAAGCCACTGGAGCTCATG

	GTTGCTTATTCAGTCAAGTCAGAG AGAGCAAACAAGTGGAAGACTTA ATGCCTCGCTGGATAAATCATCA GGACGTAGTACTTTATACATTGCA GCTTCTCAGCCTGGTGACTCAGCC ACCTACCTCTGTGCTGTGGGAGGC AATAACAATGACATGCGCTTTGG AGCAGGGACCAGACTGACAGTAA AACCA (SEQ ID NO:171)	TTTGTCTACAACCTTTAAAGAACAG ACTGAAAACAACAGTGTGCCAAG TCGCTTCTCACCTGAATGCCCAA CAGCTCTCACTTATTCCTTCACCT ACACACCCTGCAGCCAGAAGACT CGGCCCTGTATCTCTGTGCCAGCA GCCAAGTTGGGACTAGCGGGAGG GGCGGGGAGCTGTTTTTTGGAGA AGGCTCTAGGCTGACCGTACTG (SEQ ID NO:174)
TCR_A0132	GCCCAGACAGTCACTCAGTCTCA ACCAGAGATGTCTGTGCAGGAGG CAGAGACTGTGACCCTGAGTTGC ACATATGACACCAGTGAGAGTAA TTATTATTTGTTCTGGTACAAACA GCCTCCCAGCAGGCAGATGATTC TCGTTATTCGCCAAGAAGCTTATA AGCAACAGAATGCAACGGAGAAT CGTTTCTCTGTGAACTTCCAGAAA GCAGCCAAATCCTTCAGTCTCAA GATCTCAGACTCACAGCTGGGGG ACACTGCGATGTATTTCTGTGCTT <u>TCATGGAGGCGGATAGCAACTAT</u> <u>CAGTTAATCTGGGGCGCTGGGAC</u> <u>CAAGCTAATTATAAAGCCA</u> (SEQ ID NO:186)	AAGGCTGGAGTCACTCAAACCTCC AAGATATCTGATCAAAACGAGAG GACAGCAAGTGACACTGAGCTGC TCCCCTATCTCTGGGCATAGGAGT GTATCCTGGTACCAACAGACCCC AGGACAGGGCCTTCAGTTCCTCTT TGAATACTTCAGTGAGACACAGA GAAACAAAGGAAACTTCCCTGGT CGATTCTCAGGGCGCCAGTTCTCT AACTCTCGCTCTGAGATGAATGTG AGCACCTTGGAGCTGGGGGACTC GGCCCTTTATCTTTGCGCCAGCAA <u>GGGCAGGCGGGGGCCGGACTATA</u> <u>ATTCACCCCTCCACTTTGGGAACG</u> <u>GGACCAGGCTCACTGTGACA</u> (SEQ ID NO:187)

The exemplary TCR_A0001 nucleotide sequences set forth in Kamga et al. 2019, are detailed as follows: TCR α variable region:

GCCCAGTCTGTGAGCCAGCATAACCACCACGTAATTCTCTCTGAAGCAGCCTCAC
TGGAGTTGGGATGCAACTATTCCTATGGTGGAACTGTTAATCTCTTCTGGTATGTC
CAGTACCCTGGTCAACACCTTCAGCTTCTCCTCAAGTACTTTTCAGGGGATCCACT
GGTTAAAGGCATCAAGGGCTTTGAGGCTGAATTTATAAAGAGTAAATTCTCCTTT
AATCTGAGGAAACCCTCTGTGCAGTGGAGTGACACAGCTGAGTACTTCTGTGCCG
TGAAAGACACCGACAAGCTCATCTTTGGGACTGGGACCAGATTACAAGTCTTTCC
AA(SEQ ID NO:79);

and TCR β variable region:

GATGCTGATGTTACCCAGACCCCAAGGAATAGGATCACAAAGACAGGAAAGAGG
ATTATGCTGGAATGTTCTCAGACTAAGGGTCATGATAGAATGTACTGGTATCGAC
AAGACCCAGGACTGGGCCTACGGTTGATCTATTACTCCTTTGATGTCAAAGATAT
AAACAAAGGAGAGATCTCTGATGGATACAGTGTCTCTCGACAGGCACAGGCTAA
ATTCTCCCTGTCCCTAGAGTCTGCCATCCCCAACCAGACAGCTCTTTACTTCTGTG
CCACCAGTGATTGGGACGACAGCACCGGGGAGCTGTTTTTTGGAGAAGGCTCTA
GGCTGACCGTACTGG(SEQ ID NO:94).

The CDR3 regions are underlined.

In some embodiments, the TCR α chain variable domain codon-optimized nucleotide sequence is selected from the group consisting of SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:134, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, and SEQ ID NO: 188. In some embodiments, the TCR α chain variable domain codon-optimized nucleotide sequence shares at least about 80%, about 85%, about 90%, or about 95%sequence identity with a member selected from: SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117 SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:134, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, and SEQ ID NO: 188. as listed in Table 6.

In some embodiments, the TCR β chain variable region codon-optimized nucleotide sequence selected from the group consisting of SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, and SEQ ID NO: 189. In some embodiments, the TCR β chain variable region codon-optimized nucleotide sequence shares at least about 80%, about 85%, about 90%, or about 95%sequence identity with a member selected from: SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, and SEQ ID NO: 189 as listed in Table 6.

Table 6. Codon-optimized nucleotide sequences of the TCR α and TCR β variable regions. The CDR3 region is underlined.

TCR ID	TCR α variable region	TCR β variable region
TCR_A0002	>COATCR_A0002 GCGCAGAGCGTTTCGCAACACAA CCACCACGTCATCCTGTCCGAGGC TGCTTCTCTGGAGCTGGGGTGCAA CTACAGCTACGGTGGCACGGTCA ATCTATTTTGGTACGTGCAGTATC CAGGACAGCATCTCCAGCTGCTGC	>COBTCR_A0002 GACACCGCCGTTTCCCAGACACC GAAGTACCTGGTGACCCAGATGG GCAACGACAAGAGCATCAAGTGC GAGCAGAACCTGGGCCATGACAC GATGTATTGGTACAAGCAGGACT CCAAGAAATTTCTGAAGATCATG

	TCAAGTACTTTTCAGGGGACCCGT TGGTGAAAGGCATCAAGGGCTTC GAAGCAGAGTTCATTAAGTCGAA ATTTTCCTTCAACCTGCGTAAGCC TTCCGTGCAGTGGTCTGATACTGC CGAGTACTTCTGTGCCGTGAAGGA <u>CACCGACAAGCTTATCTTCGGTAC</u> CGGCACCCGCCTGCAGGTGTTCCC C (SEQ ID NO:108)	TTTAGCTACAACAACAAGGAGCT CATCATTAACGAGACCGTGCCCA ACCGCTTCTACCAAAGTCGCCC GACAAAGCGCACTTGAATCTACA CATCAATTCTCTGGAGCTGGGTG ATTCTGCCGTGTACTTCTGTGCTT <u>CCTCGCCGGATTTC AACGAACAG</u> <u>TTCTTCGGCCCTGGGACTCGTCTG</u> ACCGTCCTT (SEQ ID NO:121)
TCR_A0003	>COATCR_A0003 GCGCAGAGCGTGTCCCAACACAA CCACCACGTCATCCTGTCCGAGGC TGCTTCCCTGGAGCTGGGGTGCAA CTACAGCTACGGCGGCACCGTCA ATTTGTTCTGGTACGTGCAGTATC CGGGACAGCATCTCCAGCTGCTGC TCAAGTACTTTAGTGGTGATCCAC TTGTAAAGGCATCAAGGGCTTCG AAGCCGAGTTCATTAAGTCGAAA TTTTCAATTCAACCTGCGCAAGCCC TCTGTGCAGTGGTCTGACACCGCA GAGTACTTCTGTGCCGGGGGCGC <u>GGCCGCAACAAGCTGACCTTCG</u> GAGGCGGTACTCGTGTGCTGGTG AAGCCT (SEQ ID NO:109)	>COBTRCR_A0003 GAAGCAGGGGTGGCTCAGAGCCC GCGCTACAAGATTATTGAGAAGC GCCAGTCCGTGGCGTTCTGGTGC AATCCCATCTCTGGCCACGCCAC TCTTTATTGGTACCAACAGATCCT GGGACAGGGCCCTAAATTGCTCA TCCAGTTCCAGAACAAACGGTGTG GTCGATGACAGCCAGCTGCCCAA GGACAGGTTTTTCAGCCGAGCGCC TGAAGGGCGTCGACTCGACCCTC AAAATCCAGCCAGCCAAGCTGGA GGACAGTGCGGTGTACCTGTGCG <u>CCTCCTCCTCTCCTCTGGGGCGCT</u> <u>TCGCGGGGGCCAACGTGCTGACC</u> <u>TTCCGGTGCTGGCTCCCGTCTGACC</u> GTTCTA (SEQ ID NO:122)
TCR_A0004	>COATCR_A0004 GCGCAGAGCGTGTCCCAACACAA CCACCACGTTATCCTGTCCGAGGC TGCATCCCTGGAGCTGGGGTGCA ACTACAGCTACGGTGGCACCCTC AATCTATTTTGGTACGTGCAGTAT CCTGGACAGCATTTGCAGCTGCTG CTCAAGTACTTCAGTGGGGACCCG CTGGTGAAAGGCATCAAGGGCTT CGAAGCTGAGTTCATTAAGTCGA AATTTTCATTCAACCTGCGCAAGC CCTCTGTGCAGTGGTCTGATACGG CCGAGTACTTTTGTGCCGTGAAGG <u>ACACCGACAAGCTTATCTTCGGTA</u> CCGGCACTCGTCTCCAGGTCTTCC CC (SEQ ID NO:110)	>COBTRCR_A0004 GATGCGGACGTGACCCAGACTCC CCGCAACCGCATCACCAAGACCG GCAAGCGCATCATGTTGGAGTGC TCTCAAACAAAGGGCCACGACAG GATGTACTGGTACCGGCAGGACC CGGGGCTGGGCCTCCGTCTTATCT ACTACTCCTTCGACGTGAAGGAC ATCAATAAGGGTGAGATCAGCGA TGGCTACTCCGTGTGCGGACAGG CTCAGGCCAAATTTTCACTATCTC TGGAGTCCGCCATCCCCAACCAG ACGGCACTGTACTTCTGTGCCACC <u>TCCGACTTCATTAGTGACACCCA</u> <u>GTATTTTCGGACCTGGTACTCGCCT</u> GACCGTGCTG (SEQ ID NO:123)
TCR_A0005	>COATCR_A0005 GCACAGAAGATCACCCAGACTCA ACCTGGTATGTTTGTGCAGGAGAA GGAGGCTGTCACATTGGACTGTAC CTACGACACCTCCGACCAGAGCT ACGGCCTTTTCTGGTACAAGCAGC CGAGTTCGGGGGAGATGATCTTCC TGATCTATCAGGGCTCCTACGACG AACAGAACGCGACGGAGGGCCGC	>COBTRCR_A0005 TCGGCAGTGATTAGCCAGAAGCC CTCTCGGGACATCTGCCAGCGTG GTACAAGTTTGACCATCCAGTGC CAAGTTGATTCTCAGGTCACCAT GATGTTTTGGTACCGCCAGCAGC CGGGACAGAGCCTAACTCTTATC GCGACGGCCAACCAGGGCTCCGA GGCTACCTACGAGAGCGGCTTCG

	TACTCCCTCAACTTCCAGAAGGCC CGCAAAAGCGCGAACCTGGTGAT TTCTGCTTCCCAGCTGGGTGATTC TGCCATGTATTTCTGCGCCATGCG <u>TGAGGGCGGCAACTTCAACAAGT</u> <u>TCTACTTCGGATCAGGGACCAAGC</u> TGAATGTGAAGCCC (SEQ ID NO:111)	TCATTGACAAGTTTCCCATCTCCC GCCCTAACCTGACCTTCTCGACTC TCACCGTGTCCAATATGTCTCCTG AAGACAGCTCCATCTATCTGTGCT <u>CCGTGGGCGGCACCTCCGGCACC</u> <u>CTGCCAGCCAACGAGCAGTTCTT</u> <u>CGGTCCCGGGACCCGCCTGACCG</u> TGCTG (SEQ ID NO:124)
TCR_A0015	>COATCR_A0015 GCGCAGAGCGTCACCCAGTTGGA TTCTCAGGTCCCAGTGTTGAGGA GGCTCCGGTGGAGCTTCGTTGTAA CTACTCCTCGTCAGTATCCGTGTA CCTCTTTTGGTACGTGCAGTATCC CAACCAGGGTCTGCAGCTGCTGCT CAAGTACCTGTCTGGCTCCACTCT GGTGAAGGGCATTAAATGGCTTCG AAGCAGAGTTCAACAAGTCGCAG ACCTCCTTCCATCTGCGCAAGCCC TCTGTCCACATCTCCGACACCGCC GAGTACTTTTGCGCCGTGTCCGCC <u>CTGAGCTACAACCAAGGGGGTAA</u> <u>GCTAATCTTCGGACAGGGCACCG</u> AGCTGAGTGTTAAACCT (SEQ ID NO:112)	>COBTRCR_A0015 GACGCAGGGGTGATCCAGAGCCC GCGCCATGAAGTCACCGAGATGG GCCAGGAGGTGACTCTTAGGTGT AAACCCATCTCTGGCCACAACCTC CCTCTTTTGGTACCGCCAGACTAT GATGCGTGGTCTGGAGCTGCTGA TTTACTTCAACAACAATGTGCCCA TCGATGACTCTGGTATGCCTGAG GACCGCTTTTCAGCCAAGATGCC CAACGCGTCCTTCTCGACCCTGA AGATCCAGCCGTCCGAGCCACGG GACAGCGCCGTGTACTTCTGCGC <u>TTCCAGTTGGACCGGCAACGAGC</u> <u>AGTATTTCGGACCTGGCACCCGC</u> TTGACGGTTACA (SEQ ID NO:125)
TCR_A0061	>COATCR_A0061 AAGCAGGAGGTGACACAAATTCC CGCCGCCCTGTCCGTCCCCGAGGG CGAGAATCTGGTGCTCAACTGCTC TTTTACCGACAGTGCCATCTACAA CCTGCAGTGGTTCCGCCAGGACCC GGGCAAGGGTCTGACCTCCCTGCT GCTCATCCAGAGCTCACAGCGGG AACAGACTTCCGGCCGCCTGAAC GCGTCTTTGGACAAAAGCTCCGG GCGCTCGACCCTGTACATCGCCGC TTCCAGCCAGGTGATTCTGCTAC CTACCTGTGCGCCGTGCTGATGGA <u>CAGCAACTATCAGCTTATTTGGGG</u> <u>CGCCGGCACCAAGCTGATCATCA</u> AGCCT (SEQ ID NO:113)	>COBTRCR_A0061 GATGCAGGCATCACCCAGAGCCC GCGCTACAAGATTACAGAGACCG GCCGCCAGGTACCCCTGATGTGC CACCAGACCTGGTCTCATAGTTA CATGTTTTGGTACAGGCAGGACC TGGGCCACGGTCTCCGTCTTATCT ACTACTCCGCTGCTGCCGACATC ACCGACAAAGGGGAGGTGCCCGA CGGCTACGTGGTGTGCGGGTCCA AGACTGAGAACTTCCCTTTGACTC TGGAGAGCGCCACTCGCTCGCAA ACGTCCGTTTATTTCTGCGCCTCC <u>TCTAGCGATGGTATGAACACGGA</u> <u>AGCGTTCTTCGGACAGGGCACCC</u> GCCTGACCGTGGTC (SEQ ID NO:126)
TCR_A0062	>COATCR_A0062 TCACAACAGGGCGAGGAAGATCC TCAGGCCCTCAGCATCCAGGAGG GGGAGAATGCAACAATGAACTGC TCTTACAAGACCAGCATTAACAAC CTGCAGTGGTACCGCCAGAACTCC GGTCGTGGTTTGGTGCAATTTGATC CTGATCCGCAGCAACGAGAGGGA GAAGCACAGTGGACGCCTGCGGG TCACCCTGGACACCTCCAAGAAGT CGTCCTCTCTGCTCATCACCGCTT	>COBTRCR_A0062 AATGCAGGTGTCACCCAGACTCC GAAATTTAGGTCTTGAAGACCG GTCAGAGCATGACTTTGCAGTGC GCCAGGACATGAACCATGAGTA CATGAGTTGGTACCGCCAGGATC CAGGAATGGGCCTTCGGCTCATT CACTACTCCGTGGGGGGCCGGCAT CACCGACCAGGGGGAGGTGCCTA ACGGCTACAACGTGTCCCCTCG ACCACAGAGGACTTCCCCCTGCG

	CCCGCGCCGCGGACACTGCTAGCT <u>ATTTTGTGCCACCGAGGGCTCCT</u> <u>CTGGCTACTCCACTCTTACCTTCG</u> GCAAAGGCACCATGCTGCTGGTG TCGCCC (SEQ ID NO:114)	TCTGCTGTCCGCGCCCCCTCTCA AACGAGCGTGTA CTTCTGTGCTTC <u>TTCCAAGCAGGGCGGTGGATACG</u> <u>GCTATACCTTCGGCTCCGGCACC</u> CGCCTGACCGTGGTT (SEQ ID NO:127)
TCR_A0064	>COATCR_A0064 GGACAGCAGGTCATGCAAATTCC TCAGTACCAGCATGTCCAGGAGG GCGAGGACTTCACCACTTACTGCA ATAGCTCGACCACTTTGAGCAACA TCCAGTGGTACAAGCAGCGTCCG GCGGCCACCCCGTGTTCTTGATC CAGCTGGTGAAGTCTGGGGAAGT TAAGAAACAGAAGCGCCTGACCT TCCAGTTTGGAGAGGCCAAGAAG AACTCCTCTCTTCACATCACCGCC ACCCAGACAACCGATGTGGGGAC CTACTTTTGTGCTGGTGC GGGTGC <u>AGGCTCCTATCAGCTCACCTTCGG</u> CAAAGGCACCAAGCTGTCCGTGA TCCCA (SEQ ID NO:115)	>COBTRCR_A0064 AAAGCCGGCGTGACCCAGACTCC GCGCTACCTAATTAAGACTCGTG GTCAACAGGTCACCCTGAGCTGT TCGCCCATCTCTGGCCACCGGTCC GTTAGTTGGTACCAGCAGACGCC AGGACAGGGCCTCCAGTTCTGT TCGAGTACTTCTCCGAGACCCAG CGCAACAAGGGCAACTTTCTCTGG GCGATTCTCTGGTTCGCCAGTTTTC AAATTCCAGGTCGGAGATGAACG TGTCCACCCTTGAGCTGGGGGAC AGCGCGCTGTACCTGTGCGCTTCC <u>TCTTTGGAGGGCCAGGCCAGCAG</u> <u>CTACGAACAGTATTTTCGGACCCG</u> GCACCCGCCTGACCGTGACA (SEQ ID NO:128)
TCR_A0065	>COATCR_A0065 GGACAGCAGGTCATGCAAATTCC TCAGTATCAGCATGTGCAGGAGG GCGAAGACTTCACCACTTACTGTA ATTCCTCGACCACTTGAGCAACA TCCAGTGGTACAAGCAGCGTCCC GCGGCCACCCCGTGTTCTTGATC CAGCTGGTGAATCTGGCGAGGT GAAGAAACAGAAGCGCCTGACCT TCCAGTTTGGGGAGGCCAAGAAG AACTCCAGCCTTCACATCACCGCC ACCCAGACTACAGATGTGGGGAC CTACTTTTGCGCTGTTTCTGGTGC <u>GGGCTCCTACCAGCTCACCTTCGG</u> CAAGGGCACCAAGCTGAGTGTCA TCCCG (SEQ ID NO:116)	>COBTRCR_A0065 AAAGCCGGCGTGACCCAGACGCC ACGATACCTAATTAAGACCCGTG GTCAACAGGTCACCCTTTCATGCT CTCCCATCTCGGGCCACCGGTCC GTGAGTTGGTACCAGCAGACTCC GGGACAGGGCCTCCAGTTCTGT TCGAGTACTTCTCCGAGACCCAG CGCAACAAGGGCAACTTTCCCGG GCGCTTCTCTGGACGCCAGTTTTC CAATTCCAGGTCGGAGATGAACG TGTCCACTCTGGAGCTGGGGGAC AGCGCGCTGTACCTGTGCGCCTC <u>CTCTTTGGAGGGCCAGGCCAGCA</u> <u>GCTACGAACAGTATTTTCGGTCTT</u> GGCACCCGCCTGACCGTTACA (SEQ ID NO:129)
TCR_A0066	>COATCR_A0066 GGACAGCAGGTCATGCAAATTCC TCAGTACCAGCATGTGCAGGAGG GCGAAGACTTCACCACTTACTGTA ATTCCTCGACCACTCAGCAACA TCCAGTGGTACAAGCAGCGTCCC GCGGCCACCCCGTGTTCTTGATC CAGCTGGTGAAGTCTGGGGAGGT TAAGAAACAGAAGCGCCTGACCT TTCAGTTCGGAGAGGCCAAGAAG AACTCCTCTTTGCACATCACCGCC ACCCAGACGACTGATGTGGGGAC CTACTTTTGCGCTGGTGCAGGTGC <u>GGGCTCCTATCAGCTTACCTTCGG</u>	>COBTRCR_A0066 AAAGCCGGTGTTACCCAGACTCC GCGCTACCTCATTAAGACCAGAG GACAACAGGTCACTCTTTCATGCT CTCCCATCTCTGGCCACCGGTCCG TGAGTTGGTACCAGCAGACGCCA GGACAGGGCTTGCAGTTCCTGTT CGAGTACTTCTCCGAGACCCAGC GCAACAAGGGCAACTTTCCCGGG CGTTTCTCTGGTCGCCAGTTTTC AATTCCAGGTCGGAGATGAACGT GTCGACCCTGGAGCTAGGGGACA GCGCGCTGTACCTGTGCGCCTCC <u>AGCGCAGAGGGCCAGGCCTCCAG</u>

	CAAAGGCACCAAGCTGAGCGTCA TCCCG (SEQ ID NO:117)	CTACGAACAGTATTTTCGGCCCTG GCACCCGCTGACCGTGACA (SEQ ID NO:130)
TCR_A0068	>COATCR_A0068 TCACAGCAAGGCGAGGAAGATCC TCAGGCCCTCAGCATCCAGGAGG GGGAGAATGCAACTATGAACTGC AGCTACAAGACCAGTATTAACAA CCTGCAGTGGTACCGCCAGAACTC CGGACGTGGTCTAGTGCATTTGAT CCTGATCCGCAGCAACGAGAGGG AGAAGCACTCGGGTCGCCTGCGG GTCACCCTGGACACCTCCAAGAA GTCTTCTTCTCTGCTCATCACTGCT TCCCGCGCCGCGGACACAGCTAG CTATTTTTGTGCCACCGAGGGCGG <u>CTCCGGCTACTCCACCCTTACCTT</u> <u>CGGCAAAGGCACCATGCTGCTGG</u> TGTCGCCC (SEQ ID NO:118)	>COBTRC_A0068 AACGCGGGTGTACCCAGACTCC GAAGTTTCAGGTCCTGAAGACCG GTCAGAGCATGACTTTGCAGTGC GCCAGGACATGAATCATGAGTA CATGAGTTGGTACAGGCAGGATC CAGGAATGGGCCTCCGTCTTATTC ACTACTCCGTGGGGGCCGGCATC ACCGACCAGGGGGAGGTGCCTAA CGGCTACAACGTGTCCCGCTCGA CCACAGAGGACTTCCCCCTGCGG CTGCTGAGCGCAGCTCCCTCTCA AACGTCCGTGTACTTCTGTGCTTC <u>TAGCCGCCAGGGCGGGTTCAGGCT</u> <u>CCGGCTATACCTTCGGCTCGGGC</u> ACCCGCCTGACCGTGGTG (SEQ ID NO:131)
TCR_A0069	>COATCR_A0069 TCACAACAGGGCGAGGAGGACCC TCAGGCCCTCTCTATCCAGGAGGG CGAGAATGCAACAATGAACTGCA GCTACAAGACCAGCATTAACAAC CTGCAGTGGTACCGGCAGAACTC CGGCCGTGGTTTGGTGCATCTAAT CCTGATCCGCAGCAACGAGAGGG AGAAGCACAGTGGGCGCCTGCGC GTCACCCTGGACACCTCCAAGAA GTCGTCTCTCTGCTCATCACCGC TTCCCGCGCCGCGGACACTGCTAG CTATTTTTGTGCCACTGAAGGTGA <u>TTCTGGCTACTCCACCCTTACCTT</u> <u>CGGCAAAGGCACCATGCTGCTGG</u> TGTCGCCC (SEQ ID NO:119)	>COBTRC_A0069 AACGCGGGTGTACCCAGACTCC TAAGTTTCAGGTCCTGAAGACTG GACAGAGCATGACACTGCAGTGT GCCAGGACATGAACCATGAGTA CATGAGTTGGTACCGCCAGGACC CGGGAATGGGCCTCCGTCTTATTC ACTACTCCGTGGGTGCTGGCATC ACCGACCAGGGGGAGGTGCCAAA TGGCTACAACGTGTCCCGCTCAA CGACCGAGGATTTCCCCCTGCGG CTGCTGTCTGCAGCTCCCTCTCAA ACTAGCGTGTACTTCTGCGCCTCG <u>ACCACCCAGGGCGGGGCCTACGG</u> <u>CTATACCTTCGGCTCCGGCACCC</u> GCCTGACCGTGGTT (SEQ ID NO:132)
TCR_A0070	>COATCR_A0070 TCACAACAGGGAGAGGAGGACCC TCAGGCCCTCAGCATCCAGGAGG GCGAGAATGCCACTATGAACTGC TCTTACAAGACCAGCATTAACAAC CTGCAGTGGTACCGCCAGAACAG TGGGCGTGGTTTGGTGCATCTCAT CCTGATCCGCAGCAACGAGCGCG AAAAGCACTCGGGTCGCCTGCGG GTCACCTTGGATACCTCCAAGAAG TCCTCTTCTCTGCTGATCACTGCTT CCAGGGCGGGCGGACACCGCAAGC TATTTTTGTGCTACAGCCGGCAAC <u>TCCGGCTACTCCACCCTGACCTTC</u> <u>GGCAAAGGCACCATGCTTCTGGT</u> GTCGCCC (SEQ ID NO:120)	>COBTRC_A0070 AACGCAGGTGTACCCAGACTCC GAAGTTTCAGGTCCTGAAGACCG GCCAGAGCATGACGCTGCAGTGC GCCAGGACATGAATCATGAGTA CATGAGTTGGTACCGCCAGGATC CAGGTATGGGCCTTCGTCTCATTC ACTACTCCGTGGGGGCCGGCATC ACCGACCAGGGGGAGGTGCCTAA CGGCTACAACGTGTCCCGGTCTGA CCACAGAAGACTTCCCCCTGCGC CTGCTGTCCGCCGCCCTCTCAA ACGTCTGTTTATTTCTGTGCTTCC <u>ACTCCTCAGGGAGGGCAACGAGGC</u> <u>GTTCTTCGGACAGGGCACCCGCC</u> TGACCGTGGTG (SEQ ID NO:133)

TCR_A0099	ATACTGAACGTGGAACAAAGTCC TCAGTCACTGCATGTTACAGGAGGG AGACAGCACCAATTTACCTGCA GCTTCCCTTCCAGCAATTTTATG CCTTACACTGGTACAGATGGGAA ACTGCAAAAAGCCCCGAGGCCTT GTTTGTAAATGACTTTAAATGGGGA TGAAAAGAAGAAAAGGACGAATAA GTGCCACTCTTAATACCAAGGAG GGTTACAGCTATTTGTACATCAAA GGATCCCAGCCTGAAGACTCAGC CACATACCTCTGTGCCGTTAATGC <u>TGGTGGTACTAGCTATGGAAAGCT</u> <u>GACATTTGGACAAGGGACCATCTT</u> GACTGTCCATCCA (SEQ ID NO:134)	GAAGCTGGAGTTGCCCAGTCTCC CAGATATAAGATTATAGAGAAAA GGCAGAGTGTGGCTTTTTGGTGC AATCCTATATCTGGCCATGCTACC CTTTACTGGTACCAGCAGATCCTG GGACAGGGCCCCAAAGCTTCTGAT TCAGTTTCAGAATAACGGTGTAG TGGATGATTCACAGTTGCCTAAG GATCGATTTTCTGCAGAGAGGCT CAAAGGAGTAGACTCCACTCTCA AGATCCAACCTGCAAAGCTTGAG GACTCGGCCGTGTATCTCTGTGCC <u>AGCAGCTCCGATTGGACAGCGAA</u> <u>CAATGAGCAGTTCTTCGGGGCCAG</u> GGACACGGCTCACCGTGCTA (SEQ ID NO:135)
TCR_A0130	GCACAGACGGTCACCCAGAGC CAGCCGGAGATGTCTGTGCAG GAGGCTGAAACCGTGACCTTGT CATGCACTTACGACACCTCCGA GAGCAACTACTACCTGTTTTGG TACAAGCAGCCACCCTCTCGTC AGATGATCCTGGTGATTCGCCA GGAGGCCTACAAGCAACAGAA CGCGACTGAGAACCGCTTCTCC GTAAATTTCCAGAAGGCCGCCA AATCGTTTTCCCTCAAAATCTC CGACAGTCAGCTGGGTGATAC AGCCATGTACTTCTGTGCGTTC <u>ATGATCCCCGACAGCAACTATC</u> <u>AGCTTATTTGGGGCGCTGGCAC</u> CAAGCTGATCATCAAGCCT (SEQ ID NO:175)	GAGACTGGCGTCACCCAGACT CCGCGCCACCTGGTGATGGGA ATGACCAACAAGAAATCTCTT AAATGCGAGCAACATCTAGGC CACAACGCCATGTATTGGTAC AAGCAGAGCGCCAAGAAGCCC CTGGAGCTGATGTTCTGTGTAC AACTTCAAGGAGCAGACGGAG AACAACCTCCGTGCCCTCTCGG TTCAGCCCTGAATGCCCAAAT TCGAGTCACTTGTTCCTGCACT TGCATACACTCCAGCCGGAGG ACAGCGCGCTGTACCTGTGCG <u>CCTCCTCACAGGTTGGCACCTC</u> <u>CGGTCGTGGTGGGGAGCTCTT</u> <u>TTTCGGCGAGGGCTCCCGCCT</u> GACCGTGCTG (SEQ ID NO:178)
TCR_A0131	GCGCAGACGGTTACCCAGAGCCA ACCTGAGATGTCCGTGCAGGAGG CTGAAACCGTGACCTTGTCATGCA CTTACGACACCTCCGAGAACA ATTACCTGTTTTGGTACAAGCAGC CGCCCTCTCGTCAGATGATCCTGG TGATCCGCCAGGAGGCCTACAAA CAGCAGAACGCAACCGAGAATCG GTTTTCGGTCAACTTCCAGAAGGC TGCCAAATCCTTCTCCCTCAAGAT CAGCGATTCTCAGCTGGGCGACA CGGCCATGTATTTCTGTGCGTTCA <u>TGCTTATTGACAGTGGCACCTACA</u> <u>AGTACATCTTCGGGACAGGTACTC</u> GCCTGAAGGTGCTGGCC (SEQ ID NO:176)	GAAGCTCAGGTCACCCAGAAT CCACGTTATCTCATCACAGTCA CCGGCAAGAAGCTCACGGTTA CCTGCTCTCAGAACATGAACC ACGAGTACATGAGTTGGTACA GGCAGGACCCGGGCCTTGGCT TGCGGCAAATTTACTACTCCAT GAACGTGGAGGTGACCGACAA AGGTGATGTGCCTGAGGGCTA CAAGGTGTCCCGCAAGGAGAA GCGCAACTTTCCCCTGATCCTG GAGAGCCCTTCCCCCAACCAG ACTTCTCTGTACTTCTGTGCCA <u>GCTCGCTAGGACAGGGCACCG</u> <u>AGACCCAGTATTTCCGGTCCCG</u> GGACTCGCCTGCTGGTGCTG (SEQ ID NO_179)

TCR_A0100	AAACAGGAGGTGACACAGATT CCTGCAGCTCTGAGTGTCCCAG AAGGAGAAAACCTTGGTTCTCA ACTGCAGTTTCACTGATAGCGC TATTTACAACCTCCAGTGGTTT AGGCAGGACCCTGGGAAAGGT CTCACATCTCTGTTGCTTATTC AGTCAAGTCAGAGAGAGCAAA CAAGTGGGAAGACTTAATGCCTC GCTGGATAAATCATCAGGACG TAGTACTTTATACATTGCAGCT TCTCAGCCTGGTGACTCAGCCA CCTACCTCTGTGCTGTGGGAGG <u>CAATAACAATGACATGCGCTTT</u> GGAGCAGGGACCAGACTGACA GTAAAACCA (SEQ ID NO:177)	GCTGCTGGAGTCATCCAGTCC CCAAGACATCTGATCAAAGAA AAGAGGGAAACAGCCACTCTG AAATGCTATCCTATCCCTAGA CACGACACTGTCTACTGGTAC CAGCAGGGTCCAGGTCAGGAC CCCCAGTTCCTCATTTTCGTTTT ATGAAAAGATGCAGAGCGATA AAGGAAGCATCCCTGATCGAT TCTCAGCTCAACAGTTCAGTG ACTATCATTCTGAACTGAACA TGAGCTCCTTGAGCTGGGGG ACTCAGCCCTGTACTTCTGTGC <u>CAGCAGCTTAATTAACACTGA</u> <u>AGCTTTCTTTGGACAAGGCAC</u> CAGACTCACAGTTGTA (SEQ ID NO:180)
TCR_A0132	GCGCAGACGGTGACCCAGAGCCA GCCGGAGATGTCCGTGCAGGAGG CTGAGACCGTCACCCTGTCGTGCA CTTACGACACCTCCGAGAGCAACT ACTACCTGTTTTGGTACAAGCAGC CACCCTCTCGCCAGATGATCCTGG TGATTTCGTCAGGAGGCCTACAAA CAGCAGAACGCGACAGAGAACCG CTTCTCGGTTAATTTCCAGAAGGC AGCCAAGTCCTTCTCCCTCAAAAT TAGCGATTCTCAATTGGGTGACAC TGCCATGTACTTCTGTGCTTTTAT <u>GGAAGCGGACAGTA</u> <u>AACTATCAGC</u> <u>TTATCTGGGGCGCCGGCACCAAG</u> CTGATCATCAAGCCT (SEQ ID NO:188)	AAGGCCGGCGTTACCCAGACGCC TCGTTATCTTATTAAGACCCGAGG ACAGCAGGTCACACTATCTTGCT CTCCCATCTCTGGCCACCGCTCCG TGAGTTGGTACCAACAGACTCCG GGTCAGGGCCTCCAGTTCCTGTTC GAGTACTTCAGCGAAACCCAGCG CAACAAGGGCAACTTCCCAGGGC GCTTCAGCGGACGCCAGTTTTCA AATTCCAGGTCGGAGATGAACGT GTCGACCCTGGAGCTGGGTGATA GCGCGCTGTACCTGTGCGCCTCC <u>AAAGGCCGGCGTG</u> <u>GGGCCCCGACTA</u> <u>CAACTCCCCTTTGCATTTTGGCAA</u> CGGCACCCGCCTGACCGTGACT (SEQ ID NO:189)

In some exemplary embodiments, TCRs A0100, A0130, A0131 or A0132 are expressed as a hybrid TCR construct, comprising a human TCR α variable region amino acid sequence selected from the group consisting of SEQ ID NO: 162, 163, 164 or 66 in combination with a TCR β variable region amino acid selected from the group consisting of SEQ ID NO: 166, 167, 168 or 91, whereby the constant part of the TCR comprises a mouse constant region comprising TCR α constant region of SEQ ID NO: 190 and TCR β constant region of SEQ ID NO:191 as listed in Table 7.

Table 7: Mouse TCR constant region amino acid sequences

SEQ ID	Sequence name	Sequence
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(SEQ ID NO:190)	mTRAC	NIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMES GTFITDKCVLDMKAMDSKSNGAIAWSNQTSFTCQDIFKE TNATYPSSDVPCDATLTEKSFETDMNLFQNLVIVLRIL LLKVAGFNLLMTLRLWSS
(SEQ ID NO:191)	mTRBC	EDLRNVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDH VELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVS ATFWHNPРНHFRСQVQFHGLSEEDKWPEGSPKPVTQNI SAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVL VSTLVVMAMVКRKNS

In an exemplary embodiment, there is provided human TCRs binding to EBV-derived antigenic peptides, as listed in Table 2. In an exemplary embodiment, the human TCRs bind to EBV-derived antigenic peptides presented on HLA-A*2:01. In other embodiments, the human TCRs bind to EBV-derived antigenic peptides from a peptide pool presented on PBMCs expressing 01:01, 02:01, 03:01 or 11:01 and HLA-B alleles 07:02, 08:01 or 35:01 and HLA-C alleles 04:01 and 07:01.

In various embodiments, the human T cell receptors bind to EBV-derived peptides comprising the amino acid sequence YVLDHLIVV (SEQ ID NO:105) derived from BRLF1, or amino acid sequences CLGGLLTMV (SEQ ID NO:106), FLYALALLL (SEQ ID NO:107), or MGSLEMVPM (SEQ ID NO:146) derived from LMP2, or EPLPQGQLTAY (SEQ ID NO:145) derived from BZLF1. In various embodiments, said antigenic peptides are presented on HLA-A*2:01 or HLA-B*35:01.

In other embodiments, the human T cell receptor binds to a splice variant-derived peptide, comprising the amino acid sequence RLPGVLPRA (SEQ ID NO:147) derived from mutant splice factor-induced peptide of MAPK8IP2. In some embodiments, said antigenic peptide is presented on HLA-A*2:01.

In other embodiments, the human T cell receptor binds to HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148) derived from HERV-K gag protein. In some embodiments, said antigenic peptide is presented on HLA-A*2:01.

In various embodiments, the invention provides a T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO: 147) presented on HLA-A*02, comprising a TCR alpha chain variable domain comprising a complementary determining region (CDR)3 CDR3 selected from sequences SEQ ID NOs: 151 and.

In various embodiments, the invention provides a T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO: 147) presented on HLA-A*02, comprising a TCR beta chain variable domain comprising a complementary determining region (CDR)3 CDR3 selected from sequences SEQ ID NOs: 159 and 160.

In various embodiments, the invention provides a T cell receptor (TCR) comprising a variable domain comprising a member selected from the TCR alpha chain and TCR beta chain CDR3 pairs of SEQ ID NO: 162 and 166, and SEQ ID NO: 163 and 167.

The invention provides in various embodiments, a T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO: 147) presented on HLA-A*02, comprising a TCR alpha chain variable domain comprising a complementary determining region (CDR)3 CDR3 of a sequence selected from SEQ ID NO: 14, 151, and 152 in combination with a TCR beta chain variable domain comprising a complementary determining region (CDR)3 CDR3 selected from SEQ ID NO: 42, 159, and 160.

The invention provides in various embodiments, T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO: 147) presented on HLA-A*02, comprising a TCR alpha chain with the variable region amino acid sequence selected from SEQ ID NO: 66, 162, and 163 as set forth in Table 4, in combination with a TCR beta chain with the variable region amino acid sequence selected from SEQ ID NO: 92, 166 and 167.

In various embodiments, there is provided a T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO:147) presented on HLA-A*02, comprising a TCR α chain with the variable region nucleotide sequence selected from SEQ ID NOS:169, 170, 175, 176, 186 and 188 in combination with a TCR β chain with the variable region amino acid sequence selected from SEQ ID NOS:172, 173, 178, 179, 187, and 189.

The invention provides in various embodiments, a T cell receptor (TCR) binding to an HERV-K-derived peptide comprising amino acid sequence FLQFKTWWI (SEQ ID NO: 148) presented on HLA-A*02, comprising a TCR alpha chain variable domain comprising a complementary determining region (CDR)3 CDR3 of sequence SEQ ID NO: 153.

The invention provides in various embodiments, a T cell receptor (TCR) binding to an HERV-K-derived peptide comprising amino acid sequence FLQFKTWWI (SEQ ID NO: 148) presented on HLA-A*02, comprising a TCR beta chain variable domain comprising a complementary determining region (CDR)3 CDR3 of sequence SEQ ID NO: 161.

The invention provides in various embodiments, a TCR comprising a variable domain comprising the TCR alpha chain CDR3 and TCR beta chain CDR3 of SEQ ID NOs: 153 and 161.

Fields of application: diseases treatable with TCR-based therapy including cancers where the relevant antigen is expressed.

Exemplary T cell receptors comprise a TCR α chain variable domain comprising a complementarity determining region (CDR) 3 (CDR3) selected from the group consisting of SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:138, SEQ ID NO:151, SEQ ID NO:152, and SEQ ID NO:153, combined with a TCR β chain CDR3 selected from the group consisting of SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:139, SEQ ID NO:159, SEQ ID NO:160, and SEQ ID NO:161, and a combination thereof, as listed in Table 3.

In some embodiments, the TCR alpha chain variable domain comprises a CDR3 alpha motif selected from the group consisting of SEQ ID NO:181, and SEQ ID NO:183, combined with a TCR beta chain CDR3 beta motif selected from the group consisting of SEQ ID NO:182 and SEQ ID NO:184. In some embodiments, the TCR alpha chain variable domain comprises a CDR3 alpha motif of SEQ ID NO:185, combined with a TCR beta chain CDR3 selected from the group consisting of SEQ ID NO: 159, 160 or 42.

In some embodiments, the TCR α chain variable domain is selected from the group of amino acid sequences: SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:140, , SEQ ID NO:162, SEQ ID NO:163, and SEQ ID NO:164, combined with a TCR β chain variable domain selected from the group consisting of SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:91, SEQ ID NO:141, SEQ ID NO:166, SEQ ID NO:167, and SEQ ID NO:168, and a combination thereof, as listed in Table 4.

In some embodiments, the TCR α chain variable domain amino acid sequence is at least 80%, or 85%, or 90%, or 95%, or 99% identical to a sequence selected from SEQ ID NO:55, SEQ

ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:162, SEQ ID NO:163, or SEQ ID NO:164, and a combination thereof, as listed in Table 4.

In some embodiments, the TCR α chain variable domain is combined with a TCR β chain variable domain at least 80%, or 85%, or 90%, or 95%, or 99% identical to an amino acid sequence selected from SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:141, SEQ ID NO:166, SEQ ID NO:167, or SEQ ID NO:168, and a combination thereof, as listed in Table 4.

D. Antigen-presenting cells

In various embodiments, the antigen-presenting cells (APCs) are the T2 cell line which is transporter associated with antigen processing (TAP) protein deficient and expresses a low amount of HLA-A*02:01. T2 cells can only present exogenous peptides. In some embodiments, the APCs are peripheral blood mononuclear cells (PBMCs) expressing HLA-A alleles 01:01, 02:01, 03:01 or 11:01 and HLA-B alleles 07:02, 08:01 or 35:01 and HLA-C alleles 04:01 and 07:01.

E. Effector cells

Cytotoxic T lymphocytes (cytotoxic T cells, CTLs) are an immune effector cell population that can mediate specific immune responses against cancer. Based on this concept, tumor immunotherapy protocols have been developed using adoptive transfer of in vitro-expanded autologous T cells that can kill cancer cells (Vignali and Kallikourdis, (2017) *Cytokine Growth Factor Rev* 36:107-116). Effector functions of cytotoxic T lymphocytes include but are not limited to cytokine production and cytolysis of target cells.

In some embodiments, peripheral blood mononuclear cells (PBMCs) from healthy donors were used as a source of primary T cells. CD4⁺ and CD8⁺ T cells were positively enriched using CD4 and CD8 microbeads, LS columns and magnets from Miltenyi. Cells were resuspended in AIM V medium with 10% heat-inactivated human AB serum and 10ng/ml IL-15. For T cell activation, cells were incubated with TransAct™ beads (Miltenyi). On the same or the next day, Lentiviruses encoding for the TCR of interest were added to the activated T cells and incubated for three days. Half of the cells were not transduced with lentivirus and were used as control cells. Transduction efficiency was verified by flow

cytometry, using an anti-mouse TCR antibody to verify that at least 50% of T cells express the transduced TCR.

F. Cytokines

In some embodiments, the functionality of TCRs is assessed by quantification of cytokine secretion in the cell culture media.

It is well known that cytokines and their signaling pathways exert potent effects on T cell activation, differentiation, and function. Interferon gamma (IFN γ) is crucial for Th1 differentiation and induction of IFN- γ release. In other subsets, IFN- γ inhibits the differentiation of Th2 and Th17 cells but has been shown to promote TReg and antigen-specific memory T cell generation (Bishop et al. Front Immunol. 2021 Apr 13). IFN γ is a key moderator of cell-mediated immunity with diverse, mainly pro-inflammatory actions on immunocytes and target tissue. Recent studies have shown it may enhance anti-tumor and antiviral effects of CD8 T cells. IFN γ is released in large amounts by macrophages, activated CD8 T cells, natural killer T cells, and Th1 CD4 T cells (Bhat et al. Cell Death Dis. 2017 Jun 1;8(6):e2836).

G. HLA/MHC

In an exemplary embodiment, the invention provides an engineered T cell expressing a TCR of the invention in which the TCR is specifically bound to a cell expressing an EBV antigen, which is presented by a MHC molecule.

Unlike antibodies, which are closely related proteins that recognize intact protein antigens, TCRs bind, via their CDR loops, to peptides presented by molecules of the major histocompatibility complex (MHC). This TCR-MHC interaction is crucially important in cell mediated immunity, with the specificity in the cellular immune response being attributable to MHC polymorphism, an extensive TCR repertoire, and a variable peptide cargo. The conventional T-cell response is mediated by TCR recognition of short peptide fragments bound to MHC class I or MHC class II molecules. Generally, MHC-I present peptides derived from endogenous protein that are recognized by cytotoxic T-cells, whereas MHC-II present exogenously-derived peptides to T helper cells (Bhati et al., Protein Science, 23:260-272 (2014)).

In humans, MHCs are encoded by the human leukocyte antigen (HLA) locus on chromosome 6. This locus is highly polymorphic, spans over 5 mega bases and covers over 200 genes,

with more than 7000 HLA allelic sequences identified to date. Individual subjects normally express 6 different classical MHC-I and 6 MHC-II molecules that can differ from each other by a single amino acid, or by more than 30 amino acids. These polymorphisms mostly affect the MHC binding cleft, thus dictate the diversity of peptides presented by each MHC molecule (Bhati et al., Protein Science, 23:260-272 (2014)). For this reason, HLA allele frequencies is a subject of intense research, and can vary according to ethnic background, geographical location, as well as individual variations. The frequency distribution of most common HLA alleles is publicly available (<http://www.allelefrequencies.net/top10dist.asp>).

In some embodiments, the TCR binds to an EBV-derived antigenic peptide presented through the HLA-A*02:01 allele. In some embodiments, the TCR specifically binds to an EBV-derived antigenic peptide presented through another HLA-A*02 allele, including but not restricted to: HLA-A*02:02, HLA-A*02:03, HLA-A*02:04, HLA-A*02:05, HLA-A*02:06, HLA-A*02:07, HLA-A*02:11, HLA-A*02:12, HLA-A*02:19, HLA-A*02:24, HLA-A*02:264, or HLA-A*02:52. In some embodiments, the TCR specifically binds to a BRLF1-derived antigenic peptide presented through the HLA-A*02:01 allele. In some embodiments, the TCR specifically binds to an BRLF1-derived antigenic peptide presented through another HLA-A*02 allele, including but not restricted to: HLA-A*02:02, HLA-A*02:03, HLA-A*02:04, HLA-A*02:05, HLA-A*02:06, HLA-A*02:07, HLA-A*02:11, HLA-A*02:12, HLA-A*02:19, HLA-A*02:24, HLA-A*02:264, or HLA-A*02:52. In some embodiments, the TCR specifically binds to an LMP2-derived antigenic peptide presented through the HLA-A*02:01 allele. In some embodiment, the TCR specifically binds to an LMP2-derived antigenic peptide presented through another HLA-A*02 allele, including but not restricted to: HLA-A*02:02, HLA-A*02:03, HLA-A*02:04, HLA-A*02:05, HLA-A*02:06, HLA-A*02:07, HLA-A*02:11, HLA-A*02:12, HLA-A*02:19, HLA-A*02:24, HLA-A*02:264, or HLA-A*02:52.

In some embodiments, the TCR specifically binds to an EBV-derived antigenic peptide presented through another HLA allele, including but not restricted to HLA-B*35:01.

In some embodiments, the TCR specifically binds to a splice variant of MAPK8IP2-derived peptide presented on HLA-A*02:01. In some embodiment, the TCR specifically binds to an splice variant of MAPK8IP2-derived antigenic peptide presented through another HLA-A*02 allele, including but not restricted to: HLA-A*02:02, HLA-A*02:03, HLA-A*02:04, HLA-A*02:05, HLA-A*02:06, HLA-A*02:07, HLA-A*02:11, HLA-A*02:12, HLA-A*02:19, HLA-A*02:24, HLA-A*02:264, or HLA-A*02:52.

In some embodiments, the TCR specifically binds to HERV-K gag protein-derived peptide presented on HLA-A*02:01. In some embodiment, the TCR specifically binds to an ERVK-9 gag protei-derived antigenic peptide presented through another HLA-A*02 allele, including but not restricted to: HLA-A*02:02, HLA-A*02:03, HLA-A*02:04, HLA-A*02:05, HLA-A*02:06, HLA-A*02:07, HLA-A*02:11, HLA-A*02:12, HLA-A*02:19, HLA-A*02:24, HLA-A*02:264, or HLA-A*02:52.

H. EBV

The present compositions and methods are of great value, because Epstein-Barr virus (EBV) is a WHO class I carcinogen, and is estimated to cause 1-2% of all tumors in humans.

Epithelial cancers such as nasopharyngeal carcinoma (NPC), and the 10% of gastric carcinomas associated to EBV outnumber in incidence the EBV-associated lymphomas, which include Burkitt's lymphoma, Hodgkin's lymphoma, diffuse large B cell lymphoma, natural killer (NK)/T cell lymphoma, and primary effusion lymphoma. B cell lymphomas emerge spontaneously or during immune suppression. Thus, EBV causes various tumors owing to failing immune control, some of which can be restored by adoptive transfer of blocking of inhibitory receptors (Munz, Nature Rev 17:691-700 (2019)).

In contrast, other EBV-associated pathologies seem to result from excessive immune responses, but still fail to clear the virus. Such immunopathologies include symptomatic primary EBV infection or mononucleosis, EBV-associated haemophagocytic lymphohistocytosis, and a growing body of evidence also points at the autoimmune disease multiple sclerosis (MS). The symptoms of these conditions could be related to stimulation of T cell-mediated cytokine production by latently EBV-infected B cells. In MS, adoptive transfer of EBV-specific T cells has shown promising initial results (Munz, Nature Rev 17:691-700 (2019)).

EBV replication occurs in 2 ways: infected B cell proliferation, or lytic virion production. EBV persists in latently infected B cells, that initially express no EBV protein (latency 0). During homeostatic proliferation of infected memory B cells, the EBNA1 viral protein is transiently expressed (latency I), soon followed LMP1 and LMP2 (latency II). The virus then infects B cells in secondary lymphoid tissues, that additionally express EBNA2, EBNA3A-EBNA3C (latency III) (Munz, Nature Rev 17:691-700 (2019)). Each of these latency phases are associated to different diseases: nasopharyngeal carcinomas (NPC; associated to type II latency EBV proteins), gastric cancers (associated to type I latency EBV proteins), Burkitt's

lymphoma (associated to type I latency EBV proteins), Hodgkin's disease (associated to type II latency EBV proteins), Non-Hodgkin's lymphoma (associated to latency type II EBV proteins), NK/T cell lymphoma (associated to latency type II EBV proteins), etc... (Khan and Hashim, 2014; Thompson and Kurzrock, 2004; US Patent Application No. 20090305324, incorporated here by reference).

Other EBV proteins are expressed during the lytic replication phase of the virus. The expression of the early lytic EBV protein BZLF1 appears to play a trigger role in this process, often co-expressed with the early transcription factor BRLF1. These two early lytic proteins are believed to play a crucial role in EBV-associated tumor formation (Munz, Nature Rev 17:691-700 (2019)).

1. BRLF1

BRLF1 is an early lytic transcription factor expressed during the lytic replication phase of EBV. Thus far, clinical trials directing BRLF1-specific TCR transgenic T cells has been limited, underscoring the need for new constructs and/or strategies (Munz, Cells 9:1400 (2020)).

In some embodiments, a TCR, e.g., A0002, A0003, A0004 and A0005, specific for EBV lytic gene BRLF1, is isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g. a lentivirus vector) for expression in T cells.

The inventors have performed the above process using Jurkat luciferase reporter cells as a model for T cells. Jurkat cells transduced with the lentiviral vector and successfully expressing the novel TCRs TCR_A0002, TCR_A0003, TCR_A0004 and TCR_A0005 were further tested in a specificity assay. Antigen presenting cells (APCs) expressing HLA-A*02:01 are incubated with BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105) and mixed with the said Jurkat cells. Jurkat cells specifically activated by peptide YVLDHLIVV (SEQ ID NO:105) via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain variable domain CDR3 amino acid sequence selected from the group consisting of: SEQ ID NO:15;

SEQ ID NO:16; and SEQ ID NO:17, in combination with a TCR β chain variable domain CDR3 amino acid sequence selected from the group consisting of: SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; and SEQ ID NO:46. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain variable domain CDR3 amino acid sequence shares at least about 95% sequence identity with the amino acid sequence selected from the group consisting of: SEQ ID NO:15; SEQ ID NO:16; and SEQ ID NO:17, in combination with a TCR β chain variable domain CDR3 amino acid sequence shares at least about 95% sequence identity to the amino acid sequence with the amino acid sequence selected from the group consisting of: SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; and SEQ ID NO:46.

In some embodiments, a TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β pair of amino acid sequences selected from the group consisting of: SEQ ID NO:15 and SEQ ID NO:43; SEQ ID NO:16 and SEQ ID NO:44; SEQ ID NO:15 and SEQ ID NO:45; and; SEQ ID NO:17 and SEQ ID NO:46. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pairs which shares at least about 95% sequence identity with an amino acid sequences selected from the group consisting of: SEQ ID NO:15 and SEQ ID NO:43; SEQ ID NO:16 and SEQ ID NO:44; SEQ ID NO:15 and SEQ ID NO:45; and; SEQ ID NO:17 and SEQ ID NO:46.

In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain amino acid sequence selected from the group consisting of: SEQ ID NO:55; SEQ ID NO:56; and SEQ ID NO:57, in combination with a TCR β chain amino acid sequence selected from the group consisting of: SEQ ID NO:67; SEQ ID NO:68; SEQ ID NO:69; and SEQ ID NO:70. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain variable domain CDR3 amino acid sequence which shares at least about 80%, about 85%, about 90%, or about 95% sequence identity with an amino acid sequence selected from the group consisting of: SEQ ID NO:55; SEQ ID NO:56; and SEQ ID NO:57, in combination with a TCR β chain variable domain CDR3 amino acid sequence which shares at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NO:67; SEQ ID

NO:68; SEQ ID NO:69; and SEQ ID NO:70. In some embodiments, a TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain and TCR β chain amino acid sequence pair selected from the group consisting of: SEQ ID NO:55 and SEQ ID NO:67; SEQ ID NO:56 and SEQ ID NO:68; SEQ ID NO:55 and SEQ ID NO:69; and; SEQ ID NO:57 and SEQ ID NO:70. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NO:55 and SEQ ID NO:67; SEQ ID NO:56 and SEQ ID NO:68; SEQ ID NO:55 and SEQ ID NO:69; and; SEQ ID NO:57 and SEQ ID NO:70.

In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain encoded by a nucleotide sequence selected from the group consisting of: SEQ ID NO:79; SEQ ID NO:80; SEQ ID NO:81; SEQ ID NO:108; SEQ ID NO:109; SEQ ID NO:110; and SEQ ID NO:111, in combination with a TCR β chain encoded by a nucleotide sequence selected from the group consisting of: SEQ ID NO:92; SEQ ID NO:93; SEQ ID NO:94; SEQ ID NO:95; SEQ ID NO:121; SEQ ID NO:122; SEQ ID NO:123; and SEQ ID NO:124. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NO:79; SEQ ID NO:80; SEQ ID NO:81; SEQ ID NO:82; SEQ ID NO:108; SEQ ID NO:109; SEQ ID NO:110; and SEQ ID NO:111, in combination with a TCR β chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity to a member selected from: SEQ ID NO:92; SEQ ID NO:93; SEQ ID NO:94; SEQ ID NO:95; SEQ ID NO:121; SEQ ID NO:122; SEQ ID NO:123; and SEQ ID NO:124.

In some embodiments, the TCR binding to an HLA-A*02:01-restricted EBV BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β encoded by nucleotide sequence pairs selected from the group consisting of: the nucleotide sequences underscored in SEQ ID NO:55 and SEQ ID NO:67; SEQ ID NO:56 and SEQ ID NO:68; SEQ ID NO:55 and SEQ ID NO:69; and; SEQ ID NO:57 and SEQ ID NO:70. In some embodiments, the TCR binding to a HLA-A*02:01-restricted EBV

BRLF1-derived antigenic peptide YVLDHLIVV (SEQ ID NO:105), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β encoded by a nucleotide sequence pair sharing at least about 95% sequence identity to a member selected from: the nucleotide sequences underscored in SEQ ID NO:55 and SEQ ID NO:66; SEQ ID NO:55 and SEQ ID NO:67; SEQ ID NO:56 and SEQ ID NO:68; SEQ ID NO:55 and SEQ ID NO:69; and; SEQ ID NO:57 and SEQ ID NO:70.

2. LMP2

In exemplary embodiments, the TCR specifically binds to an EBV-derived antigen. In exemplary embodiments, the TCR specifically binds to an EBV-derived antigen expressed by a cell (e.g., on a cell surface). In some embodiments, the TCR specifically binds to an EBV-derived antigen expressed by a cell in vivo, e.g., a cell which is part of a subject suffering from a disease related to the expression of the EBV-derived antigen. In various embodiments, a TCR specific for EBV latent gene LMP2 is isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g. a lentivirus vector) for expression in T cells.

TCR_A0015 was predicted in silico to bind to an EBV protein. Exemplary methods for designing and/or engineering TCRs are provided in commonly-owned applications: Singapore Patent Application No.: 10202109992T; “Systems and Methods for the Identification of Target-Specific T cells and Their Receptor Sequences Using Machine Learning”; Applicant(s): IMMUNOSCAPE PTE. LTD.; Filing Date: 10 September 2021; and Singapore Patent Application No. 10202204588Y; “Systems and Methods for Identification of Target-Specific T cells and Their Receptor Sequences Using Machine Learning”; Applicant(s): IMMUNOSCAPE PTE. LTD.; Filing Date: 28 April 2022. The disclosures of these applications are incorporated herein by reference in their entirety for all purposes.

This TCR was isolated, modified and cloned into a lentivirus vector for expression in Jurkat luciferase reporter cells. Jurkat cells transduced with the lentiviral vector and successfully expressing this novel TCR were further tested in a specificity assay. Therefore, APCs expressing HLA-A*02:01 were incubated with a pool of antigenic peptides derived from EBV LMP2 and mixed with the said Jurkat cells. In some embodiments, overlapping peptides including peptide MGSLEMVPM (SEQ ID NO: 146) from EBV LMP2 were tested. Therefore, APCs expressing HLA-A*02:01 were incubated peptide MGSLEMVPM (SEQ ID NO: 146) and mixed with the said Jurkat cells. Jurkat cells that are specifically activated by the peptide via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then

added along with additional reagents enabling a chemical reaction producing light.

Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

TCRs specific for EBV latent gene LMP2 were isolated, modified and cloned into a lentivirus vector for expression in Jurkat luciferase reporter cells. Jurkat cells transduced with the lentiviral vector and successfully expressing the novel TCRs TCR_A0061, TCR_A0062, TCR_A0064, TCR_A0065, TCR_A0066, TCR_A0068, TCR_A0069 and TCR_A0070 were further tested in a specificity assay. APCs expressing HLA-A*02:01 were incubated with LMP2-derived antigenic peptides CLGGLTMMV (SEQ ID NO:106) or FLYALALLL (SEQ ID NO:107) and mixed with the Jurkat cells. Jurkat cells specifically activated by peptide CLGGLTMMV (SEQ ID NO:106) or FLYALALLL (SEQ ID NO:107) via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide MGSLEMVPM (SEQ ID NO:146) from a peptide pool, comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair of SEQ ID NO:18 and SEQ ID NO:47. In some embodiments, the TCR binding a HLA-A*02:01-restricted unidentified EBV LMP2-derived antigenic peptide from a peptide pool, comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to the amino acid sequence pair of SEQ ID NO:18 and SEQ ID NO:47.

In some embodiments, the TCR binding a HLA-A*02:01-restricted unidentified EBV LMP2-derived antigenic peptide MGSLEMVPM (SEQ ID NO:146) from a peptide pool, comprises a TCR α chain and TCR β chain amino acid sequence pair of SEQ ID NO:58 and SEQ ID NO:71. In some embodiments, the TCR binding a HLA-A*02:01-restricted unidentified EBV LMP2-derived antigenic peptide from a peptide pool, comprises a TCR α chain and TCR β chain amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to the amino acid sequence pair of SEQ ID NO:58 and SEQ ID NO:71.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide MGSLEMVPM (SEQ ID NO:146) from a peptide pool, comprises a TCR α chain and TCR β chain encoded by the nucleotide sequence pair underscored in SEQ ID NO:82 and SEQ ID NO:96; and in SEQ ID NO:112 and SEQ ID NO:125. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide MGSLEMVPM (SEQ ID NO:146) from a peptide pool, comprises the TCR α chain and TCR β chain encoded by a nucleotide sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to the nucleotide sequence pair underscored in SEQ ID NO:82 and SEQ ID NO:96; and SEQ ID NO:112 and SEQ ID NO:125.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain variable domain CDR3 amino acid sequence selected from the group consisting of: SEQ ID NO:19; SEQ ID NO:21, and; SEQ ID NO:22, in combination with a TCR β chain variable domain CDR3 amino acid sequence selected from the group consisting of: SEQ ID NO:48; SEQ ID NO:50; and SEQ ID NO:51. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain variable domain CDR3 amino acid sequence at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO:19; SEQ ID NO:21, and; SEQ ID NO:22, in combination with a TCR β chain variable domain CDR3 amino acid sequence at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO:48; SEQ ID NO:50; and SEQ ID NO:51.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β amino acid sequence pair selected from the group consisting of: SEQ ID NO:19 and SEQ ID NO:48; SEQ ID NO:21 and SEQ ID NO:50; SEQ ID NO:22 and SEQ ID NO:50; and; SEQ ID NO:21 and SEQ ID NO:51. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence pair selected from the group consisting of: SEQ ID NO:19 and SEQ ID NO:48; SEQ ID NO:21 and SEQ ID NO:50; SEQ ID NO:22 and SEQ ID NO:50; and; SEQ ID NO:21 and SEQ ID NO:51.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain CDR3 α motif of amino acid sequence C-A-X¹-X²-G-A-G-S-Y-Q-L-T-F (SEQ ID NO:183), in combination with a TCR β chain CDR3 β amino acid sequence of amino acid sequence C-A-S-S-X³-E-G-Q-A-S-S-Y-E-Q-Y-F (SEQ ID NO:184), wherein:

- i) X¹ is a member selected from G, V, and any of the following amino acids with related properties: A, I and L
- ii) X² is a member selected from A, S, and any of the following amino acids with related properties: G and T
- iii) X³ is a member selected from L, A, and any of the following amino acids with related properties: I, V and G.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain amino acid sequence selected from the group consisting of: SEQ ID NO:59; SEQ ID NO:61; and SEQ ID NO:62, combined with a TCR β chain amino acid sequence selected from the group consisting of: SEQ ID NO:72; SEQ ID NO:74; and SEQ ID NO:75. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence pair selected from the group consisting of: SEQ ID NO:59; SEQ ID NO:61; and SEQ ID NO:62, combined with a TCR β chain amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO:72; SEQ ID NO:74; and SEQ ID NO:75.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β encoded by a nucleotide sequence pair selected from the group consisting of: the nucleotide sequences underscored in SEQ ID NO:83 and SEQ ID NO:97; SEQ ID NO:85 and SEQ ID NO:99; SEQ ID NO:86 and SEQ ID NO:100; and; SEQ ID NO:87 and SEQ ID NO:101. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β encoded by a nucleotide sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to a

nucleotide acid sequence pair selected from the group consisting of: the nucleotide sequences underscored in SEQ ID NO:83 and SEQ ID NO:97; SEQ ID NO:85 and SEQ ID NO:99; SEQ ID NO:86 and SEQ ID NO:100; and; SEQ ID NO:87 and SEQ ID NO:101.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain variable domain encoded by a nucleotide sequence selected from the group consisting of: SEQ ID NO:83; SEQ ID NO:85; SEQ ID NO:86; SEQ ID NO:87; SEQ ID NO:113; SEQ ID NO:115; SEQ ID NO:116; and SEQ ID NO:117, in combination with a TCR β chain variable domain is encoded by a nucleotide sequence selected from the group consisting of: SEQ ID NO:97; SEQ ID NO:99; SEQ ID NO:100; SEQ ID NO:101; SEQ ID NO:126; SEQ ID NO:128; SEQ ID NO:129; and SEQ ID NO:130. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide CLGGLLTMV (SEQ ID NO:106), comprises a TCR α chain variable domain encoded by a nucleotide sequence at least 80%, or at least 85%, or at least 90%, or at least 95% identical to nucleotide sequence selected from the group consisting of: SEQ ID NO:83; SEQ ID NO:85; SEQ ID NO:86; SEQ ID NO:87; SEQ ID NO:113; SEQ ID NO:115; SEQ ID NO:116; and SEQ ID NO:117, in combination with a TCR β chain variable domain CDR3 encoded by a nucleotide sequence at least 80%, or at least 85%, or at least 90%, or at least 95% identical to a nucleotide sequence selected from the group consisting of: SEQ ID NO:97; SEQ ID NO:99; SEQ ID NO:100; SEQ ID NO:101; SEQ ID NO:126; SEQ ID NO:128; SEQ ID NO:129; and SEQ ID NO:130.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide FLYALALL (SEQ ID NO:107), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β amino acid sequence pair selected from the group consisting of: SEQ ID NO:20 and SEQ ID NO:49; SEQ ID NO:23 and SEQ ID NO:52; SEQ ID NO:23 and SEQ ID NO:53; and; SEQ ID NO:24 and SEQ ID NO:54. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide FLYALALL (SEQ ID NO:107), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β amino acid sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence pair selected from the group consisting of: SEQ ID NO:20 and SEQ ID NO:49; SEQ ID NO:23 and SEQ ID NO:52; SEQ ID NO:23 and SEQ ID NO:53; and; SEQ ID NO:24 and SEQ ID NO:54.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide FLYALALL (SEQ ID NO:107), comprises a TCR α chain CDR3 α of

amino acid sequence C-A-T-X¹-G-X²-S-G-Y-S-T-L-T-F (SEQ ID NO:181), in combination with a TCR β chain CDR3 β amino acid of amino acid sequence C-A-S-X³-X⁴-Q-G-G-(S)-X⁵-X⁶-G-Y-T-F (SEQ ID NO:182), whereby (S) is optional, and wherein:

- i) X¹ is selected from E and A;
- ii) X² is selected from D, G, N, S, and any of the following amino acids with related properties: E, A, Q and T;
- iii) X³ is selected from S and T, and any of the following amino acids with related properties: N and Q;
- iv) X⁴ is selected from K, R and T, and any of the following amino acids with related properties: H, and S;
- v) X⁵ is selected from G and A;
- vi) X⁶ is selected from Y and S, and any of the following amino acids with related properties: F, W, H and T.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide FLYALALL (SEQ ID NO:107), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β encoded by a nucleotide sequence pair selected from the group consisting of: the nucleotide sequences underscored in SEQ ID NO:84 and SEQ ID NO:98; the nucleotide sequences underscored in SEQ ID NO:88 and SEQ ID NO:102; the nucleotide sequences underscored in SEQ ID NO:89 and SEQ ID NO:103; and; the nucleotide sequences underscored in SEQ ID NO:90 and SEQ ID NO:104. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV LMP2-derived antigenic peptide FLYALALL (SEQ ID NO:107), comprises a TCR α chain CDR3 α and a TCR β chain CDR3 β encoded by a nucleotide sequence pair at least 80%, or at least 85%, or at least 90%, or at least 95% identical to a nucleotide acid sequence pair selected from the group consisting of: the nucleotide sequences underscored in SEQ ID NO:84 and SEQ ID NO:98; the nucleotide sequences underscored in SEQ ID NO:88 and SEQ ID NO:102; the nucleotide sequences underscored in SEQ ID NO:89 and SEQ ID NO:103; and; the nucleotide sequences underscored in SEQ ID NO:90 and SEQ ID NO:104.

3. BZLF1

In exemplary embodiments, the TCR specifically binds to an EBV-derived antigen. In exemplary embodiments, the TCR specifically binds to an EBV-derived antigen expressed by a cell (e.g., on a cell surface). In some embodiments, the TCR specifically binds to an EBV-

derived antigen expressed by a cell in vivo, e.g., a cell which is part of a subject suffering from a disease related to the expression of the EBV-derived antigen. In various embodiments, a TCR specific for EBV immediate-early gene BZLF1 is isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g. a lentivirus vector) for expression in T cells.

Cancers driven by EBV viral oncogenes include Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma (NPC), T/NK lymphomas, and others. EBV latent infection also causes lymphoproliferative disease (LPD) (Gottschalk et al., 2009).

TCR_A0099 was predicted in silico to bind to an EBV protein. Exemplary methods for designing and/or engineering TCRs are provided in commonly-owned applications: Singapore Patent Application No.: 10202109992T; “Systems and Methods for the Identification of Target-Specific T cells and Their Receptor Sequences Using Machine Learning”; Applicant(s): IMMUNOSCAPE PTE. LTD.; Filing Date: 10 September 2021; and Singapore Patent Application No. 10202204588Y; “Systems and Methods for Identification of Target-Specific T cells and Their Receptor Sequences Using Machine Learning”; Applicant(s): IMMUNOSCAPE PTE. LTD.; Filing Date: 28 April 2022. The disclosures of these applications are incorporated herein by reference in their entirety for all purposes.

In some embodiments, TCR_A0099 predicted to be specific for an EBV-derived antigenic peptide is isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g., a lentivirus vector) for expression in T cells. As set forth herein, the inventors have performed this process on Jurkat luciferase reporter cells as a model for T cell transduction. Jurkat cells were transduced with a lentiviral vector and successfully expressed the novel TCRs TCR_A0099. These cells were further tested in a specificity assay. Therefore, in an exemplary embodiment, PBMCs expressing HLA-A alleles 02:01 and 03:01 and HLA-B alleles 07:02 and 35:01, are incubated with the unidentified EBV-derived antigenic peptide and mixed with the said Jurkat cells. In some embodiments, selected EBV peptides, including BZLF1 peptide EPLPQGQLTAY (SEQ ID NO:145), were tested. Therefore, in an exemplary embodiment, PBMCs expressing 01:01 and 11:01 and HLA-B alleles 08:01 and 35:01 and HLA-C alleles 04:01 and 07:01 were incubated with the peptide EPLPQGQLTAY (SEQ ID NO:145) and mixed with said Jurkat cells. Peptide EPLPQGQLTAY (SEQ ID NO:145) has been described in the literature to be HLA-B 35:01-restricted, which is in line with the alleles expressed by the PBMCs tested in the embodiments described here. Jurkat cells specifically activated by the antigenic peptide via the TCR produce luciferase. Luciferin, the substrate for

luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In some embodiments, the TCR binding a HLA-B*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair of SEQ ID NO:138 and SEQ ID NO:139. In some embodiments, the TCR binding a HLA-B*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair sharing at least about 95% sequence identity to the amino acid sequence pair SEQ ID NO:140 and SEQ ID NO:141.

In some embodiments, the TCR binding a HLA-A*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a TCR α chain CDR3 α and TCR β chain CDR3 β encoded by the nucleotide sequence pair underscored in SEQ ID NO:134 and SEQ ID NO:135. In some embodiments, the TCR binding a HLA-A*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises the TCR α chain CDR3 α and TCR β chain CDR3 β encoded by a nucleotide sequence pair sharing at least about 95% sequence identity to the nucleotide sequence pair underscored in SEQ ID NO:142 and SEQ ID NO:143.

In some embodiments, the TCR binding an HLA-A*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a TCR α chain encoded by an amino acid sequence of SEQ ID NO:140 in combination with a TCR β chain encoded by an amino acid sequence of SEQ ID NO:141. In some embodiments, the TCR binding a HLA-A*35:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a TCR α chain encoded by an amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NO:140, in combination with a TCR β chain encoded by an amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NO:141.

In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises a

TCR α chain and TCR β chain encoded by the nucleotide sequence SEQ ID NO:134 and SEQ ID NO:135. In some embodiments, the TCR binding a HLA-A*02:01-restricted EBV BZLF1-derived antigenic peptide EPLPQGQLTAY (SEQ ID NO: 145) from a peptide pool, comprises the TCR α chain and TCR β chain encoded by a nucleotide sequence pair sharing at least about 95% sequence identity to SEQ ID NO:138 and SEQ ID NO:139.

I. Mutant splice-factor associated splice variant of MAPK8IP

Splicing of pre-mRNA by spliceosomes is a cellular process that removes non-coding introns in transcripts and produces alternative splice forms of proteins. Splicing by spliceosomes produces mature mRNA consisting of only coding exons, which form the templates for protein translation. Splicing Factor 3B subunit 1 (SF3B1) is part of the major spliceosome that comprises five small nuclear ribonucleoprotein particles (snRNPs) (Nguyen et al., 2020). SF3B1 and other splicing factors have been reported to be mutated in several types of cancers including uveal melanoma (Bigot et al., 2021; Nguyen et al., 2020), myelodysplastic syndrome (MDS), non-small cell lung cancer (NSCLC) (Oka et al., 2021) chronic lymphocytic leukemia, pancreatic cancer (Leeksa et al., 2021) acute myeloid leukemia and chronic myelomonocytic leukemia (Cheruiyot et al., 2021).

Mutations in SF3B1 (SF3B1mut) can lead to errors in splicing and, for example, premature translation termination. Resulting incomplete or misfolded proteins are rapidly degraded in cells. This degradation occurs via the proteasome, whereby peptides from the degraded proteins are presented on MHC-I molecules, in which form they can be recognized by T cells that express a TCR that is specific for the peptide presented in the context of an MHC-I molecule.

Genetic alterations of other splicing factors such as SUGP1, which interacts with SF3B1 during the cellular splicing mechanism, can also result in similar splicing patterns as seen for SF3B1mut (Alsafadi et al., 2020).

Mutated splice-factor-induced peptides are a promising target for TCR-mediated cancer therapy because of the tumor-specific expression of such peptides, the sharedness of such peptides between patients and between cancer indications, and because of the potential increased immunogenicity.

Mutated splice factor-induced peptides, including peptide RLPGVLPRA (SEQ ID NO:147) have been reported in the literature (Bigot et al., 2021). The therapeutic value of TCR-based approaches targeting these peptides, however, is not known. The current invention proposes

TCR sequences that can be used for the treatment of diseases associated with mutated forms of SF3B1, or other splicing factors including SUGP1. The current invention proposes TCRs and TCR sequences binding for peptide RLPGVLPRA that is comprised in a splice-factor-induced altered version of protein mitogen-activated protein kinase 8 interacting protein 2 (MAPK8IP2).

In some embodiments, TCRs_A0130 and A0131 specific for a mutant splice factor-induced peptide of MAPK8IP are isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g., a lentivirus vector) for expression in T cells. As set forth herein, the inventors have performed this process on Jurkat luciferase reporter cells as a model for T cell transduction. Jurkat cells were transduced with a lentiviral vector and successfully expressed the novel TCRs TCR_A0130 and TCR_A0131. These cells were further tested in a specificity assay. Therefore, in an exemplary embodiment, PBMCs expressing HLA-A alleles 02:01, are incubated with the mutant splice factor-induced antigenic peptide of MAPK8IP and mixed with the said Jurkat cells. In some embodiments, mutant splice factor-induced peptide of MAPK8IP peptide RLPGVLPRA (SEQ ID NO:147), were tested. Jurkat cells specifically activated by the antigenic peptide via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In some embodiments, the TCR binding a HLA-A*02:01-restricted mutant splice factor-induced splice variant MAPK8IP-derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair selected from SEQ ID NO:151 and SEQ ID NO:159; or SEQ ID NO:152 and SEQ ID NO:160, or SEQ ID NO: 14 and SEQ ID NO: 42. In some embodiments, the TCR binding a HLA-A*02:01-restricted mutant splice factor-induced splice variant MAPK8IP-derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair sharing at least about 95% sequence identity to the amino acid sequence pair selected from SEQ ID NO:151 and SEQ ID NO:159; or SEQ ID NO:152 and SEQ ID NO:160, or SEQ ID NO:14 and SEQ ID NO:42.

In various embodiments, the invention provides a T cell receptor (TCR) binding to a peptide comprising amino acid sequence RLPGVLPRA (SEQ ID NO: 147) presented on HLA-A*02, comprising a TCR α chain variable domain comprising a complementary determining

region (CDR)3 CDR3 of the following sequence: C-A-F-M-X¹-X²-D-S-X³-X⁴-Y-X⁵-X⁶-I-X⁷ (SEQ ID NO: 185) in combination with a TCR beta chain variable domain comprising a complementary determining region (CDR)3 CDR3 with a sequence selected from SEQ-ID NOs: 42, 159 and 160, wherein

- i) X¹ is L or I or E, or any of the following amino acids with related properties V or D
- ii) X² is P or I or A, or any of the following amino acids with related properties: V, L or G
- iii) X³ is G or N, or any of the following amino acids with related properties: Q, A, C or S
- iv) X⁴ is T or no AA at this position, or S as an amino acid with related properties
- v) X⁵ is K or Q, or any of the following amino acids with related properties: R, H or N
- vi) X⁶ is L or Y, or any of the following amino acids with related properties: I, V, F, W or H
- vii) X⁷ is F or W.

In some embodiments, the TCR binding a HLA-A*02:01-restricted mutant splice factor-induced peptide of MAPK8IP -derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β encoded by the nucleotide sequence pair underscored in SEQ ID NO:169 and SEQ ID NO:175; or SEQ ID NO:170 and SEQ ID NO:176. In some embodiments, the TCR binding a HLA-A*02:01-restricted mutant splice factor-induced peptide of MAPK8IP -derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises the TCR α chain CDR3 α and TCR β chain CDR3 β encoded by a nucleotide sequence pair sharing at least about 95% sequence identity to the nucleotide sequence pair underscored in SEQ ID NO:169 and SEQ ID NO:172; or SEQ ID NO:170 and SEQ ID NO:173, or SEQ ID NO:186 and SEQ ID NO:187.

In some embodiments, the TCR binding an HLA-A*02:01-restricted mutant splice factor-induced peptide of MAPK8IP -derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises a TCR α chain encoded by a nucleotide sequence of SEQ ID NOS:169, 170, 186, 175, 188 or 176, in combination with a TCR β chain encoded by a nucleotide sequence of SEQ ID NOS:172, 173, 187, 189, 178, or 179. In some embodiments, the TCR binding a HLA-A*02:01-restricted mutant splice factor-induced peptide of MAPK8IP -derived antigenic peptide RLPGVLPRA (SEQ ID NO:147), comprises a TCR α chain encoded by a

nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NOS:169, 170, 186, 175, 188 or 176, in combination with a TCR β chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NOS:172, 173, 187, 178, 189 or 179.

J. Human endogenous retroviruses (HERVs)

About 9% of the human genome consists of genetic information from human endogenous retroviruses (HERVs) that was incorporated into germline as humans evolved (Jansz and Faulkner, 2021). The majority of HERV genetic information is fragmented and/or epigenetically repressed, and no HERV proteins are expressed. However, HERV protein can be expressed in various cancers, including breast cancer, pancreatic cancer, germ cell tumors, leukemia, prostate cancer, bladder cancer, ovarian cancer, lung cancer, hepatocellular carcinoma, lymphoma, choriocarcinoma, colorectal carcinoma, soft tissue sarcoma and Kaposi's sarcoma (Gao et al., 2021; Jansz and Faulkner, 2021). HERV-K is a group of HERVs with relatively intact open reading frames, making the expression of HERV-K proteins more likely compared to other HERVs (Gao et al., 2021). T cell responses to HERV-K proteins have been reported previously, including T cell responses to HERV-K gag protein-derived peptide FLQFKTWWI (Rakoff-Nahoum et al., 2006; Saini et al., 2020; Wang-Johanning et al., 2008).

Since expression of HERV-K proteins is preferentially seen in cancer cells, T cell receptor-mediated therapy against HERV-K T cell epitopes, including FLQFKTWWI, is an attractive strategy for the treatment of cancer that has not yet been tested clinically.

In some embodiments, TCR_A0100 specific for HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148) is isolated, optionally modified and cloned into a vector (e.g., a viral vector, e.g., a lentivirus vector) for expression in T cells. As set forth herein, the inventors have performed this process on Jurkat luciferase reporter cells as a model for T cell transduction. Jurkat cells were transduced with a lentiviral vector and successfully expressed the novel TCRs TCR_A0100. These cells were further tested in a specificity assay.

Therefore, in an exemplary embodiment, APC expressing HLA-A alleles 02:01, are incubated with the HERV-K-derived antigenic peptide and mixed with the said Jurkat cells. Jurkat cells specifically activated by the antigenic peptide via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can

thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In some embodiments, the TCR binding HLA-A*02:01-restricted ERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair SEQ ID NO:153 and SEQ ID NO:161. In some embodiments, the TCR binding a HLA-A*02:01-restricted HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β amino acid sequence pair sharing at least about 95% sequence identity to the amino acid sequence pair SEQ ID NO:153 and SEQ ID NO:161.

In some embodiments, the TCR binding HLA-A*02:01-restricted HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises a TCR α chain CDR3 α and TCR β chain CDR3 β encoded by the nucleotide sequence pair underscored in SEQ ID NO:171 and SEQ ID NO:174. In some embodiments, the TCR binding a HLA-A*02:01-restricted HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises the TCR α chain CDR3 α and TCR β chain CDR3 β encoded by a nucleotide sequence pair sharing at least about 95% sequence identity to the nucleotide sequence pair underscored in SEQ ID NO:171 and SEQ ID NO:174.

In some embodiments, the TCR binding HLA-A*02:01-restricted HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises a TCR α chain encoded by a nucleotide sequence of SEQ ID NOS:171 or 177, in combination with a TCR β chain encoded by a nucleotide sequence of SEQ ID NOS:174, or 180. In some embodiments, the TCR binding HLA-A*02:01-restricted HERV-K-derived peptide FLQFKTWWI (SEQ ID NO:148), comprises a TCR α chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NOS:171 or 177, in combination with a TCR β chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NOS:174, or 180.

K. Plasmids, Lentiviral vector production and transduction of Jurkat cells

In some embodiments, a TCR nucleotide sequence is cloned into a plasmid for viral transduction. In an exemplary embodiment, a TCR sequence is cloned into a plasmid for lentivirus transduction. In an exemplary embodiment, a TCR sequence is cloned into a plasmid for lentivirus transduction with the TCR transgene flanked by long-terminal repeat sequences to enable packaging into lentiviral vectors. Lentiviral vectors are produced for

each TCR by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors collected from the transfected HEK293 cells are then used to transduce each TCR into the T cells. Transduction efficiency and expression of the introduced TCR are confirmed by flow cytometry.

TCR sequences suitable for expression of an exemplary TCR polypeptide in the form of an exogenous receptor on the surface of T cells or as part of a fusion construct, are presented herein. In some embodiments, the TCR α chain and TCR β chain pairs comprising a sequence selected from the combinations set forth in Table 5 or Table 6 as part of a fusion construct, whereby said fusion construct consists of a TCR and a single-chain fragment that binds to a molecule specifically expressed on T cells, including but not limited to CD3.

L. TCR binding to antigenic peptides

In various embodiments, the TCRs specifically recognize and bind antigenic peptides presented on MHC class I molecules.

The immense diversity of the T-cell receptor (TCR) enables specific antigen recognition. Successful recognition of antigenic peptides bound to Major Histocompatibility Complexes (pMHCs) requires specific binding of the TCR to these complexes, which in turn modulates the cell's fitness, clonal expansion, and acquisition of effector properties. The affinity of a TCR for a given peptide epitope and the specificity of the binding are governed by the heterodimeric $\alpha\beta$ T-cell receptors. Within the TCR β chain, the complementarity-determining region 1 (CDR1) and CDR2 loops of the TCR contact the MHC alpha-helices while the hypervariable complementary determining regions (CDR3) interact mainly with the peptide. In both TCR α and TCR β chains, CDR3 loops have the highest sequence diversity and are the principal determinants of receptor binding specificity. Following specific binding of T cell receptors to viral and bacterial-derived peptides bound to MHC, or from neo-antigens, the appropriate T cells expand, resulting in the increased frequency of T cells carrying such receptors (Springer et al., *Front. Immunol.* 25 August 2020).

M. Dose-response testing of transduced Jurkat cells

In various embodiments, the T cells expressing the TCRs exhibit a dose-responsive effect on cells expressing the target antigen.

For example, in a model system, the cell line T2 (ATCC) was used as APCs and seeded into 96 well plates at 50,000 cells per well. 50,000 transduced or non-transduced Jurkat cells were added to the T2 cells. In a separate plate, peptide dilutions were prepared to the desired range of concentrations and added to the plate containing T2 and Jurkat cells. Plates were incubated at 37° C in a cell culture incubator for 4h. To reveal the luciferase signal, Bio-Glo-NL™ reagent was added to all wells, reacted for 5 min and then read on a Spectra plate reader. Peptides used were either purified EBV peptides or mixtures of peptides.

N. Codon optimization of TCR nucleotide sequences

In various embodiments, the nucleotide sequence encoding one or more polypeptides of the TCR is codon optimized.

Codon optimization is a common method used to increase the expression of recombinant proteins, especially in the field of biotherapeutics. Its basis lies in the use of synonymous codon mutations in messenger RNA (mRNA) coding regions. Codon optimization is known to maximize protein expression by overcoming expression limitations associated with codon usage. This routine method has been reported to increase protein expression by up to >1000-fold. This method is often applied in order to fine-tune the expression of one of two light chain genes of a bispecific antibody (Mauro, BioDrugs 32;69-81 (2018)).

Altering codon usage is possible since the 20 amino acids are encoded by 61 codons. Except for methionine and tryptophane, which are encoded by a single codon each, all other amino acids are specified by two to six redundant codons. Synonymous codon usage is not random, as it varies between different organisms, between different tissues of the same organism, and even between different parts of the same gene (Mauro, BioDrugs 32;69-81 (2018)).

The sequences were codon optimised with an algorithm provided by Genscript (GenSmart Codon Optimisation). The optimisation was done for expression in human T cells.

(https://www.genscript.com/gensmart-free-gene-codon-optimization.html?page_no=1&position_no=1&sensors=googlesearch). See, e.g., WIPO Pat. Appl. No. WO2020024917A1, incorporated here by reference.

In some embodiments, a TCR α encoding nucleotide sequence selected from SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:142, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:186, (as listed in Table 5) is codon-optimized to produce the TCR α nucleotide sequences SEQ ID

NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:134, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, and SEQ ID NO:188, respectively (as listed in Table 6).

In some embodiments, a TCR β -encoding nucleotide sequence selected from SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:143, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, and SEQ ID NO:187, (as listed in Table 5) is codon-optimized to produce the TCR β nucleotide sequences SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, and SEQ ID NO:189, respectively (as listed in Table 6).

The following examples are offered to illustrate certain embodiments of the invention and should not be taken to limit the scope thereof.

O. Quantification of cytotoxicity

In various embodiments, the functionality of TCRs is assessed using primary human T cells transduced with said TCRs.

Peripheral blood mononuclear cells (PBMCs) from healthy donors were used as a source of primary T cells for the preparation of effector cells. CD4⁺ and CD8⁺ T cells were positively enriched using CD4 and CD8 microbeads, LS columns and magnets from Miltenyi. Cells were resuspended in AIM V medium with 10% heat-inactivated human AB serum and 10ng/ml IL-15. For T cell activation, cells were incubated with TransActTM beads (Miltenyi). On the same or the next day, lentiviruses encoding for the TCR of interest were added to the activated T cells and incubated for three days. Half of the cells were not transduced with lentivirus and were used as control cells. Transduction efficiency was verified by flow cytometry, using an anti-mouse TCR antibody to verify that at least 50% of T cells express the transduced TCR.

1. Cytometry-based cytotoxicity assay

In some embodiments, the functionality of TCRs is assessed by quantification of cytotoxicity by flow cytometry assay.

TCR-expressing T cells were used as effector cells and were labelled with Cell trace Violet (CTV) for 30 mins and resuspended in assay buffer (99% RPMI, 1%FBS). T2 cells were used as target cells and seeded in 96 well plates. Effector cells were added at the ratio of effector:target cells indicated in the figures. Target peptide of the tested TCR was added to the wells at a range of concentrations as indicated in the figures, and cells were incubated for 20-24 hours. To analyze the cytotoxicity of effectors, cells were collected after centrifugation in a 96 well round bottom plate. Cell culture supernatant was kept for the analysis of secreted cytokines. Cells were stained with 7AAD for 15 mins and analyzed on an Attune flow cytometer (Thermo Fisher Scientific). The percentage of killing for each peptide concentration and effector cell tested was assessed by quantifying the % of 7AAD+CTV- (target) cells per condition, using FlowJo software.

2. Cytotoxicity with xCelligence impedance readout

In other embodiments, the functionality of TCRs is assessed by quantification of cytotoxicity with xCelligence impedance readout.

Cancer cell lines endogenously expressing the target antigen of interest and the HLA allele that tested TCRs are restricted for, were used as target cells. As effector cells, primary T cells transduced with the TCR to be tested were used. Non-TCR transduced T cells were used as control. Target cell lines were seeded in xCelligence 96well E plates at 10,000-25,000 cells per well, depending on the cell line used. Effector cells were added the next day at the Effector:Target ratio indicated in the figure legend, preparing each condition in duplicate. Impedance readings were recorded for up to 90 hours. The % of cytolysis per condition and time point was calculated with xCelligence Immunotherapy software.

P. Quantification of cytokine secretion

In some embodiments, the functionality of TCRs is assessed by quantification of cytokine secretion in the cell culture media.

IFN γ secreted by T cells into the culture medium during the cytotoxicity assay was quantified by ELISA methodology. The OptEIA IFN γ Kit from Becton Dickinson (BD) was used.

IV. EXAMPLES

Example 1: TCRs binding to EBV protein BRLF1

FIG. 1 shows the binding of Jurkat cells expressing EBV-BRLF1-specific TCRs A0001, A0002, A0003, A0004 and A0005 to T2 cells, used as antigen-presenting cells, presenting BRLF1 peptide YVLDHLIVV (SEQ ID NO:105). TCRs binding to BRLF1109-117 peptide YVLDHLIVV (SEQ ID NO:105) were isolated from human donors. Modified TCR sequences were cloned into plasmids for lentivirus production. Lentiviral vectors were produced for each TCR by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce each TCR into Jurkat cells. Successful expression of the TCR was validated by flow cytometry. Specific binding of successfully engineered luciferase reporter T cells was validated by a dose-response experiment whereby increasing amount of YVLDHLIVV (SEQ ID NO:105) peptide was presented to engineered T cells on APCs. Activation of engineered reporter T cells that bound to the peptide was detected via luciferase expression. A TCR α -driven selection mechanism has been reported for BRLF1 whereby a TCR α chain comprising CDR3 α CAVKDTDKLIF (SEQ ID NO:15) was found in several human donors (Kamga et al., 2019). In the current studies, TCR α variable regions comprising CDR3 α CAVKDTDKLIF (SEQ ID NO:15) were identified in TCR_A0002 and TCR_A0004, but these TCR α chains pair with different TCR β chains, representing novel TCRs that are distinct from those reported in Kamga et al. TCR sequence TCR_A0001, which has been reported previously (Kamga et al., 2019), was included for comparison

TCR_A0002, TCR_A0003, TCR_A0004 and TCR_A0005 were expressed successfully and recognized BRLF1 peptide YVLDHLIVV presented on HLA-A*02:01-expressing APCs.

Example 2: TCRs binding to EBV protein LMP2.

FIG. 2 shows binding of EBV LMP2-specific TCR_A0015 to an LMP2 peptide pool and to LMP2 peptide MGSLEMVPM (SEQ ID NO:146) presented on T2 cells used as antigen-presenting cells. TCR_A0015 was predicted in silico to bind to an EBV protein. A modified TCR sequence was cloned into a plasmid for lentivirus production. Lentiviral vectors were produced for this TCR by transfection of this transgene plasmid along with packaging

plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce this TCR into Jurkat cells. Binding to EBV protein was then tested with peptide pools.

TCR_A0015 was expressed successfully and the TCR expressing Jurkat cells were activated by an LMP2 peptide pool and by peptide MGSLEMVPM (SEQ ID NO:146) presented on HLA-A*02:01-expressing APCs.

Example 3: TCRs binding to EBV protein BZLF1

FIG. 3 shows binding of BZLF1-specific TCR_A0099 to an EBV peptide pool and to BZLF1-derived peptide EPLPQGQLTAY (SEQ ID NO: 145) presented on PBMCs used as antigen-presenting cells. TCR_A0099 was predicted in silico to bind to an unknown EBV protein. A modified TCR sequence was cloned into a plasmid for lentivirus production. Lentiviral vectors were produced for this TCR by transfection of this transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce this TCR into Jurkat cells. Binding to EBV-derived epitopes was then tested with peptide pools of different peptides derived from multiple EBV proteins. Based on possible HLA restriction and peptides reported in the literature, a selected number of individual EBV peptides, including EPLPQGQLTAY (SEQ ID NO:145), was tested. TCR_A0099 was expressed successfully and the TCR expressing Jurkat cells were activated by an EBV peptide pool presented on PBMCs expressing HLA-A alleles 02:01 and 03:01 and HLA-B alleles 07:02 and 35:01, and by peptide EPLPQGQLTAY presented on PBMCs expressing HLA-A alleles 01:01 and 11:01 and HLA-B alleles 08:01 and 35:01 and HLA-C alleles 04:01 and 07:01.

TCR_A0099 was expressed successfully and recognized EBV peptide EPLPQGQLTAY (SEQ ID NO:145) presented on HLA-A*35:01-expressing PBMCs.

Example 4: TCRs binding to EBV protein LMP2, specific for peptide CLGGLLTMV.

FIG. 4 shows binding of EBV-LMP2 specific TCRs to LMP2 peptide CLGGLLTMV (SEQ ID NO:106) presented on T2 cells used as antigen-presenting cells. TCRs binding to LMP2426-434 peptide CLGGLLTMV (SEQ ID NO:106) were isolated from human donors. Modified TCR sequences were cloned into plasmids for lentivirus production. Lentiviral vectors were produced for these TCRs by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce each TCR into Jurkat cells. Successful

expression of TCRs was validated by flow cytometry. Specific binding of successfully engineered luciferase reporter T cells was validated by a dose-response experiment whereby increasing amount of CLGGLLTMV (SEQ ID NO:106) peptide was presented to engineered T cells on APCs. Activation of engineered reporter T cells that bound to the peptide was detected via luciferase expression.

TCR_A0061, TCR_A0064, TCR_A0065 and TCR_A0066 were expressed successfully and recognized LMP2 peptide CLGGLLTMV (SEQ ID NO:106) presented on HLA-A*02:01-expressing APCs.

Example 5: TCRs binding to EBV protein LMP2, specific for peptide FLYALALLL

FIG. 5 shows binding of EBV-specific TCRs to LMP2 peptide FLYALALLL (SEQ ID NO:107) presented on T2 cells used as antigen-presenting cells. TCRs binding to LMP2356-364 peptide FLYALALLL (SEQ ID NO:107) were isolated from human donors. Modified TCR sequences were cloned into plasmids for lentivirus production. Lentiviral vectors were produced for these TCRs by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce each TCR into Jurkat cells. Successful expression of TCRs was validated by flow cytometry. Specific binding of successfully engineered luciferase reporter T cells was validated by a dose-response experiment whereby increasing amount of FLYALALLL (SEQ ID NO:107) peptide was presented to engineered T cells on APCs. Activation of engineered reporter T cells that bound to the peptide was detected via luciferase expression.

TCR_0062, TCR_A0068, TCR_A0069 and TCR_A0070 were expressed successfully and recognized LMP2 peptide FLYALALLL (SEQ ID NO:107) presented on HLA-A*02:01-expressing APCs.

Example 6: TCRs binding to mutated splice factor-induced peptide RLPGVLPRA

TCRs specific for mutated splice factor-induced peptide RLPGVLPRA (SEQ ID NO:147) were identified, modified and cloned into a lentivirus vector for expression in Jurkat luciferase reporter cells. Jurkat cells transduced with the lentiviral vector and successfully expressing the novel TCRs TCR_A0130 and TCR_A0131 were further tested in a specificity assay. Therefore, antigen presenting cells (APCs) expressing HLA-A*02:01 were incubated with peptide RLPGVLPRA (SEQ ID NO:147) and mixed with the said Jurkat cells. Jurkat cells that are specifically activated by peptide RLPGVLPRA (SEQ ID NO:147) via the TCR

produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system.

In **FIG. 8** is described how T cells specifically bind to peptide RLPGVLPRA (SEQ ID NO:147) that can be presented on cells that express a mutated form of SF3B1 (SF3B1mut) and potentially other genetically altered splice factors including SUGP1. Since mutated forms of splice factors are expressed in various types of cancers including myelodysplastic syndrome, peptide RLPGVLPRA (SEQ ID NO:147) is a potential target for TCR-based immunotherapies. TCRs binding to peptide RLPGVLPRA (SEQ ID NO:147) were isolated from human donors. Modified TCR sequences were cloned into plasmids for lentivirus production. Lentiviral vectors were produced for each TCR by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to for transduce each TCR into Jurkat cells. Successful expression was validated by flow cytometry. Specific binding of successfully engineered luciferase reporter T cells was validated by a dose-response experiment whereby increasing amount of peptide RLPGVLPRA (SEQ ID NO:147) was presented to engineered T cells on APCs. Activation of engineered reporter T cells that bound to the peptide was detected via luciferase expression.

TCR_A0130 and TCR_A0131 were expressed successfully and recognized peptide RLPGVLPRA presented on HLA-A*02:01-expressing APCs.

Example 7: TCRs binding human HERV-K-derived peptide FLQFKTWWI

TCRs specific for human endogenous retrovirus group K gag protein-derived peptide FLQFKTWWI (SEQ ID NO:148) were identified, modified and cloned into a lentivirus vector for expression in Jurkat luciferase reporter cells. Jurkat cells transduced with the lentiviral vector and successfully expressing the novel TCR TCR_A0100 were further tested in a specificity assay. Therefore, antigen presenting cells (APCs) expressing HLA-A*02:01 were incubated with peptide FLQFKTWWI (SEQ ID NO:148) and mixed with the said Jurkat cells. Jurkat cells that are specifically activated by peptide FLQFKTWWI (SEQ ID NO:148) via the TCR produce luciferase. Luciferin, the substrate for luciferase, is then added along with additional reagents enabling a chemical reaction producing light. Expression of

luciferase following TCR activation can thus be quantified as relative light units (RLU). An increasing response with increasing amount of peptide added to the cells is expected until reaching saturation in the system. TCR sequences suitable for expression of TCR protein in the form of exogenous receptor on the surface of T cells or as part of a fusion construct, are presented.

FIG. 10 describes the binding of HERV-K-specific T cells to HERV-K-derived peptide FLQFKTWWI. TCRs binding to peptide FLQFKTWWI (SEQ ID NO:148) were isolated from human donors. Modified TCR sequences were cloned into plasmids for lentivirus production. Lentiviral vectors were produced for each TCR by transfection of the transgene plasmid along with packaging plasmids encoding the additional lentiviral components into HEK293 cells. Lentiviral vectors were then used to transduce each TCR into Jurkat cells. Successful expression was validated by flow cytometry. Specific binding of successfully engineered luciferase reporter T cells was validated by a dose-response experiment whereby increasing amount of peptide FLQFKTWWI (SEQ ID NO:148) was presented to engineered T cells on APCs. Activation of engineered reporter T cells that bound to the peptide was detected via luciferase expression.

TCR_A0100 were expressed successfully and recognized peptide FLQFKTWWI presented on HLA-A*02:01-expressing APCs.

Example 8: Cytotoxicity measurement of TCR-transduced T cells specific for HERV-K

TCR A0100 was expressed with a modified mouse constant region for functional testing. TCR A0100 with a mouse constant domain is named A0194. Mouse/human hybrid TCRs have been shown previously to express more efficiently in human cells compared to fully human TCRs, and hybrid TCR constructs are now being used in the clinic for adoptive T cell therapy (Cohen et al. (2006) *Cancer Res* 1;66(17):8878-8886; Leidner et al. (2022) *New Engl J of Med* 386:2112-2119; Yin et al. (2018) *JCI Insight* 3(8):e99488). As an additional advantage, tracing of the transferred TCR-transfected T cells is facilitated when they express a hybrid TCR, since an antibody binding specifically to the mouse constant region can be used to monitor and quantify the TCR-transfected T cells in the patient after adoptive transfer. The binding of the hybrid TCRs to the target antigen is anticipated to be comparable to the fully human TCR since the TCR variable region, which is interacting with its target, is not modified in the hybrid constructs.

IFN γ secreted by T cells into the culture medium during the cytotoxicity assay was quantified by ELISA methodology. The OptEIA IFN γ Kit from Becton Dickinson (BD) was used.

FIG. 11 describes the reactivity of TCR-expressing primary T cells to peptide-pulsed HLA-A*02-positive (+) target cells (T2 cell line) 4 hours after co-culture; Interferon Gamma (IFN- γ) secreted by the cells was quantified by ELISA.

Primary T cells transduced with TCR A0194, which is TCR A0100 with a mouse constant region, were used as effector cells. Non-TCR transduced T cells were used as control.

FIG. 12 shows cytolysis induced by TCR-expressing Primary T cells co-cultured with target cells in a real-time cell analyzer (Agilent xCelligence). Target cell index, measuring survival and growth of adherent target cells over time was used to calculate cytotoxicity of target cells using standard protocols and xCelligence Immunotherapy Software. Effectors were added at an effector to target ratio of 1:1. Timepoints indicate time elapsed after adding effectors.

Example 9: Cytotoxicity measurement of TCR transduced T cells specific for mutant splice factor-induced peptide of MAPK8IP2

Three TCRs targeting mutant splice factor-induced peptide of MAPK8IP2, known to be shared across patients with multiple types of cancer, were successfully isolated from a renal cell carcinoma patient. The TCR SEQ ID NOs are A0130 (A0130 with modified mouse constant region is named A0191), A0131 (A0131 with modified mouse constant region is named A0192) and A0132 (A0132 with modified mouse constant region is named A0193).

TCR-expressing T cells were used as effector cells and were labelled with Cell trace Violet (CTV) for 30 mins and resuspended in assay buffer (99% RPMI, 1%FBS). T2 cells were used as target cells and seeded in 96 well plates. Effector cells were added at the ratio of effector:target cells indicated in the brief description of the figures. Target peptide of the tested TCR was added to the wells at a range of concentrations as indicated in the figures, and cells were incubated for 20-24 hours. To analyze the cytotoxicity of effectors, cells were collected after centrifugation in a 96 well round bottom plate. Cells were stained with 7AAD for 15 mins and analyzed on an Attune flow cytometer (Thermo Fisher Scientific) (**FIG.13A**). The percentage of killing for each peptide concentration and effector cell tested was assessed by quantifying the % of 7AAD+CTV- (target) cells per condition, using FlowJo software. Cell culture supernatant was kept for the analysis of secreted cytokines (**FIG. 13B**).

WHAT IS CLAIMED IS:

1. An isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain binding to an Epstein-Barr Virus (EBV)-derived antigenic peptide when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprise one, two or three complementarity determining regions selected from CDR1, CDR2, and CDR3, each respectively comprising an amino acid sequence having at least about 95% sequence identity with an amino acid sequence selected from Table 3.
2. The TCR according to claim 1, wherein said TCR binds to an HLA-A*02-restricted EBV-derived antigenic peptide having a sequence selected from SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107 or SEQ ID NO: 146; or an HLA-B*35-restricted EBV-derived antigenic peptide of SEQ ID NO: 146.
3. The TCR according to claim 2, wherein the HLA-A*02-restricted EBV BRLF1-derived antigenic peptide has a sequence according to SEQ ID NO: 105 comprising:
 - a CDR3 α amino acid sequence having at least about 95% sequence identity with a member selected from: SEQ ID NOS:15, 16, and 17; in combination with:
 - a CDR3 β amino acid sequence sharing at least about 95% sequence identity with a member selected from: SEQ ID NOS:43, 44, 45, and 46.
4. The TCR according to claim 3, wherein said TCR comprises a variable domain comprising the CDR3 α and CDR3 β of polypeptide SEQ ID pairs selected from: SEQ ID NOS:15 and 43; SEQ ID NOS:16 and 44; SEQ ID NOS:15 and 45; and SEQ ID NOS:17 and 46.
5. The TCR according to claim 3, comprising:
 - a TCR α chain amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:55; 56; and 57; in combination with:
 - a TCR β chain amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:67; 68; 69; and 70.

6. The TCR according to claim 5 comprising a variable domain comprising a TCR α chain and TCR β chain of polypeptide SEQ ID pairs selected from:
SEQ ID NOS:55 and 67; SEQ ID NOS:56 and 68; SEQ ID NOS:55 and 69; and SEQ ID NOS:57 and 70.
7. The TCR according to claim 3, comprising:
a TCR α chain encoded by a nucleotide sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:79; 80; 81; 108; 109; 110; and 111; in combination with:
a TCR β chain encoded by a nucleotide sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:92; 93; 94; 95; 121; 122; 123; and 124.
8. The TCR according to claim 7 comprising a variable domain comprising a TCR α chain and TCR β chain of nucleotide SEQ ID pairs selected from the group consisting of:
SEQ ID NOS:79 and 92; SEQ ID NOS:80 and 93; SEQ ID NOS:79 and 94; SEQ ID NOS:81 and 95; SEQ ID NOS:108 and 121; SEQ ID NOS:109 and 122; SEQ ID NOS:110 and 123; and SEQ ID NOS:111 and 124.
9. The TCR according to claim 2, wherein the HLA-A*02-restricted EBV LMP2-derived antigenic peptide has a sequence according to SEQ ID NO:107, comprising:
a TCR α chain variable domain comprising a CDR3 α of the following sequence:
C-A-T-X¹-G-X²-S-G-Y-S-T-L-T-F (SEQ ID NO:181),
in combination with:
a TCR β chain variable domain comprising a CDR CDR3 β of the following sequence:
C-A-S-X³-X⁴-Q-G-G-(S)-X⁵-X⁶-G-Y-T-F (SEQ ID NO:182), whereby (S) is optional, and wherein:
 - i. X¹ is selected from E and A;
 - ii. X² is selected from D, G, N, S, and any of the following amino acids with related properties: E, A, Q and T;
 - iii. X³ is selected from S and T, and any of the following amino acids with related properties: N and Q;

- iv. X⁴ is selected from K, R and T, and any of the following amino acids with related properties: H, and S;
- v. X⁵ is selected from G and A;
- vi. X⁶ is selected from Y and S, and any of the following amino acids with related properties: F, W, H and T.

10. The TCR according to claim 9, comprising:

a CDR3 α having at least about 95% sequence identity with a member selected from:

SEQ ID NOS:20; 23; 24; in combination with:

a CDR3 β having at least about 95% sequence identity with a member selected from:

SEQ ID NOS:49; 52; 53 and 54.

11. The TCR according to claim 10 comprising a CDR3 α and CDR3 β of polypeptide SEQ ID pairs selected from:

SEQ ID NOS:20 and 49; SEQ ID NO:23 and 52; SEQ ID NOS:23 and 53; and SEQ ID NOS:24 and 54.

12. The TCR according to claim 9, comprising:

a TCR α chain amino acid sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS: 60; 63; 64; and 65; in combination with:

a TCR β chain amino acid sequence shares at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:73; 76; 77; and 78.

13. The TCR according to claim 12 comprising a variable domain comprising a TCR α chain and TCR β chain of polypeptide SEQ ID pairs selected from the group consisting of:

SEQ ID NOS:60 and 73; SEQ ID NOS:63 and 76; SEQ ID NOS:64 and 77; and SEQ ID NOS:65 and 78.

14. The TCR according to claim 9, comprising:

a TCR α chain encoded by a nucleic acid having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:84; 88; 89; 90; 114; 118; 119; and 120; in combination with:

a TCR β chain encoded by a nucleic acid having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:98; 102; 103; 104; 127; 131; 132; and 133.

15. The TCR according to claim 14 comprising a variable domain comprising a TCR α chain and TCR β chain encoded by a nucleotide SEQ ID pair selected from the group consisting of:

SEQ ID NOS:84 and 98; SEQ ID NOS:88 and 102; SEQ ID NOS:89 and 103; SEQ ID NOS:90 and 104; SEQ ID NOS:114 and 127; SEQ ID NOS:118 and 131; SEQ ID NOS:119 and 132; and SEQ ID NOS:120 and 133.

16. The TCR according to claim 2, wherein the HLA-A*02-restricted EBV LMP2-derived antigenic peptide has a sequence according to SEQ ID NO:106, comprising:

a CDR3 α of the following amino acid sequence: C-A-X¹-X²-G-A-G-S-Y-Q-L-T-F (SEQ ID NO:183), in combination with:

a CDR3 β of the following amino acid sequence: C-A-S-S-X³-E-G-Q-A-S-S-Y-E-Q-Y-F (SEQ ID NO:184), wherein:

- i. X¹ is a member selected from G, V, and any of the following amino acids with related properties: A, I and L
- ii. X² is a member selected from A, S, and any of the following amino acids with related properties: G and T
- iii. X³ is a member selected from L, A, and any of the following amino acids with related properties: I, V and G.

17. The TCR according to claim 16, comprising:

a CDR3 α amino acid sequence having at least about 95% sequence identity with a member selected from: SEQ ID NOS:19; 21; and 22; in combination with:

a CDR3 β amino acid sequence having at least about 95% sequence identity with a member selected from: SEQ ID NOS:48; 50; and 51.

18. The TCR according to claim 17 consisting of a variable domain comprising the CDR3 α and CDR3 β of amino acid pairs selected from:

SEQ ID NOS:19 and 48; SEQ ID NOS:21 and 50; SEQ ID NOS:22 and 50; and SEQ ID NOS:21 and 51.

19. The TCR according to claim 16, comprising:
a TCR α chain amino acid sequence having at least about 80%, about 85, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:59; 61; and 62; in combination with:
a TCR β chain amino acid sequence having at least about 80%, about 85, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:72; 74; and 75;.
20. The TCR according to claim 19 comprising a TCR α chain and TCR β chain of polypeptide SEQ ID pairs selected from the group consisting of:
SEQ ID NOS:59 and 72; SEQ ID NOS:61 and 74; SEQ ID NO:62 and 74; and SEQ ID NOS:61 and 75.
21. The TCR according to claim 16, comprising:
a TCR α chain encoded by a nucleic acid sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:83; 85; 86; 87; 113; 115; 116; and 117; in combination with:
a TCR β chain encoded by a nucleic acid sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:97; 99; 100; 101; 128; 129; and 130.
22. The TCR according to claim 21 comprising a TCR α chain and TCR β chain of nucleotide SEQ ID pairs selected from the group consisting of:
SEQ ID NOS:83 and 97; SEQ ID NOS:85 and 99; SEQ ID NOS:86 and 102; SEQ ID NOS:87 and 101; SEQ ID NOS:115 and 128; SEQ ID NOS:116 and 129; SEQ ID NOS:117 and 130.
23. A TCR according to claim 2, wherein the HLA-A*02-restricted EBV LMP2-derived antigenic peptide has a sequence according to SEQ ID NO:146, comprising:
a CDR3 α of amino acid sequence having at least about 95% sequence identity with SEQ ID NO:18; in combination with:
a CDR3 β of amino acid sequence sharing at least about 95% sequence identity with SEQ ID NO:47.
24. The TCR according to claim 23, comprising:

a TCR α chain of amino acid sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NO:58; in combination with:

a TCR β chain of amino acid sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NO:71.

25. The TCR according to claim 23, comprising:

a TCR α chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:82; and 112; in combination with:

a TCR β chain encoded by a nucleotide sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:96; and 125.

26. The TCR according to claim 25 comprising a TCR α chain and TCR β chain of nucleotide SEQ ID pairs selected from:

SEQ ID NOS:82 and 96; and SEQ ID NOS:112 and 125.

27. A TCR according to claim 2, wherein the HLA-B*35-restricted EBV BZLF1-derived antigenic peptide has a sequence according to SEQ ID NO:145, comprising:

a CDR3 α of amino acid sequence having at least about 95% sequence identity with SEQ ID NO:138; in combination with:

a CDR3 β of amino acid sequence having at least about 95% sequence identity with SEQ ID NO:139.

28. The TCR according to claim 27, comprising:

a TCR α chain of amino acid sequence having at least about 80%, about 85%, about 90%, or about 95% sequence identity with SEQ ID NO:140; in combination with:

a TCR β chain of amino acid sequence SEQ ID NO:141.

29. The TCR according to claim 27, comprising:

a TCR α chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NO:142; and SEQ ID NO:134; in combination with:

a TCR β chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NO:143; and SEQ ID NO:135.

30. The TCR according to claim 29 comprising a TCR α chain and TCR β chain of nucleotide SEQ ID pairs selected from:

SEQ ID NOS:142 and 143; and SEQ ID NOS:134 and 135.

31. An isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain binding to a mutated splice factor-induced splice variant-derived antigenic peptide when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprise one, two or three complementarity determining regions selected from CDR1, CDR2, and CDR3, each respectively comprising an amino acid sequence having at least about 95% sequence identity with an amino acid sequence selected from Table 3.

32. The TCR according to claims 31, said TCR binding to an HLA-A*02-restricted Mutant splice factor-induced MAPK8IP2 splice variant-derived peptide having the amino acid sequence SEQ ID NO:147.

33. A TCR according to claim 32, comprising:

a CDR3 β of amino acid sequence selected from SEQ ID NOS:42; 159; and 160, in combination with

a CDR3 α of the following sequence: C-A-F-M-X¹-X²-D-S-X³-X⁴-Y-X⁵-X⁶-I-X⁷ (SEQ ID NO:185), wherein:

X¹ is L or I or E, or any of the following amino acids with related properties V or D;

X² is P or I or A, or any of the following amino acids with related properties: V, L or G;

X³ is G or N, or any of the following amino acids with related properties: Q, A, C or S;

X⁴ is T or no AA at this position, or S as an amino acid with related properties;

X⁵ is K or Q, or any of the following amino acids with related properties: R, H or N;

X⁶ is L or Y, or any of the following amino acids with related properties: I, V, F, W or H;
X⁷ is F or W.

34. The TCR according to claim 33, comprising:

a CDR3 α amino acid sequence sharing at least 95% sequence identity with a member selected from SEQ ID NOS:14; 151; or 152, in combination with:

a CDR3 β amino acid sequence sharing at least 95% sequence identity with a member selected from SEQ ID NOS:42; 159; or 160.

35. The TCR according to claim 34 comprising a variable domain comprising the CDR3 α and CDR3 β of polypeptide SEQ ID pairs selected from:

SEQ ID NOS:14 and 42; SEQ ID NOS:151 and 159; and SEQ ID NOS:152 and 160.

36. The TCR according to claim 33, comprising:

a TCR α chain with the variable region amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:66; 162; or 163, in combination with:

a TCR β chain with the variable region amino acid sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from SEQ ID NOS:91; 166; or 167.

37. The TCR according to claim 36 comprising a variable domain comprising a TCR α chain and a TCR β chain of polypeptide SEQ ID pairs selected from:

SEQ ID NOS: 66 and 91; SEQ ID NOS:162 and 166; and SEQ ID NOS:163 and 167.

38. The TCR according to claim 32, comprising:

a TCR α chain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:169; 170; 175; 176; 186; or 188, in combination with:

a TCR β chain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:172; 173; 178; 179; 187; or 189.

39. The TCR according to claim 38 comprising a variable domain comprising a TCR α chain and a TCR β chain of nucleotide SEQ ID pairs selected from the group consisting of:

SEQ ID NOS:169 and 172; SEQ ID NOS:170 and 173; SEQ ID NOS:175 and 178;
SEQ ID NOS:176 and 179; SEQ ID NOS:186 and 187; and SEQ ID NOS:188
and 189.

40. An isolated T cell receptor (TCR) comprising a TCR α chain and a TCR β chain binding to a Human Endogenous Retrovirus (HERV)-derived antigenic peptide when presented by a major histocompatibility complex (MHC) molecule, wherein said TCR α chain and said TCR β chain each comprise one, two or three complementarity determining regions selected from CDR1, CDR2, and CDR3, each respectively comprising an amino acid sequence having at least about 95% sequence identity with an amino acid sequence selected from Table 3.

41. The TCR according to claim 40, wherein the TCR binds to an HLA-A*02-restricted HERV-K-derived -antigenic peptide has a sequence according to SEQ ID NO:148, comprising:

a CDR3 α amino acid sequence sharing at least about 95% sequence identity with
SEQ ID NO:153; in combination with:
a CDR3 β amino acid sequence sharing at least about 95% sequence identity with
SEQ ID NO:161.

42. A TCR according to claim 41, comprising a TCR α chain with the variable region amino acid sequence SEQ ID NO:164, in combination with a TCR β chain with the variable region amino acid sequence SEQ ID NO:168.

43. The TCR according to claim 41, comprising:

a TCR α chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:171 and 177; in combination with:

a TCR β chain encoded by a nucleotide sequence sharing at least about 80%, about 85%, about 90%, or about 95% sequence identity with a member selected from: SEQ ID NOS:174 and 180.

44. The TCR according to claim 43 comprising a TCR α chain and a TCR β chain of nucleotide SEQ ID pairs selected from the group consisting of: SEQ ID NOS:171 and 174; and SEQ ID NOS:177 and 180.

45. An expression vector comprising a nucleotide sequence pair according to any one of claims 8, 15, 21, 26, 30, 39, or 44.

46. A host cell comprising the expression vector according to claim 45.

47. The host cell according to claim 46 wherein the host cell is an isolated host cell.

48. The host cell according to claim 46 or 47 expressing the TCR.

49. Use of the TCR-expressing T-cells according to claim 48 for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering a splice-variant of MAPK8IP2-, or HERV-K-, or EBV-associated cancer.

50. The use according to claim 49, wherein the ACT is used in combination with immune modulating agents, selected from the group consisting of cytokines, TLR agonists, RIG-I like receptor (RLR) agonists, immune checkpoint inhibitors, chemotherapeutic agents, antibodies, radiotherapy, and a combination thereof.

51. Use of the host cell according to claim 48 for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering a cancer, condition, disease, disorder, or pathology associated with expression of SF3B1mut- or other genetically altered splice factors.

52. The use according to claim 51 wherein said SF3B1mut- or other genetically altered splice factor-associated condition, disease, disorder, or pathology includes:

SF3B1mut expressing cancers including but not limited to: myelodysplastic syndrome (MDS), non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia, pancreatic cancer, acute myeloid leukemia and chronic myelomonocytic leukemia.

53. Use of the host cell according to claim 48 for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering a cancer, condition, disease, disorder, or pathology associated with expression of human endogenous retrovirus protein HERV-K.

54. Use of the TCR α chain and TCR β chain pairs comprising a nucleotide sequence selected from the combinations set forth in Table 5 or Table 6 as part of a fusion construct, whereby said fusion construct consists of a TCR and a single-chain fragment that binds to a molecule specifically expressed on T cells, including but not limited to CD3.

55. An expression vector comprising a nucleotide sequence pair encoding mouse constant regions SEQ ID NO:190 or SEQ ID NO:191, and human variable regions of TCR pairs with SEQ ID NOS:162 and 166; SEQ ID NOS:163 and 167; SEQ ID NOS:164 and 168; and SEQ ID NOS:66 and 91.

56. A host cell comprising the expression vector according to claim 55.

57. Use of the TCR-expressing T-cells according to claim 56 for T-cell-based adoptive cell transfer (ACT) as a therapeutic treatment in a subject suffering a splice-variant of MAPK8IP2 or HERV-K-associated cancer.

58. A T cell that expresses a TCR according to any one of claims 8, 15, 21, 26, 30, 39, or 44, wherein the heterologous TCR of desired antigen specificity is inserted into the genome of said T cell.

59. The T cell according to claim 58, wherein the T cell is a human T cell.

60. The TCR according to any one of claims 8, 15, 21, 26, 30, 39, or 44, wherein said TCR is expressed by a T cell, and both the T cell and the cell expressing the selected antigen are present in a single subject.