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(54) Title: COMPOSITIONS AND METHODS FOR TARGETING HPV-INFECTED CELLS

(57) Abstract: Disclosed are compositions and methods for targeted treatment of cancer, such as HPV-associated cancer. In particular, modified T cell receptor (TCR) T cells are disclosed that can be used with adoptive cell transfer to target and kill cancer cells with reduced antigen escape. Therefore, also disclosed are methods of providing an anti-tumor immunity in a subject with HPV-associated cancer that involves adoptive transfer of the disclosed TCR-T cells.



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COMPOSITIONS AND METHODS FOR TARGETING HPV-INFECTED CELLS

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application serial number 62/993,442, filed March 23, 2020, which is incorporated by reference in its entirety.

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BACKGROUND

Adoptive cell transfer (ACT) involves implanting or infusing particular cells, typically immune cells and/or cells derived from the immune system (*e.g.*, sensitized, modified, and/or engineered lymphocytes), into a patient with the aim of recognizing, targeting, and/or destroying disease-associated cells. Adoptive immunotherapies (*e.g.*, T cell therapies) have become a promising approach for the treatment of many diseases and disorders, including post-transplant lymphoproliferative disorders, infectious diseases (*e.g.*, viral infections), and autoimmune diseases. Adoptive T cell therapy is also a promising cancer treatment modality, showing encouraging results in clinical trials. Infusion of tumor-infiltrating lymphocytes (TIL), isolated from metastatic tumors of the patient and expanded *ex vivo* have been associated with complete regression of metastatic melanoma and cervical cancer in some patients. However, manufacturing of such autologous adoptive T cell therapies is often time-consuming and of limited use to terminally ill patients. Thus, there exists an urgent and unmet need to develop an "off-the-shelf" strategy for rapid delivery of adoptive T cell therapy. This can potentially be achieved by genetically engineering lymphocytes (*e.g.*, T cells such as cytotoxic T cells) to express a tumor or disease-targeting moiety, such as a chimeric antigen receptor (CAR) or an engineered T cell receptor (TCR). This strategy has shown encouraging early results in clinical trials for B-cell malignancies, melanoma, and synovial cell sarcoma. However, efforts to extend this approach to epithelial cancers have generally relied on targets (*e.g.*, antigens) that are shared by both tumors and healthy tissues, and are thus limited by T cell-mediated on-target, off-tumor toxicity. Such off-tumor toxicity might be avoided by targeting a tumor antigen that is not expressed by healthy tissues, but few antigens are both exclusive to malignant cells and expressed commonly by a particular family of epithelial cancers.

Selective infection of skin or mucous membranes is a classic feature of HPVs, and their replication is closely linked to the maturation of the cells in these membranes. Globally, HPV infection accounts for an estimated 530,000 cervical cancer cases (~270,000 deaths) annually, with the majority (86% of cases, 88% of deaths) occurring in developing countries. In total, HPV accounts for 5.2% of the worldwide cancer burden. Each year in the United States, an estimated 26,000 new cancers are attributable to HPV, about 17,000 in women and 9,000 in men. The most common HPV types are the low-risk HPV-6 and HPV-11, which are responsible for 90% of genital warts and a disease known as recurrent respiratory papillomatosis, in which tumors grow in the airway. HPV also plays a role in the development of non-melanoma skin cancer (NMSC), including cutaneous squamous cell carcinoma (SCC), among chronic lymphocytic leukemia (CLL) and blood and marrow transplant (BMT) patients. HPV-16 and HPV-18, in particular, account for the majority of head and neck cancers (HNSCCs) and cancers of the cervix, anus, vagina, vulva, penis, tongue base, larynx, and tonsil. Current standard therapeutic options for HNSCCs include and incorporate surgery and radiotherapy with concurrent chemotherapy (*e.g.*, cisplatin and/or cetuximab). Unfortunately, the post-treatment burden on the patient following such modalities can be significant and permanent and may include dysphagia, dysphonia, xerostomia, scarring and disfigurement, and trismus. However, HPV-associated precancerous lesions, such as those of the vulva, vagina, anus, penis, as well as genital warts, are typically treated using physical elimination by cryotherapy (*i.e.*, using extreme cold to destroy tissue), chemical cauterization (*i.e.*, using a chemical to destroy tissue), and laser or surgical removal. Notably, in such pre-cancerous lesions physical elimination alone is not very effective, since 20–30% or more cases recur, with lesions both at previously treated sites due to failure of the procedure to eliminate the HPV, and at new sites due to new infections. When this occurs, radiotherapy and chemotherapy are then used with relative success; however, about 50% of the HPV-associated cancer patients still die of the disease. Clearly, new treatment strategies are urgently needed to control the burden of HPV-related cancer.

SUMMARY

The present invention is based, at least in part, on the discovery that HPV antigens, particularly those apart from E6 and E7, can be used for the targeted treatment of HPV-associated

diseases (*e.g.*, HPV-associated cancers such as head and neck, gastrointestinal, genitourinary, and gynecologic cancers). In some aspects, provided herein are immune cells that express an engineered TCR (*e.g.*, TCR-T cells, TCR-Ts) that target HPV antigens.

Aspects of the invention disclosed herein include a T cell receptor (TCR) polypeptide having antigenic specificity for human papillomavirus (HPV) 16. In some embodiments, said TCR comprises at least one complementary determining region 3 α (CDR3 α) and at least one CDR3 β amino acid sequence selected from the amino acid sequences set forth in Tables 1 and/or 13. In some embodiments of the invention, TCR polypeptides disclosed herein are specific for antigens comprising at least one epitope having an amino acid sequence selected from the amino acid sequences set forth in Tables 1, 11 and/or 13, *e.g.*, SEQ ID NOs: 1-12, 217, or 218.

In certain aspects of the invention, disclosed herein are methods of treating a cancer or precancerous lesions in a subject, the method comprising administering an effective amount of an adoptive immunotherapy composition comprising the cells expressing the TCR polypeptides contemplated herein. In preferred embodiments, the cancer or lesion is an HPV-associated cancer or lesion. In some aspects of the invention, disclosed herein are cell banks comprising cells for adoptive immunotherapy. In some embodiments, the cells of such banks express the TCRs contemplated herein. In certain preferred embodiments, the HLA restriction of said TCR-expressing cells is known. In certain embodiments, treating an HPV-associated cancer or precancerous lesion, as disclosed herein, comprises administering an effective amount of an adoptive immunotherapy composition comprising TCR-expressing cells selected from the cell banks contemplated herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the sorting path of HPV16-E5-NLD epitope specific CD8⁺ T cells detected by a dual cytokine capture assay, and sorted by double positive (IFN γ and TNF α) single cells into 96 well PCR plates.

Figure 2 shows an agarose gel electrophoresis image of TCR segments containing CDR3 α and CDR3 β . Briefly, RT-PCR is performed on individual cells and the resultant cDNA is subjected to two rounds of nested PCR. In the first round, TCR α and TCR β transcript amplification is achieved with a multiplexed, comprehensive panel of external, sense V α and V β segment-specific

primers and antisense C α and C β segment-specific primers. The first-round PCR products are subjected to two separate second-round PCRs, incorporating, respectively, (1) a multiplexed panel of external sense V α and antisense C α segment-specific primers or (2) external sense V β and antisense C β segment-specific primers. Paired TCR α and TCR β products from the same cell were
5 loaded in adjacent lanes and shown in paired, labeled columns. Negative control (H1-H12) PCR reactions are shown in the bottom row (right lanes). In the ladder lane, a 300 bp label is shown.

Figure 3 shows the E2-TLQ-TCR amino acid sequence (SEQ ID NO. 209), indicating relevant features.

Figure 4 shows the E5-NLD-TCR amino acid (SEQ ID NO. 210), indicating relevant
10 features.

Figure 5 shows an exemplary lentiviral construct (E5-NLD-TCR), indicating relevant features. Figure 5 discloses "SGSG linker" as SEQ ID NO: 233.

Figure 6 shows the E6-AFR-TCR amino acid sequence (SEQ ID NO. 211), indicating relevant features.

Figure 7 shows the E6-TIH-TCR amino acid sequence (SEQ ID NO. 212), indicating
15 relevant features.

Figure 8 shows the E6-HDI-TCR amino acid sequence (SEQ ID NO. 213), indicating relevant features.

Figure 9 shows the E6-KQR-TCR amino acid sequence (SEQ ID NO. 214), indicating
20 relevant features.

Figure 10 shows the E7-TPT-TCR amino acid sequence (SEQ ID NO. 215), indicating relevant features.

Figure 11 shows the E5-SAF-TCR amino acid sequence (SEQ ID NO. 216), indicating relevant features.

Figure 12, A-C, shows lentiviral transfer of HPV-specific TCR into Jurkat cells, TCR
25 expression confirmed by flow cytometry. Dot plots show the TCR expression in nontransduced controls and Jurkat cells transduced with (A) E2-TLQ-TCR, (B) E5-NLD-TCR, and (C) E6-TIH-TCR.

Figure 13, A and B, shows lentiviral transfer of HPV-specific TCR into Jurkat cell confers antigen specificity. Lentiviral TCR-transduced Jurkat cells were co-incubated with peptide-pulsed, HLA-matched or mismatched LCLs. After 24 hours, CD69 expression was checked by flow cytometry. Cytometric analysis shows (A) E5-NLD-lentiTCR (restricted to HLA-C*05:01 & C*08:02) and (B) E2-TLQ-lentiTCR (restricted to HLA A*02:01) transduced Jurkat cell express CD69.

Figure 14 shows lentiviral transfer of HPV-specific TCR into PBMCs confers TCR expression. Briefly, lentiviral transduction of PBMC was performed 48h post stimulation. At day 8 and day 15 (day 7 after re-stimulation) TCR expression was assessed by flow cytometry.

Representative data is shown for E5-NLD-TCR-transduced PBMC TCR expression, *i.e.*, anti-TCRV α 12.1-positive, CD8⁺ cells.

Figure 15 shows antigenic specificity of transgenic TCR assessed by multiparametric intracellular cytokine staining (ICS) assay. Briefly, nontransduced and E5-NLD-lentiviral-transduced PBMCs were stimulated with the E5 antigen peptide (NLD peptide; SEQ ID NO. 1) and incubated for 5 hours. Dot plots show CD107, IFN γ , TNF α and IL-2 expression in CD8⁺ cells and CD4⁺ cells (last row).

Figure 16 shows avidity of TCR-T cells for cognate antigen measured by recall ICS assay. Transduced and nontransduced PBMC were stimulated with HLA-matched LCL pulsed with different concentration of peptide (10^{-6} , 10^{-7} , 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} and 10^{-13} mole/L) for 4 hours and IFN γ expression was measured by ICS assay. The line graph is showing E5-NLD lentivirus transduced PBMC IFN γ expression after stimulating with HLA matched (C*05:01 and C*08:02) LCL.

Figure 17, A-C, shows cytolysis for CaSki cell line (HPV16⁺ and HLA-A*02:01⁺) with E2-TLQ-T (A), cytolysis for CaSki cell line (HPV16⁺ and HLA-A*02:01 +ve) with untransduced T cells (B), and cytolysis for SCC70 cell line (HPV16-ve and HLA-A*02:01⁺) with E2-TLQ-T and untransduced T cells (C). UT = untransduced T cells; E2 TCR = E2-TLQ-TCR-transduced T cells.

DETAILED DESCRIPTION

General

The use of engineered TCR therapy provides several advantages. The patients' own T cells may be equipped with desired specificities and allow generation of sufficient numbers of T cells in a short period of time while avoiding T cell exhaustion. In some embodiments of the invention, as disclosed herein, TCRs may be transduced into immune effector cells such as central memory T cells or T cells with stem cell characteristics, which may ensure better persistence and function upon transfer. Preferably, TCRs are transduced into cytotoxic T cells (CD8⁺ T cells; CTLs). Such TCR-engineered T cells (TCR-T cells) can be infused into cancer patients, such as cancer patients rendered lymphopenic by chemotherapy or irradiation, allowing for efficient engraftment but inhibiting immune suppression. As disclosed herein, the present invention relates, at least in part, to immune cells which recombinantly express an artificial T cell receptor (TCR) that targets HPV antigens.

Notably, HPV oncoproteins E6 and E7 are constitutively expressed and important for the survival of HPV-associated cancers but are absent from healthy tissues. In at least HNSCCs, HPV16 has been reported to integrate into the host genome leading to disruption of E2 early genes, which is a negative regulator of E6 and E7 oncogene expression, thus making E6 and E7 antigens the primary focus of research. However, recent cancer genome sequencing in HNSCCs suggests that the majority of such cancers (*e.g.*, tumors) that contain hybrid episomal forms of HPV, comprise other HPV antigens, apart from E6 and E7. In addition, higher E2 expression represses E6 and E7 expression, further changing the expression profile of HPV antigens and subsequent immune T cell infiltration within tumors. Moreover, adoptive T cell therapies directed against HPV oncoproteins have typically been restricted to HLA-A*02:01 which is the most common class I allele in the United States, expressed in approximately 40–50 percent of people of European descent.

Unfortunately, HPV infection can selectively downregulate HLA-A and HLA-B from the surface of infected cells without affecting HLA-C expression. Thus, other early proteins might be targeted instead of, or in combination with, E6 and E7 antigens through adoptive T cell therapy (*e.g.*, TCR-T therapy), offering better efficacy than targeting E6 and E7 alone. Likewise, TCR sequences specific

for different early antigens (*e.g.*, other than, or in addition to, E6 and E7 antigens) and restricted to HLA B and HLA-C alleles may provide better efficacy and prognosis of HPV-associated disease, including various cancers. Accordingly, aspects of the invention disclosed herein include TCRs that specifically target HPV16 antigens, preferably early HPV16 antigens E1, E2, E4, and E5, with
5 restriction to HLA-A, HLA-B and HLA-C alleles. Also provided herein are immune effector cells (*e.g.*, T cells) genetically engineered to express said antigen-specific TCRs (*e.g.*, TCR-Ts).

In some embodiments, TCR-T cells, as described herein, are engineered to counteract any tolerogenic effects of the malignant cellular microenvironment (*e.g.*, a tumor microenvironment) by, for example and without limitation, suppressing or inhibiting PD-1 signaling. In certain

10 embodiments, the TCRs described herein may be sensitized to or selectively target a viral or non-viral antigen. An ideal target should not be expressed on any normal tissue/organ, or at least not in vital normal tissues (heart, liver, CNS, lung, and other tissues that may be particularly sensitive to transient damage) nor in closely related normal cellular counterparts (*e.g.*, stem and/or progenitor cells), in order to minimize side effects (*e.g.*, on target/off tumor or bystander effects). Also

15 disclosed herein are immune effector cells, such as T cells or Natural Killer (NK) cells, that are engineered to express recombinant TCR polypeptides that selectively bind HPV antigens (*e.g.*, wildtype and/or mutant HPV16). Therefore, also disclosed are methods for providing targeted immunity (*e.g.*, anti-tumor immunity) in a subject with an HPV-associated disease or malignancy that involves adoptive transfer of the disclosed immune effector cells engineered to express the
20 disclosed TCR polypeptides.

In the tumor microenvironment cancer cells and host immune cells interact, potentially leading to promotion or inhibition of cancer progression. Ideally, the immune system would identify cancer cells and mobilize an immune response to eliminate the cancer. Unfortunately, at the T cell level, upregulation of inhibitory receptors, such as PD-1 and Tim-3, correlates with T cell
25 dysfunction. This has been observed on both hepatitis C virus (HCV)-specific and HCV-nonspecific CD8⁺ T cells in the circulation and livers of patients with chronic HCV infection. Partial restoration of T cell proliferation and IFN- γ secretion can be achieved *ex vivo* by inhibiting the binding of PD-1 and Tim-3 to their respective ligands (*i.e.*, B7-H1, also known as PD-L1, and Galectin-9). What is more, recent reports have demonstrated that prolonged administration of IFN- α , a standard therapy

for persistent HCV infection, promoted telomere loss in naïve T cells. Given the correlation between shortened T cell telomeres and terminal differentiation (characterized by diminished proliferative potential), IFN- α -induced T cell “exhaustion” likely represents a significant barrier for immunotherapy in HCV-infected patients. In certain aspects disclosed herein, the invention employs checkpoint inhibition strategies. Checkpoint inhibitor therapies target key regulators of the immune system that either stimulate or inhibit the immune response. Such immune checkpoints can be exploited in the cancer disease state (*e.g.*, by tumors) to evade attacks by the immune system. Checkpoint inhibitor studies have noted the activity of PD-1 inhibitor therapy (El-Khoueiry et al., (2017). “Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial.” *Lancet* 389 (10088): 2492-2502) and the FDA has approved Nivolumab for second line treatment of HCC with an objective response rate of 20%.

Definitions

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

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

As used herein, the term “administering” means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering. Such an agent can contain, for example, peptide described herein, an antigen presenting cell provided herein and/or a CTL provided herein.

The term “*amino acid*” is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of the foregoing.

As used herein, the term “*antibody*” may refer to both an intact antibody and an antigen binding fragment thereof. Intact antibodies are glycoproteins that include at least two heavy (H)

chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain includes a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. Each light chain includes a light chain variable region (abbreviated herein as VL) and a light chain constant region. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. The term “antibody” includes, for example, monoclonal antibodies, polyclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), single-chain antibodies and antigen-binding antibody fragments.

The terms “*antigen-binding fragment*” and “*antigen-binding portion*” of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to bind to an antigen. Examples of binding fragments encompassed within the term “antigen-binding fragment” of an antibody include Fab, Fab', F(ab')₂, Fv, scFv, disulfide linked Fv, Fd, diabodies, single-chain antibodies, camelid antibodies, isolated CDRH3, a Designed Ankyrin Repeat Protein (DARPin) and other antibody fragments that retain at least a portion of the variable region of an intact antibody. These antibody fragments can be obtained using conventional recombinant and/or enzymatic techniques and can be screened for antigen binding in the same manner as intact antibodies.

The term “*antigen binding site*” refers to a region of an antibody or T cell that specifically binds the epitope(s) of an antigen.

The term “*binding*” or “*interacting*” refers to an association, which may be a stable association, between two molecules, *e.g.*, between a peptide and a binding partner or agent, *e.g.*, small molecule, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

The term “*biological sample*,” “*tissue sample*,” or simply “*sample*” each refers to a collection of cells obtained from a tissue of a subject. The source of the tissue sample may be solid tissue, as from a fresh, frozen and/or preserved organ, tissue sample, biopsy, or aspirate; blood or

any blood constituents, serum, blood; bodily fluids such as cerebral spinal fluid, amniotic fluid, peritoneal fluid or interstitial fluid, urine, saliva, stool, tears; or cells from any time in gestation or development of the subject.

As used herein, the term “*cancer*” includes, but is not limited to, solid tumors and blood borne tumors. The term cancer includes diseases of the skin, tissues, organs, bone, cartilage, blood, and vessels, including the cervix, anus, vagina, vulva, penis, tongue base, larynx, and tonsil. The term “*cancer*” further encompasses primary and metastatic cancers.

The term “chimeric molecule” refers to a single molecule created by joining two or more molecules that exist separately in their native state. The single, chimeric molecule has the desired functionality of all of its constituent molecules. One type of chimeric molecules is a fusion protein.

The term “*epitope*” means a protein determinant capable of specific binding to an antibody or immune cell (*e.g.*, T cell). Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains. Certain epitopes can be defined by a particular sequence of amino acids to which a T cell receptor (TCR) or antibody is capable of binding.

The term “fusion protein” refers to a polypeptide formed by the joining of two or more polypeptides through a peptide bond formed between the amino terminus of one polypeptide and the carboxyl terminus of another polypeptide. The fusion protein can be formed by the chemical coupling of the constituent polypeptides, or it can be expressed as a single polypeptide from nucleic acid sequence encoding the single contiguous fusion protein. A single chain fusion protein is a fusion protein having a single contiguous polypeptide backbone. Fusion proteins can be prepared using conventional techniques in molecular biology to join the two genes in frame into a single nucleic acid, and then expressing the nucleic acid in an appropriate host cell under conditions in which the fusion protein is produced.

“Gene construct” refers to a nucleic acid, such as a vector, plasmid, viral genome or the like which includes a “coding sequence” for a polypeptide or which is otherwise transcribable to a biologically active RNA (*e.g.*, antisense, decoy, ribozyme, etc.), may be transfected into cells, *e.g.*, mammalian cells, and may cause expression of the coding sequence in cells transfected with the construct. The gene construct may include one or more regulatory elements operably linked to the

coding sequence, as well as intronic sequences, polyadenylation sites, origins of replication, marker genes, etc.

The term “linker” is art-recognized and refers to a molecule or group of molecules connecting two compounds, such as two polypeptides. The linker may be comprised of a single linking molecule or may comprise a linking molecule and a spacer molecule, intended to separate the linking molecule and a compound by a specific distance.

The term “*operably linked to*” refers to the functional relationship of a nucleic acid with another nucleic acid sequence. Promoters, enhancers, transcriptional and translational stop sites, and other signal sequences are examples of nucleic acid sequences operably linked to other sequences. For example, operable linkage of DNA to a transcriptional control element refers to the physical and functional relationship between the DNA and promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA.

As used herein, the phrase “*pharmaceutically acceptable*” refers to those agents, compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase “*pharmaceutically-acceptable carrier*” means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting an agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as

propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, 5 polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

The terms "*polynucleotide*", and "*nucleic acid*" are used interchangeably. They refer to a natural or synthetic molecule, or some combination thereof, comprising a single nucleotide or two or more nucleotides linked by a phosphate group at the 3' position of one nucleotide to the 5' end of 10 another nucleotide. The polymeric form of nucleotides is not limited by length and can comprise either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal 15 RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. A polynucleotide may be further modified, such as by conjugation 20 with a labeling component. In all nucleic acid sequences provided herein, U nucleotides are interchangeable with T nucleotides. The polynucleotide is not necessarily associated with the cell in which the nucleic acid is found in nature, and/or operably linked to a polynucleotide to which it is linked in nature.

The term "*polypeptide*" or "*isolated polypeptide*" refers to a polypeptide, in certain 25 embodiments prepared from recombinant DNA or RNA, or of synthetic origin, or some combination thereof, which (1) is not associated with proteins that it is normally found with in nature, (2) is isolated from the cell in which it normally occurs, (3) is isolated free of other proteins from the same cellular source, (4) is expressed by a cell from a different species, or (5) does not occur in nature.

The terms “*polypeptide fragment*” or “*fragment*”, when used in reference to a particular polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical to that of the reference polypeptide. Such deletions may occur at the amino-terminus or carboxy-terminus of the reference polypeptide, or alternatively both. Fragments typically are at least about 5, 6, 8 or 10 amino acids long, at least about 14 amino acids long, at least about 20, 30, 40 or 50 amino acids long, at least about 75 amino acids long, or at least about 100, 150, 200, 300, 500 or more amino acids long. A fragment can retain one or more of the biological activities of the reference polypeptide. In various embodiments, a fragment may comprise an enzymatic activity and/or an interaction site of the reference polypeptide. In other embodiments, a fragment may have immunogenic properties.

The term “*precancerous lesions*” or “*precancerous condition*” refers to atypical cells and/or tissues that are associated with an increased risk of cancer. The term “*precancerous lesions*” may refer, for example, to dysplasia, benign neoplasia, or carcinoma in situ.

As used herein, a therapeutic that “*prevents*” a condition refers to a compound that, when administered to a statistical sample prior to the onset of the disorder or condition, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

As used herein, “*specific binding*” refers to the ability of an antibody or TCR to bind to a predetermined antigen or the ability of a peptide to bind to its predetermined binding partner. Typically, an antibody or peptide specifically binds to its predetermined antigen or binding partner with an affinity corresponding to a KD of about 10^{-7} M or less, and binds to the predetermined antigen/binding partner with an affinity (as expressed by KD) that is at least 10 fold less, at least 100 fold less or at least 1000 fold less than its affinity for binding to a non-specific and unrelated antigen/binding partner (*e.g.*, BSA, casein).

A “*spacer*” as used herein refers to a peptide that joins the proteins comprising a fusion protein. Generally, a spacer has no specific biological activity other than to join the proteins or to preserve some minimum distance or other spatial relationship between them. However, the

constituent amino acids of a spacer may be selected to influence some property of the molecule such as the folding, net charge, or hydrophobicity of the molecule.

The term “*specifically binds*” or “*specific binding*”, as used herein, when referring to a polypeptide (including antibodies) or receptor, refers to a binding reaction which is determinative of the presence of the protein or polypeptide or receptor in a heterogeneous population of proteins and other biologics. Thus, under designated conditions (*e.g.*, immunoassay conditions in the case of an antibody), a specified ligand or antibody “specifically binds” to its particular “target” (*e.g.*, an antibody specifically binds to an endothelial antigen) when it does not bind in a significant amount to other proteins present in the sample or to other proteins to which the ligand or antibody may come in contact in an organism. Generally, a first molecule that “specifically binds” a second molecule has an affinity constant (K_a) greater than about 10^5 M^{-1} (*e.g.*, 10^6 M^{-1} , 10^7 M^{-1} , 10^8 M^{-1} , 10^9 M^{-1} , 10^{10} M^{-1} , 10^{11} M^{-1} , and 10^{12} M^{-1} or more) with that second molecule. For example, in the case of the ability of a TCR to bind to a peptide presented on an MHC (*e.g.*, class I MHC or class II MHC); typically, a TCR specifically binds to its peptide/MHC with an affinity of at least a K_D of about 10^{-4} M or less, and binds to the predetermined antigen/binding partner with an affinity (as expressed by K_D) that is at least 10 fold less, at least 100 fold less or at least 1000 fold less than its affinity for binding to a non-specific and unrelated peptide/MHC complex (*e.g.*, one comprising a BSA peptide or a casein peptide).

As used herein, the term “*subject*” means a human or non-human animal selected for treatment or therapy.

The terms “*transformation*”, “*transfection*”, or “*transduction*” mean the introduction of a nucleic acid, *e.g.*, an expression vector, into a recipient cell (*e.g.*, a mammalian cell) including introduction of a nucleic acid to the chromosomal DNA of said cell.

As used herein, the term “*treatment*” refers to clinical intervention designed to alter the natural course of the individual being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of progression, ameliorating or palliating the pathological state, and remission or improved prognosis of a particular disease, disorder, or condition. An individual is successfully “treated,” for example, if one or more symptoms associated with a particular disease, disorder, or condition are mitigated or eliminated.

The term “*variant*” refers to an amino acid or peptide sequence having conservative amino acid substitutions, non-conservative amino acid substitutions (*e.g.*, a degenerate variant), substitutions within the wobble position of each codon (*e.g.*, DNA and RNA) encoding an amino acid, amino acids added to the C-terminus of a peptide, or a peptide having 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% sequence identity to a reference sequence.

The term “*vector*” refers to the means by which a nucleic acid can be propagated and/or transferred between organisms, cells, or cellular components. Vectors include plasmids, viruses, bacteriophage, pro-viruses, phagemids, transposons, and artificial chromosomes, and the like, to which the nucleic acid has been linked, and may or may not be able to replicate autonomously or integrate into a chromosome of a host cell. Such vectors may include any vector, (*e.g.*, a plasmid, cosmid or phage chromosome) containing a gene construct in a form suitable for expression by a cell (*e.g.*, linked to a transcriptional control element).

In certain embodiments, agents of the invention may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase “*conjoint administration*” or “*administered conjointly*” refers to any form of administration of two or more different therapeutic agents (*e.g.*, a composition comprising a TCR-T cell disclosed herein and an inhibitor of an immune checkpoint) such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (*e.g.*, the two agents are simultaneously effective in the subject, which may include synergistic effects of the two agents). For example, the different therapeutic agents can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. In some preferred embodiments, the TCR-T cells express (*e.g.*, present on the cell surface or secrete) further therapeutic agents. In certain embodiments, the different therapeutic agents (*e.g.*, TCR-Ts and immune checkpoint-blocking molecules) can be administered within about one hour, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 72 hours, or about a week of one another. Similarly, in some embodiments, such compositions as are described herein may be used conjointly in a therapeutic regimen combined with other treatments, therapies, or interventions appropriate for the particular disease, condition, injury or disorder being treated. Thus, the therapeutic agents and compositions of the invention can be administered either concomitantly or sequentially in combination with one or

more treatment modalities, *e.g.*, chemotherapy, radiotherapy, surgery, or any combination thereof. For example and without limitation, the different therapeutic agents and compositions of the invention (*e.g.*, TCR-Ts alone or in combinations with immune checkpoint-blocking molecules) can be administered during, within about one hour, within about 12 hours, within about 24 hours, within
5 about 36 hours, within about 48 hours, within about 72 hours, or within about a week of chemotherapy, radiotherapy, or surgery. Thus, a subject who receives such treatment can benefit from a combined effect of different therapeutic agents and modalities.

T cell Receptors (TCRs)

A TCR is a heterodimeric cell-surface protein of the immunoglobulin super-family which is
10 associated with invariant proteins of the CD3 complex involved in mediating signal transduction. TCRs exist in $\alpha\beta$ and $\gamma\delta$ forms, which are structurally similar but have distinct anatomical locations and functions. The extracellular domains of native $\alpha\beta$ TCRs consist of two polypeptides (an α -chain and a β -chain), each of which comprise a membrane-proximal constant domain, and a membrane-distal variable domain, each of which include an intra-chain disulfide bond. A short segment,
15 analogous to an immunoglobulin hinge region, connects the immunoglobulin-like domains to the membrane (via the transmembrane region) and contains the cysteine residue that forms an interchain disulfide bond.

The variable domain contains the highly polymorphic loops referred to as complementarity determining regions (CDRs) which are responsible for binding to the peptide-presenting major
20 histocompatibility complex (MHC). Within the variable domain, each α -chain and β -chain of a native heterodimeric $\alpha\beta$ TCR comprises variable, joining, and constant regions; the β -chain also usually contains a short diversity region between the variable and joining regions, but this diversity region is often considered as part of the joining region. Each variable region comprises three CDRs (Complementarity Determining Regions) embedded in a framework sequence, one being the hyper-
25 variable region named CDR3, the main CDR responsible for recognizing the antigen presented on the MHC. There are several types of α -chain variable ($V\alpha$) regions and several types of β -chain variable ($V\beta$) regions distinguished by their framework, CDR1 and CDR2 sequences, and by a partly defined CDR3 sequence.

In some aspects of the invention, provided herein are engineered TCRs that can be expressed in immune effector cells to enhance activity against specific targets (*e.g.*, antitumor activity). The TCR sequences provided herein are capable of specifically binding antigenic peptides comprising HPV epitopes (*i.e.*, have antigenic specificity). T cells (*e.g.*, cytotoxic T cells; CTLs) expressing such engineered TCRs are useful in the prevention and/or treatment of HPV infection, and/or cancer (*e.g.*, a cancer expressing an HPV epitope), and/or precancerous lesions. In some embodiments, the TCR sequence (and the HPV epitope sequence to which it specifically binds) comprises a sequence listed in Table 1. Therefore, in some embodiments, the antigen-recognizing constructs of the invention (*e.g.*, TCRs) comprise CDR1, CDR2 and CDR3 sequences in a combination which display the respective variable chain allele together with the CDR3 sequence. Preferred embodiments of the invention comprise TCR constructs that comprise at least one or more of the CDR3s set forth in Tables 1 and 13 (*e.g.*, SEQ ID NOs. 13 to 52, or 219 to 226), or variants thereof (*e.g.*, having conservative substitutions in the amino acid sequence, *e.g.*, 1-5 such conservative substitutions), but more preferably all three CDR sequences CDR1, CDR2 and CDR3. In some such embodiments, said TCR comprises at least one complementary determining region 3 α (CDR3 α) and at least one CDR3 β amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs. 13 to 52, or 219 to 226. In certain preferred embodiments, the TCR polypeptide comprises a CDR3 α amino acid sequence and CDR3 β amino acid set forth in SEQ ID NOs. 13 and 14, SEQ ID NOs. 15 and 16, SEQ ID NOs. 17 and 18, SEQ ID NOs. 25 and 26, SEQ ID NOs. 27 and 28, SEQ ID NOs. 29 and 30, SEQ ID NOs. 51 and 52, SEQ ID NOs. 219 and 220, or SEQ ID NOs. 225 and 226.

In some embodiments, the TCR polypeptides disclosed herein are specific for HPV antigens, preferably HPV antigens derived from HPV peptides other than E6 and E7. In particularly preferred embodiments of the invention, the TCR polypeptides disclosed herein have antigenic specificity for any one of HPV16 peptides E1, E2, E4, E5, or combinations thereof. Most preferred, the TCR polypeptides are specific for antigens comprising at least one epitope having an amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs: 1-12, 217, or 218.

Table 1: HPV-specific TCR sequences

Antigen	Epitope	HLA restriction	Population Coverage	CDR3 sequence	TCR α and TCR β gene
HPV16-E5	NLDTASTTL (SEQ ID NO. 1)	C*05:01, C*08:02 & C*04:01	42.40% (15.33%, 7.88% & 23.24%)	CDR3 α sequence: CALSEGGGSQGNLIF (SEQ ID NO. 13)	TRAV19-01
					TRAJ42-01
				CDR3 β sequence: CASSPELAGPQETQYF (SEQ ID NO. 14)	TRBV7-6*01
					TRBJ2-5*01
					TRBD2*01
				CDR3 α sequence: CAVSDRHDMRF (SEQ ID NO. 15)	TRAV8-4*07
					TRAJ43*01
				CDR3 β sequence: CASSYSPEHEQFF (SEQ ID NO. 16)	TRBV6-5*01
					TRBJ2-1*01
					TRBD2*01
HPV16-E6	HDIILECVY (SEQ ID NO. 2)	B*18:01 (B44 super family)	8.03%	CDR3 α sequence: CIVRDRSYGQNFVF (SEQ ID NO. 19)	TRAV26-1*01
					TRAJ26*01
				CDR3 β sequence: CSAREGYRSYF (SEQ ID NO. 20)	TRBV20-1*01
					TRBJ2-1*01
					TRBD1*01
				CDR3 α sequence: CARGLENAGNMLTF (SEQ ID NO. 21)	TRAV17*01
					TRAJ39*01
				CDR3 β sequence: CATSVRGTPQPHFF (SEQ ID NO. 22)	TRBV27*01
					TRBJ1-5*01
					TRBD1*01
HPV16-E2	TLQDVSLEVYL (SEQ ID NO. 3)	A*02:01	47.41%	CDR3 α sequence: CAFTYGGSQGNLIF (SEQ ID NO. 25)	TRAV38-01*03
					TRAJ42-01
				CDR3 β sequence: CASRASVGVTGELFF (SEQ ID NO. 26)	TRBV2*01
					TRBJ2-2*01
					TRBD1*01

				CDR3 α sequence: CALSGNMLTF (SEQ ID NO. 27)	TRAV38-1*01
					TRAJ39*01
				CDR3 β sequence: CASSEGVGQRDEQFF (SEQ ID NO. 28)	TRBV11-2*03
					TRBJ2-1*01
					TRBD2*01
				CDR3 α sequence: CAASWEGGGADGLTF (SEQ ID NO. 29)	TRAV27*01
					TRAJ45*01
				CDR3 β sequence: CASRGQGVYRSSYNEQFF (SEQ ID NO. 30)	TRBV27*01
HPV16-E6	TIHDIILECV (SEQ ID NO. 4)	A*02:01	47.41%		TRBJ2-1*01
					TRBD1*01
				CDR3 α sequence: CAVRDTGYGQNFVF (SEQ ID NO. 31)	TRAV1-2*01
					TRAJ26*01
				CDR3 β sequence: CASSPQGRINSPLHF (SEQ ID NO. 32)	TRBV27*01
					TRBJ1-6*02
					TRBD1*01
				CDR3 α sequence: CILSAHDYKLSF (SEQ ID NO. 33)	TRAV26-2*01
					TRAJ20*01
				CDR3 β sequence: CASSQGGGLNSPLHF (SEQ ID NO. 34)	TRBV10-2*01
					TRBJ1-6*02
					TRBD1*01
HPV16-E6	AFRDLCIVY (SEQ ID NO. 5)	C*07:02	25.32%	CDR3 α sequence: CAMRVAEGSQGNLIF (SEQ ID NO. 35)	TRAV14/DV4*03
					TRAJ42*01
				CDR3 β sequence: CASSPWGRGGSPLHF (SEQ ID NO. 36)	TRBV5-8*01
					TRBJ1-6*02
					TRBD1*01
				CDR3 α sequence: CAVKFNTDQGGKLIF (SEQ ID NO. 37)	TRAV12-2*01
					TRAJ23*01
				CDR3 β sequence: CASSPQGRINSPLHF (SEQ ID NO. 38)	TRBV9*01,
					TRBJ2-3*01
					TRBD2*01
				CDR3 α sequence: CALGSSGTYKYI (SEQ ID NO. 39)	TRAV19*01
					TRAJ40*01
HPV16-E6	AFRDLCIVY (SEQ ID NO. 5)	C*07:02	25.32%	CDR3 β sequence: CASSGPGQGHNPQHF (SEQ ID NO. 40)	TRBV25-1*01
					TRBJ1-5*01
					TRBD1*01
				CDR3 α sequence: CAMREANDMRF (SEQ ID NO. 41)	TRAV14/DV4*03
					TRAJ43*01
				CDR3 β sequence:	TRBV11-2*01

				CASSFLVLAVSYNEQFF (SEQ ID NO. 42)	TRBJ2-1*01 TRBD2*01
HPV16-E6	KQRFHNIRGRWTGRC (SEQ ID NO. 6)	DQB1*03:01 /DRB1*15:01	24.73%	CDR3 α sequence: CAETLGLDQGGKLIF (SEQ ID NO. 43)	TRAV13-2*01, TRAJ23*01
				CDR3 β sequence: CSTAGETDTQYF (SEQ ID NO. 44)	TRBV20-1*03 TRBJ2-3*01 TRBD2*01
				CDR3 α sequence: CATDEGTASKLTF (SEQ ID NO. 45)	TRAV17*01 TRAJ49*01
				CDR3 β sequence: CSVEWTSGSGETQYF (SEQ ID NO. 46)	TRBV29-1*01, TRBJ2-5*01, TRBD2*02
				CDR3 α sequence: CATDAGSDYKLSF (SEQ ID NO. 47)	TRAV17*01, TRAJ20*01
				CDR3 β sequence: CASSLEPQYF (SEQ ID NO. 48)	TRBV28*01, TRBJ2-3*01, TRBD1*01
				CDR3 α sequence: CATDEGTGNQFYF (SEQ ID NO. 49)	TRAV17*01, TRAJ49*01
				CDR3 β sequence: CASSWDTGTETQYF (SEQ ID NO. 50)	TRBV7-2*01, TRBJ2-5*01, TRBD1*01
				CAFSSSGTYKYIF (SEQ ID NO. 51)	TRAV24*01 TRAJ40*01
				CASTAGTDTQYF (SEQ ID NO. 52)	TRBV27*01 TRBJ2-3*01 TRBD1*01
HPV16-E4	WPTTPPRPI (SEQ ID NO. 7)	B*07:02	23.23%		
HPV16-E7	TPTLHEYMLDLQPET TDLY (SEQ ID NO. 217)	DRB1*03:01/ DQB1*02:01	41.63%	CDR3 α sequence: CLVGPYFGGGSYQLTF (SEQ ID NO. 219)	TRAV4*01 TRAJ28*01
				CDR3 β sequence: CASSQGTGRGNTEAFF (SEQ ID NO. 220)	TRBV3-1*01 TRBJ1-1*01 TRBD1*01
				CDR3 α sequence: CAVREKGTGNQFYF (SEQ ID NO. 221)	TRAV3*01 TRAJ49*01
				CDR3 β sequence: CASSLPQGTTPETQYF (SEQ ID NO. 222)	TRBV5-4*01 TRBJ2-5*01 TRBD1*01
					TRAV8-6*02

				CDR3 α sequence: CGLSWGDKTDKLIF (SEQ ID NO. 223)	TRAJ34*01
				CDR3 β sequence: CASSPSLAGVVPGELEFF (SEQ ID NO. 224)	TRBV14*01
					TRBJ2-2*01
HPV16-E5	SAFRCFIVY (SEQ ID NO. 218)	B*35:01	11.87%	CDR3 α sequence: CAFMPKPDGSGNTGKLIF (SEQ ID NO. 225)	TRAV38-1*01
					TRAJ37*01
				CDR3 β sequence: CASSLGQGAVGTDQYF (SEQ ID NO. 226)	TRBV7-2*01
					TRBJ2-3*01
					TRBD1*01

The α and β chains that comprise the T-cell receptors of the invention disclosed herein may be produced by recombinant methodologies and strategies known to those skilled in the art. See, for example, Wälchli et al. (2011) A Practical Approach to T-Cell Receptor Cloning and Expression.

5 PLOS ONE 6(11): e27930, incorporated herein by reference in its entirety. Gene sequences that may be used in constructing the α and β chains of the TCRs of the invention are known to those of skill in the art and can be found in immunogenetics and immunoinformatics databases such as the International ImMunoGeneTics Information System[®] (IMGT[®]), referenced herein for exemplary purposes and without limitation. Such genes may be used as the framework for inserting the

10 sequences provided herein for the TCRs of the invention. Those of skill in the relevant art, knowing that TCRs will be expressed at the cell surface of the immune cell (*e.g.*, T cell, or precursor cell thereof) will understand that a signal peptide sequence (*i.e.*, localization sequence) is generally included (*e.g.*, at the amino-terminus). It is understood that, once a polypeptide containing a signal peptide is expressed at the cell surface, the signal peptide has generally been proteolytically

15 removed during processing of the polypeptide in, for example, the endoplasmic reticulum and translocation to the cell surface. Thus, polypeptides, such as the TCRs disclosed herein, are generally expressed at the cell surface as a mature protein lacking the signal peptide, whereas the precursor form of the polypeptide includes the signal peptide. The signal peptide can be the naturally occurring signal peptide of the receptor, or alternatively can be derived from a different

20 protein, or synthetic.

Preferably, the nucleotide sequence of the TCRs of the invention (*e.g.*, the α - and β -chains) are cloned into vectors, *e.g.*, as vector inserts. Said insert sequence may be codon optimized for expression in human tissues. In some such embodiments, the TCRs of the invention are fully human TCRs. The TCRs of the invention may be partially murinized (*e.g.*, the amino acids of the constant regions of each TCR α and β chain may be replaced with those of mouse constant regions). Preferably, the vector inserts are designed such that the α - and β -chains of the TCR are synthesized from a single, contiguous open reading frame. Such vector inserts may comprise a contiguous open reading frame wherein the sequence encoding the α - and β -chains of the TCR are separated by a linker sequence, such as a linker comprising a self-cleaving 2A oligopeptide sequence that is in frame. In certain preferred embodiments, such self-cleaving linkers further comprise a Furin cleavage site. For example and without limitation, nucleotide sequences of TCR constructs contemplated herein, and their sequence features, are described in Tables 2-9.

Table 2: E5-NLD-TCR construct features

E5-NLD-TCR lentivirus construct (SEQ ID NO. 53)	
FEATURES	Location (nt)
Amp(R)	7316 ... 8176
pUC ori promoter	8377 ... 8917
RSV promoter	7 ... 235
3'LTR	5921 ... 6155
Intron	526 ... 1690
f1 origin	6730 ... 7185
5' LTR	236 ... 416
SV40 ori	6358 ... 6571
WPRE seq	5242 ... 5838
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
Furin	4308 ... 4319
SGSG linker (SEQ ID NO: 233)	4320 ... 4331
F2A	4332 ... 4403
Kozak seq	3363 ... 3371
TCR beta	3372 ... 4307
TCR apha	4404 ... 5234

Table 3: E6-HDI-TCR construct features

E6-HDI-TCR lentivirus construct (SEQ ID NO. 54)	
FEATURES	Location (nt)
Amp(R)	7307 ... 8167
pUC ori promoter	8368 ... 8908
RSV promoter	7... 235
3'LTR	5912 ... 6146
Intron	526 ... 1690
f1 origin	6721 ... 7176
5' LTR	236 ... 416
SV40 ori	6349 ... 6562
WPRE seq	5233 ... 5829
human EF1a promoter	1933 ... 2328
Intron	2361 ... 3303
<u>Furin</u>	4323 ... 4334
<u>SGSG linker</u> (SEQ ID NO: 233)	4335 ... 4346
<u>F2A linker</u>	4347 ... 4418
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4322
<u>TCR apha</u>	4419 ... 5225

Table 4: E2-TLQ-TCR construct features

E2-TLQ-TCR lentivirus construct (SEQ ID NO. 55)	
FEATURES	Location (nt)
Amp(R)	7319 ... 8179
pUC ori promoter	8380 ... 8920
RSV promoter	7 ... 235
3'LTR	5924 ... 6158
Intron	526 ... 1690
f1 origin	6733 ... 7188
5' LTR	236 ... 416
SV40 ori	6361 ... 6574
WPRE seq	5245 ... 5841
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4314 ... 4325
<u>SGSG linker</u> (SEQ ID NO: 233)	4326 ... 4337
<u>F2A linker</u>	4338 ... 4409
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4313

<u>TCR alpha</u>	4410 ... 5237
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Table 5: E6-TIH-TCR construct features

E6-TIH-TCR lentivirus construct (SEQ ID NO. 56)	
FEATURES	Location (nt)
Amp(R)	7286 ... 8146
pUC ori promoter	8347 ... 8887
RSV promoter	7 ... 235
3'LTR	5891 ... 6125
Intron	526 ... 1690
f1 origin	6700 ... 7155
5' LTR	236 ... 416
SV40 ori	6328 ... 6541
WPRE seq	5212 ... 5808
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4302 ... 4313
<u>SGSG linker</u> (SEQ ID NO: 233)	4314 ... 4325
<u>F2A linker</u>	4326 ... 4397
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4301
<u>TCR apha</u>	4398 ... 5204

Table 6: E6-AFR-TCR construct features

E6-AFR-TCR lentivirus construct (SEQ ID NO. 57)	
FEATURES	Location (nt)
Amp(R)	7307 ... 8167
pUC ori promoter	8368 ... 8908
RSV promoter	7 ... 235
3'LTR	5912 ... 6146
Intron	526 ... 1690
f1 origin	6721 ... 7176
5' LTR	236 ... 416
SV40 ori	6349 ... 6562
WPRE seq	5233 ... 5829
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4305 ... 4316
<u>SGSG linker</u> (SEQ ID NO: 233)	4317 ... 4328
<u>F2A linker</u>	4329 ... 4400

<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4304
<u>TCR apha</u>	4401 ... 5225

Table 7: E6-KQR-TCR construct features

E6-KQR-TCR lentivirus construct (SEQ ID NO. 58)	
FEATURES	Location (nt)
Amp(R)	7328 ... 8188
pUC ori promoter	8389 ... 8929
RSV promoter	7 ... 235
3'LTR	5933 ... 6167
Intron	526 ... 1690
fl origin	6742 ... 7197
5' LTR	236 ... 416
SV40 ori	6370 ... 6583
WPRE seq	5254 ... 5850
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4326 ... 4337
<u>SGSG linker</u> (SEQ ID NO: 233)	4338 ... 4349
<u>F2A linker</u>	4350 ... 4421
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4325
<u>TCR alpha</u>	4422 ... 5246

Table 8: E7-TPT-TCR construct features

E7-TPT-TCR lentivirus construct (SEQ ID NO. 227)	
FEATURES	Location (nt)
Amp(R)	7295 ... 8155
pUC ori promoter	8356 ... 8896
RSV promoter	7 ... 235
3'LTR	5900 ... 6134
Intron	526 ... 1690
fl origin	6709 ... 7164
5' LTR	236 ... 416
SV40 ori	6337 ... 6550
WPRE seq	5221 ... 5817
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4305 ... 4316

<u>SGSG linker</u> (SEQ ID NO: 233)	4317 ... 4328
<u>F2A linker</u>	4329 ... 4400
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4304
<u>TCR alpha</u>	4401 ... 5213

Table 9: E5-SAF-TCR construct features

E5-SAF-TCR lentivirus construct (SEQ ID NO. 228)	
FEATURES	Location (nt)
Amp(R)	7340 ... 8200
pUC ori promoter	8401 ... 8941
RSV promoter	7 ... 235
3'LTR	5945 ... 6179
Intron	526 ... 1690
f1 origin	6754 ... 7209
5' LTR	236 ... 416
SV40 ori	6382 ... 6595
WPRE seq	5266 ... 5862
human EF1a promoter	1933 ... 3322
Intron	2361 ... 3303
<u>Furin</u>	4326 ... 4337
<u>SGSG linker</u> (SEQ ID NO: 233)	4338 ... 4349
<u>F2A linker</u>	4350 ... 4421
<u>Kozak seq</u>	3363 ... 3371
<u>TCR beta</u>	3372 ... 4325
<u>TCR alpha</u>	4422 ... 5258

Likewise, exemplary TCRs (e.g., TCR α/β peptide chains) encoded by the constructs contemplated herein are described in in Figures 3, 4, and 6-11. In some embodiments, the TCRs expressed at the cell surface comprise at least one TCR chain comprising an amino acid sequence set forth in Table 10. In preferred embodiments, such TCRs comprise a TCR α chain and TCR β chain, each respectively comprising an amino acid sequence set forth in Table 10. For example, the TCR may comprise a TCR β chain having the amino acid sequence set forth in SEQ ID NO. 59 and a TCR α chain having the amino acid sequence set forth in SEQ ID NO. 60; or a TCR β chain having the amino acid sequence set forth in SEQ ID NO. 61 and a TCR α chain having the amino acid sequence set forth in SEQ ID NO. 62

Table 10: Engineered TCR α and β chains

TCR Construct	α/β chain	Amino Acid Sequence
E2-TLQ-TCR	TCR β	EPEVTQTTPSHQVTQMGQEVLRCVPISNHL YFYWYRQILGQ KVEFLVSFYNN EISEKSEIFDDQFSVERPDGSNFTLKIRSTKL EDSAMYFCASRASVGVGTGELFFGEGSRLTVLEDLKNVFPF EVAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSWWVNG KEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRV SATFWQNP RNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRAD CGITSASYHQGVLSATILYEILLGKATLYAVLV SALVLMAM VKRKDSRG (SEQ ID NO. 59)
	TCR α	AQTVTQSQPEMSVQEAETVTL SCTYDTSESNNYLFWYKQPP SRQMILVIRQEAYKQQNATENRFSVNFQKA AKSFSLKISDSQ LGD TAMYFCAFTYGGSGGNLIFGKGTKLSVKPNIQNPDAV YQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDSVYITDKCVL DMRSMDFKSNSA VAWSNKSDFACANAFNNSIIPEDTFFPSS DVPCDVKLVEKSFETDTNLFQNL SVIGFRILLKLVAGFNLL MTLRLWSS (SEQ ID NO. 60)
E5-NLD-TCR	TCR β	GVSQSPRYKVTKRQGDVALRCDPISGHVSLYWYRQALGQG PEFLTYFN YEAAQQDKSGLPNDRFSAERPEGSISTLTIQ RTEQR DSAMYRCASSPELAGPQETQYFGPGTRLLVLEDLKNVFPPE VAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSWWVNGK EVHSGVCTDPQPLKEQPALNDSRYCLSSRLRV SATFWQNPR NHFR CQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADC GITSASYHQGVLSATILYEILLGKATLYAVLV SALVLMAMV KRKDF (SEQ ID NO. 61)
	TCR α	AQKVTQAQTEISVVEKEDVTLD CVYETRD TTYLFWYKQP PSGELVFLIRNSFDEQNEISGRYSWNFQKSTSSFNFTITASQ VVDSAVYFCALSEGGSQGNLIFGKGTKLSVKPNIQNPDA

		VYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCV LDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSS DVPCDVKLVEKSFETDTNLFQNL SVIGFRILLKLVAGFNLL MTLRLWSS (SEQ ID NO. 62)
E6-AFR-TCR	TCR β	MTIRLLCYMGFYFLGAGLMEADYQTPRYLVIGTGKKITLEC SQTMGHDKMYWYQQDPGMELHLIHYSYGVNSTEKGDLSS ESTVSRIRTEHFPLTLESARPSHTSQYLCASSGPGQGHNPQ HFGDGTRLSEDLNKFVPEVAVFEPSKAEIAHTQKATLVC LATGFFPDHVELSWWVNGKEVHSGVCTDPQPLKEQPALND SRYCLSSRLRVSAFWQNP RNHFRCQVQFYGLSENDEWTQ DRAKPVTQIVSAEAWGRADCGITSASYHQGVLSATILYEILL GKATLYAVLV SALVLMAMVKRKDF (SEQ ID NO. 63)
	TCR α	QKVTQAQTEISVVEKEDVTLD CVYETRD TTYLFWYKQPPS GELVFLIRRNSFDEQNEISGRYSWNFQKSTSSFNFTITASQVV DSAVYFCALGSSGT YKYIFGTGTRLKVLANIQNPDPAVYQL RDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCVLDMR SMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVPC DVKLVEKSFETDTNLFQNL SVIGFRILLKLVAGFNLLMTLR LWSS (SEQ ID NO. 64)
E6-TIH-TCR	TCR β	QVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGL GLRQIYYSMNVEVTDKGDVPEGYKVS RKEKRNFLILESPSP NQTSLYFCASSPQGRINSPLHFGNGTRLTVTEDLNKFVPEV AVFEPSKAEIAHTQKATLVCLATGFFPDHVELSWWVNGKE VHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSAFWQNP RN HFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCG ITSASYHQGVLSATILYEILLGKATLYAVLV SALVLMAMVK RKDF (SEQ ID NO. 65)
	TCR α	QNIDQPTEMTATEGAIVQINCTYQTSGFNGLFWYQQHAGEA PTFLSYNVLDGLEEKGRFSSFLSRSGYSYLLKELQMKDS

		ASYLCAVRDTGYGQNFVFGPGTRLSVLPYIQNPDPVAVYQLR DSKSSDKSVCLFTDFDSQTNVSQSKDSVDYITDKCVLDMRS MDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVPCD VKLVEKSFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRL WSS (SEQ ID NO. 66)
E6-HDI-TCR	TCR β	GSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYR QFPKQSLMLMATSNEGSKATYEQGVEKDKFLINHASLTLST LTVTSAHPEDSSFYICSAREGYRSYFGPGTRLTVLEDLKNVF PPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSWWN GKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSATFWQN PRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRA DCGITSASYHQGVLSATILYEILLGKATLYAVLVSALVLM MVKRKDSRG (SEQ ID NO. 67)
	TCR α	KTTPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQG PQYIIHGLKNNETNEMASLIITEDRKSSTLILPHATLRDTAVY YCIVRDRSYGQNFVFGPGTRLSVLPYIQNPDPVAVYQLRDSKS SDKSVCLFTDFDSQTNVSQSKDSVDYITDKCVLDMRSMDFK SNSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVPCDVKL VEKSFETDTNLFQNL SVIGFRILLK VAGFNLLMTLRLWSS (SEQ ID NO. 68)
E6-KQR-TCR	TCR β	GSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFWYR QFPKQSLMLMATSNEGCKATYEQGVEKDKFLINHASLTLST LTVTSAHPEDSSFYICSTAGETDTQYFGPGTRLTVLEDLKNV FPPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSWWV NGKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSATFWQ NPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGR ADCGITSASYHQGVLSATILYEILLGKATLYAVLVSALVLM AMVKRKDSRG (SEQ ID NO. 69)

	TCR α	ESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKG PQFIIDIRSNMDKRQGQRVTVLLNKTVKHLSLQIAATQPGDS AVYFCAETLGLDQGGKLIFGQGTELSVKPNIQNPDSVKPNP AVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKC VLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFP SSDVPCDVKLVEKSFETDTNLFQNLVIGFRILLKLVAGFN LLMTLRLWSS (SEQ ID NO. 70)
E7-TPT-TCR	TCR β	DTAVSQTPKYLVTQMGNDSIKCEQNLGHDTMYWYKQDS KKFLKIMFSYNNKELIINETVPNRFSPKSPDKAHLNLHINSLE LGDSAVYFCASSQGTGRGNTEAFFGQGTRLTVVEDLNKVFP PEVAVFEPKAEIAHTQKATLVCLATGFYDPDHVELSWWVN GKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSAFTWQN PRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRA DCGITSASYHQGVLSATILYEILLGKATLYAVLVSAVLMA MVKRKDF (SEQ ID NO. 229)
	TCR α	LAKTTQPISMDSYEGQEVNITCSHNNIATNDYITWYQQFPSQ GPRFIIQGYKTKVTNEVASLFIPADRKSSSTLSLPRVSLSDTAV YYCLVGPFYFGGGSYQLTFGKGTKLSVIPNIQNPDPNAVYQLR DSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCVLDMRS MDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVPCD VKLVEKSFETDTNLFQNLVIGFRILLKLVAGFNLLMTLRL WSS (SEQ ID NO. 230)
E5-SAF-TCR	TCR β	GAGVSQSPSNKVTEKGKDVELRCDPISGHTALYWYRQSLG QGLEFLIYFQGNSAPDKSGLPSDRFSAERTGGSVSTLTIQRTQ QEDSAVYLCASSLGQGA VGTDQYFGPGTRLTVLEDKRTL KNVFPPEVAVFEPKAEIAHTQKATLVCLATGFYDPDHVELS WWVNGKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSA FTWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAE

		AWGRADCGITSASYHQGVLSATILYEILLGKATLYAVLVSA LVLMMAMVVKRKDSRG (SEQ ID NO. 231)
	TCR α	AQTVTQSQPEMSVQEAETVTLSTYDTSENNYYLFWYKQP PSRQMILVIRQEAYKQQNATENRFSVNFQKAAKSFSCLKISDS QLGDTAMYFCAFMKPDGSGNTGKLIFGQGTTTLQVKPNIQNP DPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITD KCVLDMRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTF FPSSDVPCDVKLVEKSFETDTNLNFQNLSVIGFRILLKLVAG FNLLMTLRLWSS (SEQ ID NO. 232)

Similarly, embodiments of the invention include immune effector cells (*e.g.*, T cells) which have been transduced with such constructs so as to express the engineered TCRs.

In some embodiments, the TCRs disclosed herein specifically bind an epitope listed in Table

5 11.

Table 11: HPV-specific epitopes

Antigen	Epitope	HLA restriction
HPV16-E1	YLHNRLVVF (SEQ ID NO. 8)	B*08:01
HPV16-E1	ALDGNLVSMDV (SEQ ID NO. 9)	A*02:01
HPV18-E6	TVLELTEVFEE (SEQ ID NO. 10)	A*02:01
HPV18-E5	SPATAFTVY (SEQ ID NO. 11)	B*35:01
HPV16-E7	VQSTHVDIRTLEDLLMGTL (SEQ ID NO. 12)	DQB1*03:01

In certain embodiments, the TCR (*e.g.*, the immune effector cell expressing the engineered
10 TCR) can be applied and/or administered using a plurality of strategies known in the art. For example (and without limitation), TRUCKs (T cells redirected for universal cytokine killing) co-express a modified (*e.g.*, artificial/recombinant/exogenous) TCR and an antitumor cytokine. Cytokine expression may be constitutive or induced by T cell activation. Targeted by TCR-

specificity, localized production of pro-inflammatory cytokines recruits endogenous immune cells to tumor sites and may potentiate an antitumor response.

Alternatively, allogeneic TCR-T cells may be engineered by means known in the art to no longer express *endogenous* T cell receptor (TCR) and/or major histocompatibility complex (MHC) molecules, thereby improving expression and/or function of the exogenous TCR and/or preventing or reducing graft-versus-host disease (GVHD) or rejection, respectively.

A TCR-T cell may be engineered to co-express a TCR and a chemokine receptor, which binds to a tumor ligand, thereby enhancing tumor homing.

TCR-T cells engineered to be resistant to immunosuppression may be genetically modified to no longer express various immune checkpoint molecules (*e.g.*, cytotoxic T lymphocyte-associated antigen 4 (CTLA4) or programmed cell death protein 1 (PD-1)). Exemplary “Knockdown” and “Knockout” techniques include, but are not limited to, RNA interference (RNAi) (*e.g.*, asRNA, miRNA, shRNA, siRNA, etc.) and CRISPR interference (CRISPRi) (*e.g.*, CRISPR-Cas9). In certain embodiments, TCR-T cells are engineered to express a dominant-negative form of a checkpoint molecule. In some such embodiments, the extracellular ligand-binding domain (*i.e.*, ectodomain) of the immune checkpoint molecule is fused to a transmembrane membrane in order to compete for ligand binding. For example, the extracellular ligand-binding domain of PD-1 may be fused to a CD8 transmembrane domain, thus competing for PD-1 ligand from the target cell. In some embodiments, TCR-T cells are engineered to express an immune checkpoint switch receptor to exploit the inhibitory immune checkpoint ligand present on a target cell. In such embodiments, the extracellular ligand-binding domain of the immune checkpoint molecule is fused to a signaling, stimulatory, and/or co-stimulatory domain. For example, the extracellular ligand-binding domain of PD-1 may be fused to a CD28 domain, thus providing CD28 co-stimulation while blocking PD-1 signaling. In further embodiments, the TCR-T cells may be administered with an aptamer or a monoclonal antibody that blocks immune checkpoint signaling. In some such embodiments, the TCR-T cell (*e.g.*, TCR-T cell therapy) is combined with a PD-1 blockade method, such as administration with PD-1/PD-L1 antagonistic aptamers or anti-PD-1/PD-L1 antibodies. In preferred embodiments, the TCR-T cells and PD-1 pathway-blocking antibodies are administered conjointly. In further embodiments, the TCR-T cells are engineered to express or express and secrete an

immune checkpoint-blocking antibody, such as anti-PD-1 or anti-PD-L1, or fragments thereof. In yet further embodiments, the TCR-T cells are administered with a vector (*e.g.*, an engineered virus) that expresses an immune checkpoint-blocking molecule described herein.

A self-destruct TCR-T cell may be designed using inducible apoptosis of the T cell, *e.g.*, by ganciclovir binding to thymidine kinase in gene-modified lymphocytes or by activation of human caspase 9 by a small-molecule dimerizer.

A marked TCR-T cell expresses a modified TCR plus a tumor epitope to which an existing monoclonal antibody agent binds. In the setting of intolerable adverse effects, administration of the monoclonal antibody clears the TCR-T cells and alleviates symptoms with no additional off-tumor effects.

A bi-specific TCR-T cell may further express another TCR or a chimeric antigen receptor (CAR) with different antigen/ligand binding targets relative to the first modified TCR, such as other cancer-associated antigens, including tumor antigens.

Tumor antigens include proteins that are produced by tumor cells that elicit an immune response; particularly T cell mediated immune responses. The additional antigen binding domain can be an antibody or a natural ligand of the tumor antigen. The selection of the additional antigen-binding domain will depend on the particular type of cancer to be treated. Tumor antigens are well known in the art and include, for example, a glioma-associated antigen, carcinoembryonic antigen (CEA), EGFRvIII, IL-11Ra, IL-13Ra, EGFR, FAP, B7H3, Kit, CA LX, CS-1, MUC1, BCMA, bcr-abl, HER2, β -human chorionic gonadotropin, alphafetoprotein (AFP), ALK, alternate and/or specific CD19 epitopes, TIM3, cyclin B1, lectin-reactive AFP, Fos-related antigen 1, ADRB3, thyroglobulin, EphA2, RAGE-1, RUI, RU2, SSX2, AKAP-4, LCK, OY-TES1, PAX5, SART3, CLL-1, fucosyl GM1, GloboH, MN-CA IX, EPCAM, EVT6-AML, TGS5, human telomerase reverse transcriptase, plialic acid, PLAC1, RUI, RU2 (AS), intestinal carboxyl esterase, lewisY, sLe, LY6K, HSP70, HSP27, mut hsp70-2, M-CSF, MYCN, RhoC, TRP-2, CYP1BI, BORIS, prostase, prostate-specific antigen (PSA), PAX3, PAP, NY-ESO-1, LAGE-la, LMP2, NCAM, p53, p53 mutant, Ras mutant, gp100, prostein, OR51E2, PANX3, PSMA, PSCA, Her2/neu, hTERT, HMWMAA, HAVCR1, VEGFR2, PDGFR-beta, survivin and telomerase, legumain, HPV E6,E7, sperm protein 17, SSEA-4, tyrosinase, TARP, WT1, prostate-carcinoma tumor antigen-1 (PCTA-1),

ML-IAP, MAGE, MAGE-A1, MAGE-A2, MAGE-C1, MAGE-C2, Annexin-A2, MAD-CT-1, MAD-CT-2, MelanA/MART 1, XAGE1, ELF2M, ERG (TMPRSS2 ETS fusion gene), NA17, neutrophil elastase, sarcoma translocation breakpoints, NY-BR-1, EphrinB2, CD20, CD22, CD24, CD30, TIM3, CD38, CD44v6, CD97, CD171, CD179a, androgen receptor, FAP, insulin growth factor (IGF)-I, IGFII, IGF-I receptor, GD2, o-acetyl-GD2, GD3, GM3, GPRC5D, GPR20, CXORF61, folate receptor (FRa), folate receptor beta, ROR1, Flt3, TAG72, TN Ag, Tie 2, TEM1, TEM7R, CLDN6, TSHR, UPK2, and mesothelin. In certain preferred embodiments, the tumor antigen is selected from folate receptor (FRa), mesothelin, EGFRvIII, IL-13Ra, CD123, CD19, TIM3, BCMA, GD2, CLL-1, CA-IX, MUC1, HER2, and any combination thereof.

Further non-limiting examples of tumor antigens include the following: Differentiation antigens such as tyrosinase, TRP-1, TRP-2 and tumor-specific multilineage antigens such as MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, pi 5; overexpressed embryonic antigens such as CEA; overexpressed oncogenes and mutated tumor-suppressor genes such as p53, Ras, HER-2/neu; unique tumor antigens resulting from chromosomal translocations; such as BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR; and viral antigens, such as the Epstein Barr virus antigens EBVA and the human papillomavirus (HPV) antigens E6 and E7. Other large, protein-based antigens include SCCA, GP73, FC-GP73, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, NY-ESO, pl85erbB2, pl80erbB-3, c-met, nm-23H1, PSA, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, beta-Catenin, CDK4, Mum-1, p 15, p 16, 43-9F, 5T4, 791Tgp72, alpha-fetoprotein, beta-HCG, BCA225, BTAA, CA 125, CA 15-3\CA 27.29\BCAA, CA 195, CA 242, CA-50, CAM43, CD68\PI, CO-029, FGF-5, G250, Ga733\EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG1 6, TA-90\Mac-2 binding protein\cyclophilin C-associated protein, TAAL6, TAG72, TLP, TPS, GPC3, MUC16, TAG-72, LMP1, EBMA-1, BARF-1, CS1, CD319, HER1, B7H6, L1CAM, IL6, and MET.

Generally, with respect to the methods disclosed herein, almost any strategy applied to CAR-T cells may be applied to the TCR-T cells disclosed herein.

Nucleic Acids and Vectors

Also disclosed are polynucleotides and polynucleotide vectors encoding the disclosed HPV antigen-specific TCRs that allow expression of the HPV antigen-specific TCRs in the disclosed

immune effector cells. In some embodiments, polynucleotides and polynucleotide vectors disclosed herein comprise any one of the nucleic acid sequences set forth in Tables 2-9. In certain aspects of the invention, provided herein are isolated nucleic acids comprising a nucleotide sequence encoding a peptide (or peptides) comprising a TCR α and/or TCR β chain. In some embodiments, the peptides
5 encoded by the nucleic acids disclosed herein comprise an amino acid sequence selected from any one of SEQ ID NOs. 13-52, 59-70, 209-216, or fragments thereof.

Nucleic acid sequences encoding the disclosed TCRs, and regions thereof, can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the gene, by deriving the gene from a vector known to include the same, or by isolating
10 directly from cells and tissues containing the same, using standard techniques. Alternatively, the gene of interest can be produced synthetically, rather than cloned.

Expression of nucleic acids encoding TCRs is typically achieved by operably linking a nucleic acid encoding the TCR polypeptide to a promoter, and incorporating the construct into an expression vector. Typical cloning and/or expression vectors contain transcription and translation
15 terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The nucleic acid sequences encoding the α and β chains of the TCRs of the present invention may be placed in a single expression vector by methods known in the art. For example and without limitation, the nucleic acid sequences encoding the TCRs described herein may comprise a nucleic
20 acid sequence encoding a ribosomal skip sequence such as a sequence encoding a 2A peptide. 2A peptides, which were identified in the Aphthovirus subgroup of picornaviruses, causes a ribosomal "skip" from one codon to the next without the formation of a peptide bond between the two amino acids encoded by the codons. Thus, two polypeptides can be synthesized from a single, contiguous open reading frame within an mRNA when the polypeptides are separated by a 2A oligopeptide
25 sequence that is in frame (e.g., when the alpha and beta chains of the TCR are separated by a 2A oligopeptide sequence). Such ribosomal "skip" or "self-cleaving" mechanisms are well known in the art and are known to be used by several vectors for the expression of several proteins encoded by a single messenger RNA. For example, the 2A oligopeptide sequence may be used with a furin cleavage recognition site. Preferably, the furin recognition site is upstream from the 2A oligopeptide

sequence. Most preferably, the furin recognition site sequence and the 2A oligopeptide sequence are separated by a GSG linker. Such bicistronic lentiviral vectors combining a furin cleavage site, and an amino acid spacer followed by a 2A ribosomal skip peptide are known in the art. See, for example, Yang et al. (2008) Development of optimal bicistronic lentiviral vectors facilitates high-level TCR gene expression and robust tumor cell recognition, Gene Therapy volume 15, pages 1411–1423, incorporated herein by reference in its entirety. The resultant peptide upstream from the self-cleaving furin-spacer-2A site may retain the furin recognition sequence at its carboxy-terminus (*e.g.*, the FURIN_cleavage_site sequence indicated in Figures 3, 4, and 6-11). Likewise, in the absence of any post-translational modifications, such as the removal of a signal peptide sequence, the resultant peptide downstream from the self-cleaving furin-spacer-2A site may retain amino acids at its amino-terminus (*e.g.*, the terminal proline of the F2A linker sequence indicated in Figures 3, 4, and 6-11). Alternatively the α and β chains may each be placed in a separate expression vector.

The disclosed nucleic acids can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals. Viruses which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers. In some embodiments, the polynucleotide vectors are lentiviral or retroviral vectors.

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the

art. The recombinant virus can then be isolated and delivered to cells of the subject either *in vivo* or *ex vivo*. Preferably, gene transfer is into mammalian cells (*e.g.*, PBMCs).

One example of a suitable promoter is the immediate early cytomegalovirus (CMV)

promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto.

Another example of a suitable promoter is Elongation Growth Factor-1 α (EF-1 α ; EF1a). However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, MND (myeloproliferative sarcoma virus) promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. The promoter can alternatively be an inducible promoter. Examples of inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

Additional promoter elements, *e.g.*, enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another.

In order to assess the expression of a TCR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, *e.g.*, enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells.

Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene. Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, *e.g.*, mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well known in the art. See, for example, Sambrook et al. (2001, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York).

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, *e.g.*, human cells.

Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*e.g.*, an artificial membrane vesicle).

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a “collapsed” structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes. Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine (“DMPC”) can be obtained from Sigma, St. Louis, Mo.; dicetyl phosphate (“DCP”) can be obtained from K & K Laboratories (Plainview, N.Y.); cholesterol (“Choi”) can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol (“DMPG”) and other lipids may be obtained from Avanti Polar Lipids, Inc, (Birmingham, Ala.).

Immune cells

The α and β chains of the TCRs of the invention disclosed herein may be expressed independently in different host cells or in the same host cell. In preferred embodiments, the α and β chains are introduced into the same host cell to allow for formation of a functional T-cell receptor. Most preferably, the host cells engineered to express all or part of the disclosed TCRs of the invention include immune cells (*e.g.*, immune effector cells). Such cells may be obtained from the subject (*i.e.*, the donor) to be treated (*i.e.*, autologous cells). However, in some embodiments, immune cell lines or donor cells other than the subject’s own cells (*i.e.*, allogeneic cells) are used. Immune effector cells can be obtained from a number of sources, including peripheral blood mononuclear cells (PBMCs), bone marrow, lymph node tissue, cord blood, thymus tissue, tissue

from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. Immune effector cells can be obtained from blood collected from a subject and/or donor using any number of techniques known to the skilled artisan, such as Ficoll™ separation. For example, cells from the circulating blood of an individual may be obtained by apheresis. In some embodiments, immune effector cells
5 are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient or by counterflow centrifugal elutriation. A specific subpopulation of immune effector cells can be further isolated by positive or negative selection techniques. For example, immune effector cells can be isolated using a combination of antibodies directed to surface markers unique to the positively selected cells, *e.g.*,
10 by incubation with antibody-conjugated beads for a time period sufficient for positive selection of the desired immune effector cells. Alternatively, enrichment of immune effector cells population can be accomplished by negative selection using a combination of antibodies directed to surface markers unique to the negatively selected cells.

In some embodiments, the immune effector cells comprise any leukocyte involved in
15 defending the body against infectious disease and foreign materials. For example, the immune effector cells can comprise lymphocytes, monocytes, macrophages, dendritic cells, mast cells, neutrophils, basophils, eosinophils, or any combinations thereof. For example, the immune effector cells can comprise T lymphocytes, preferably cytotoxic T lymphocytes (CTLs).

T cells or T lymphocytes can be distinguished from other lymphocytes, such as B cells and
20 natural killer cells (NK cells), by the presence of a T cell receptor (TCR) on the cell surface. They are called T cells because they mature in the thymus (although some also mature in the tonsils). There are several subsets of T cells, each with a distinct function.

T helper cells (T_H cells) assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and
25 macrophages. These cells are also known as CD4⁺ T cells because they express the CD4 glycoprotein on their surface. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs). Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response. These cells can differentiate into one of several subtypes,

including T_H1 , T_H2 , T_H3 , T_H17 , T_H9 , or T_{FH} , which secrete different cytokines to facilitate a different type of immune response.

Cytotoxic T cells (T_C cells, or CTLs) destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as $CD8^+$ T cells since they
5 express the CD8 glycoprotein at their surface. These cells recognize their targets by binding to antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells. Through IL-10, adenosine and other molecules secreted by regulatory T cells, the $CD8^+$ cells can be inactivated to an anergic state, which prevents autoimmune diseases.

Memory T cells are a subset of antigen-specific T cells that persist long-term after an
10 infection has resolved. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with “memory” against past infections. Memory cells may be either $CD4^+$ or $CD8^+$. Memory T cells typically express the cell surface protein CD45RO.

Regulatory T cells (T_{reg} cells), formerly known as suppressor T cells, are crucial for the
15 maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus. Two major classes of $CD4^+$ T_{reg} cells have been described — naturally occurring T_{reg} cells and adaptive T_{reg} cells.

Natural killer T (NKT) cells (not to be confused with natural killer (NK) cells) bridge the
20 adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, NKT cells recognize glycolipid antigen presented by a molecule called CD1d.

In some embodiments, the T cells comprise a mixture of $CD4^+$ cells. In other embodiments, the T cells are enriched for one or more subsets based on cell surface expression. For example, in
25 some cases, the T comprise are cytotoxic $CD8^+$ T lymphocytes. In some embodiments, the T cells comprise $\gamma\delta$ T cells, which possess a distinct T cell receptor (TCR) having one γ chain and one δ chain instead of α and β chains.

Natural-killer (NK) cells are $CD56^+CD3^-$ large granular lymphocytes that can kill virally infected and transformed cells, and constitute a critical cellular subset of the innate immune system

(Godfrey J, et al. Leuk Lymphoma 2012 53:1666–1676). Unlike cytotoxic CD8⁺ T lymphocytes, NK cells launch cytotoxicity against tumor cells without the requirement for prior sensitization, and can eradicate MHC-I-negative cells (Narni-Mancinelli E, et al. Int Immunol 2011 23:427–431). NK cells are safer effector cells, as they may avoid the potentially lethal complications of cytokine storms (Morgan RA, et al. Mol Ther 2010 18:843–851), tumor lysis syndrome (Porter DL, et al. N Engl J Med 2011 365:725–733), and on-target, off-tumor effects. Although NK cells have a well-known role as killers of cancer cells, and NK cell impairment has been extensively documented as crucial for progression of Multiple myeloma (MM) (Godfrey J, et al. Leuk Lymphoma 2012 53:1666–1676; Fauriat C, et al. Leukemia 2006 20:732–733), the means by which one might enhance NK cell-mediated anti-MM activity has been largely unexplored prior to the disclosed TCRs.

While innate immune responses play an important role in controlling initial HPV infection, long-term protection is dependent on adaptive immune responses including humoral and cell-mediated immunity. In immunocompetent individuals, the majority of HPV infections are cleared within 2 years of initial infection. Infiltration of CD4⁺ and CD8⁺ T cells is frequently observed in spontaneously regressing lesions. Though the HPV vaccines act prophylactically and are based on the L1 protein, this viral antigen is not relevant for the treatment of HPV-associated diseases. L1 protein is only expressed in the late stages of HPV replication especially in terminally differentiated keratinocytes. In contrast, other proteins associated with the HPV replicative cycle, *i.e.*, E1, E2, E4, E5, E6, and E7, may provide important targets for immunotherapeutic strategies. This is primarily due to the fact that the expression of all these proteins are retained through multiple stages of infection. While much of the emphasis on the design of immunotherapeutic strategies has focused on E6 and E7 antigens, it is important to appreciate that other early proteins are implicated in HPV replication and thus the expression of these proteins is retained throughout multiple stages of infection. This highlights the importance of these proteins as potential targets for immunotherapy aimed at eliminating persistently HPV-infected cells regardless of the stage of pathogenesis. Indeed, previous studies using animal models (canine and rabbit) have shown that immunization with a DNA vaccine encoding codon-optimised E1 or E2 genes results in complete regression of papillomas. The primary mode of protection in these animal models is mediated through the

induction of an effective T cell response to E1 and E2 antigens. Further clinical studies using a modified vaccinia Ankara vector encoding E2 in human subjects with HPV-induced cervical lesions (C1N1 to C1N3) demonstrated complete elimination of cervical lesions to regression from C1N3 to C1N1 and significant reduction in HPV viral load. Here again, the induction of E2-specific T cell immunity correlated strongly with clinical response. Development of anti-vector antibodies resulted in a poor response to booster immunization and some patients showed recurrence of lesions after the completion of the study. Moreover, this therapy required direct injection of the vector into uterine tissue to be effective, thus limiting its wider use in the general population.

Thus, provided herein are methods for prophylaxis and treatment of HPV-associated diseases and cancers by the adoptive transfer of autologous or allogeneic HPV-specific, TCR-expressing cells (*e.g.*, TCR-T cells described herein). Such methods may include the generation of and/or the use of peptide-specific T cells (*e.g.*, CTLs, CD8⁺ T cells, and/or CD4⁺ T cells). The generation of peptide-specific T cells is known in the art and may include, for example, incubating a sample comprising T cells (*e.g.*, a PBMC sample, an enriched sample, or a sample of isolated T cells) with antigenic peptides (*i.e.*, peptides comprising T cell epitopes) or with antigen-presenting cells (APCs) that present one or more of such T cell epitopes (*e.g.*, APCs that present a peptide comprising a CTL epitope on a class I MHC complex), thereby inducing the sensitization (*e.g.*, activation and proliferation) of peptide-specific T cells. In some embodiments, the antigenic peptides comprise a sequence of any viral protein (*i.e.*, antigen). For example, and without limitation, the immune cell (*e.g.*, CTL) is sensitized to a viral antigen from any one of human papilloma virus (HPV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), B.K. virus (BKV), John Cunningham virus (JCV), picornavirus (*e.g.*, Hepatitis A virus), hepadnavirus (*e.g.*, Hepatitis B virus), hepacivirus (*e.g.*, Hepatitis C virus), deltavirus (*e.g.*, Hepatitis D virus), hepevirus (*e.g.*, Hepatitis E virus), or any combination thereof. In preferred embodiments, a sample comprising CTLs (*i.e.*, a PBMC sample) is incubated in culture with the antigenic peptide (*e.g.*, antigenic HPV16 peptides such as those disclosed in Tables 1, 11 and 13) or with antigen-presenting cells (APC) provided herein (*e.g.*, “peptide-pulsed” cells that present said peptide, comprising an HPV epitope described herein, on a class I MHC complex). In some embodiments, the APCs are autologous to the subject from whom the T cells were obtained. In some embodiments, the sample

containing T cells is incubated 2 or more times with APCs provided herein. In some embodiments, the T cells are incubated with the APCs in the presence of at least one cytokine. In some embodiments, the cytokine is IL-4, IL-7 and/or IL-15. Exemplary methods for inducing proliferation of T cells using APCs are provided, for example, in U.S. Pat. Pub. No. 2015/0017723, which is hereby incorporated by reference. In some embodiments, the antigens are HPV antigens other than E6 and E7.

In some aspects, provided herein are compositions (*e.g.*, prophylactic and/or therapeutic compositions) comprising the TCR-T cells provided herein. In some embodiments, such compositions are used to treat and/or prevent a cancer, and/or precancerous lesions and/or an HPV infection in a subject by administering to the subject an effective amount of the composition. In some embodiments, the engineered TCR-T cells are not autologous to the subject. In some embodiments, the TCR-T cells are autologous to the subject. In some embodiments, the TCR-T cells are stored in a cell bank before they are administered to the subject. Therefore, in some embodiments, the disclosed immune effector cells that comprise one or more of the engineered TCR polypeptides of the present invention are allogeneic or autologous immune effector cells. Preferably, the allelic HLA restriction (*i.e.*, restriction to a specific HLA-A, HLA-B, or HLA-C allele) of such TCR-T cells is known. In some embodiments, the T cells used for generating the TCR-T cells of the invention are peptide-specific (*i.e.*, sensitized to an antigenic peptide such as a viral peptide). In some embodiments, the T cells used for generating the TCR-T cells of the invention are polyfunctional T cells, *i.e.*, those T cells that are capable of inducing multiple immune effector functions, that provide a more effective immune response to a pathogen than do cells that produce, for example, only a single immune effector (*e.g.* a single biomarker such as a cytokine or CD107a). Less-polyfunctional, monofunctional, or even “exhausted” T cells may dominate immune responses during chronic infections, thus negatively impacting protection against virus-associated complications. In further preferred embodiments, the TCR-T cells of the invention are polyfunctional. In certain embodiments, at least 50% of the T cells used for generating the TCR-T cells of the invention are CD4⁺ T cells. In some such embodiments, said T cells are less than 50% CD4⁺ T cells. In still further embodiments, said T cells are predominantly CD4⁺ T cells. In some embodiments, at least 50% of the T cells used for generating the TCR-T cells of the invention are

CD8⁺ T cells. In some such embodiments, said T cells are less than 50% CD8⁺ T cells. In still further embodiments, said T cells are predominantly CD8⁺ T cells. In some embodiments, the T cells (*e.g.*, the donor samples, the sensitized T cells, and/or TCR-T cells described herein) are stored in a cell library or bank before they are administered to the subject.

5 In some embodiments, the engineered TCR-T cells expressing the disclosed TCRs further express a dominant-negative mutation that effects immune checkpoint blockade (*e.g.*, express a dominant-negative form of an immune checkpoint molecule such as PD-1). Without intending to be an exhaustive list, the immune checkpoint molecule is selected from programmed death 1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTLA-4), B- and T-lymphocyte attenuator (BTLA), T cell
10 immunoglobulin mucin-3 (TIM-3), lymphocyte-activation protein 3 (LAG-3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), leukocyte-associated immunoglobulin-like receptor 1 (LAIR1), natural killer cell receptor 2B4 (2B4), and CD160. The immune checkpoint molecule may also be transforming growth factor β (TGF- β) receptor. In certain preferred embodiments, the immune checkpoint molecule is CTLA-4. In particularly preferred embodiments,
15 the immune checkpoint molecule is PD-1.

Therapeutic Methods

Immune effector cells expressing the disclosed TCRs can elicit a therapeutically beneficial immune response against HPV antigen-expressing cancer cells (*e.g.*, HPV-associated cancers). For example, an anti-tumor immune response elicited by the disclosed TCR-modified immune effector
20 cells may be an active or a passive immune response. In addition, the TCR-mediated immune response may be part of an adoptive immunotherapy approach in which TCR-modified immune effector cells induce an immune response specific to an HPV antigen, preferably an HPV antigen other than, or in addition to, E6 and E7 antigens.

Adoptive transfer of immune effector cells expressing engineered TCRs is a promising anti-
25 cancer therapy. Accordingly, in some aspects of the invention, provided herein are methods of treating a HPV-associated cancer or precancerous lesions in a subject, the method comprising administering an effective amount of an adoptive immunotherapy composition comprising the TCR-expressing cells contemplated herein. Following the collection of a patient's immune effector cells, the cells may be genetically engineered to express the disclosed HPV antigen-specific TCRs, thus

tailoring the specific antigenicity of said immune effector cells (*e.g.*, T cells) and infusing them back into the patient. Moreover, immune effector cells obtained from a donor other than the patient (*i.e.*, allogeneic to the patient) may be genetically engineered to express the disclosed HPV antigen-specific TCRs, then the TCR-containing cells are infused into the patient. In certain specific
5 embodiments, the immune effector cells which comprise an anti-HPV antigen TCR polypeptide are allogeneic HPV-specific cytotoxic T cells.

The disclosed TCR-modified immune effector cells may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2, IL-15, or other cytokines or cell populations. Briefly, pharmaceutical compositions may
10 comprise a targeting cell population as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants
15 (*e.g.*, aluminum hydroxide); and preservatives. Compositions for use in the disclosed methods are in some embodiments formulated for intravenous administration. Pharmaceutical compositions may be administered in any manner appropriate treat MM. The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

20 When “an immunologically effective amount”, “an anti-tumor effective amount”, “an tumor-inhibiting effective amount”, or “therapeutic amount” is indicated, the precise amount of the compositions of the present invention to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject).

25 In certain embodiments, it may be desired to administer activated T cells to a subject and then subsequently re-draw blood (or have an apheresis performed), activate T cells therefrom according to the disclosed methods, and reinfuse the patient with these activated and expanded T cells. This process can be carried out multiple times every few weeks. In certain embodiments, T cells can be activated from blood draws of from 10 cc to 400 cc. In certain embodiments, T cells are

activated from blood draws of 20 cc, 30 cc, 40 cc, 50 cc, 60 cc, 70 cc, 80 cc, 90 cc, or 100 cc. Using this multiple blood draw/multiple reinfusion protocol may serve to select out certain populations of T cells.

The administration of the disclosed compositions may be carried out in any convenient manner, including by injection, transfusion, or implantation. The compositions described herein may be administered to a patient by direct administration to an organ, subcutaneously, intradermally, intratumorally, intrathecally, intranodally, intramedullary, intramuscularly, intrapleurally, intracranially, by intravenous (i.v.) injection, or intraperitoneally. In some embodiments, the disclosed compositions are administered to a patient by intradermal or subcutaneous injection. In some embodiments, the disclosed compositions are administered by i.v. injection. The compositions may also be injected directly into a tumor, lymph node, or site of infection.

In certain embodiments, provided herein are methods of treating an HPV infection, and/or a cancer, and/or precancerous lesions in a subject comprising administering to the subject a pharmaceutical composition provided herein.

In some embodiments, provided herein is a method of treating an HPV infection in a subject. In certain such embodiments, the subject treated is immunocompromised. For example, the subject may have a T cell deficiency. The subject may have leukemia, lymphoma or multiple myeloma. In some embodiments, the subject is infected with HIV and/or has AIDS. In further embodiments, the subject has undergone a tissue, organ and/or bone marrow transplant. In some such embodiments, the subject is being administered immunosuppressive drugs. In some embodiments, the subject has undergone and/or is undergoing chemotherapy. In some embodiments, the subject has undergone and/or is undergoing radiation therapy.

In certain embodiments, the disclosed TCR-modified immune effector cells are administered to a patient in conjunction with (*e.g.*, before, simultaneously or following) any number of relevant treatment modalities, including but not limited to thalidomide, dexamethasone, bortezomib, and lenalidomide. In further embodiments, the TCR-modified immune effector cells may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents

such as CAM PATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation. In some embodiments, the TCR-modified immune effector cells are administered to a patient in conjunction with (*e.g.*, before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In other embodiments, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, *e.g.*, Rituxan. For example, in some embodiments, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the present invention. The expanded cells may be administered before or after surgery. In some embodiments, the subject is also administered an anti-viral drug that inhibits HPV replication. For example, in some embodiments, the subject is administered podofilox, imiquimod, sinecatechins, podophyllin resin, trichloroacetic acid, or bichloroacetic acid. In some embodiments, the subject is also treated with an intervention that physically affects the HPV infected lesions and/or HPV-associated tumors. For example, in some embodiments, the lesions are treated with surgical excision, chemical ablation, cryotherapy, or cauterization.

The cancer of the disclosed methods can be any HPV infected cell (*e.g.*, any HPV antigen-expressing cell) undergoing unregulated growth, invasion, or metastasis in a subject. In some embodiments, the subject has cancer or precancerous lesions. The methods described herein may be used to treat any such cancerous or pre-cancerous lesion. In some embodiments, the cancer and/or precancerous lesions express one or more of the HPV epitopes provided herein (*e.g.*, the HPV epitopes listed in Tables 1, 11 and 13). In some embodiments, the precancerous lesions include abnormal cell changes and/or precancerous cell changes. Precancerous lesions that may be treated by methods and compositions provided herein include, but are not limited to, cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL), or warts on the cervix. Cancers that express HPV antigens are known in the art and include, squamous cell carcinomas and solid tumors. Cancers that may be treated by methods and compositions provided herein include, but are not

limited to, cancer cells from the cervix, anus, vagina, vulva, penis, tongue base, larynx, tonsil, bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, non-melanoma skin cancer (NMSC), cutaneous squamous cell carcinoma (SCC), stomach, testis, tongue, or uterus. In addition, the

5 cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular

10 carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell

15 carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometrioid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell

20 carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; mammary paget's disease; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; malignant thymoma; malignant ovarian stromal tumor; malignant thecoma; malignant granulosa cell tumor; and malignant rhabdomyosarcoma; sertoli cell carcinoma; malignant leydig cell tumor; malignant lipid cell tumor; malignant paraganglioma;

25 malignant extra-mammary paraganglioma; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma; malignant blue nevus; sarcoma; fibrosarcoma; malignant fibrous histiocytoma; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; malignant mixed

tumor; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; malignant mesenchymoma; malignant brenner tumor; malignant phyllodes tumor; synovial sarcoma; malignant mesothelioma; dysgerminoma; embryonal carcinoma; malignant teratoma; malignant struma ovarii; choriocarcinoma; malignant mesonephroma; hemangiosarcoma; malignant

5 hemangioendothelioma; kaposi's sarcoma; malignant hemangiopericytoma; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; malignant chondroblastoma; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; malignant odontogenic tumor; ameloblastic odontosarcoma; malignant ameloblastoma; ameloblastic fibrosarcoma; malignant pinealoma; chordoma; malignant glioma; ependymoma; astrocytoma; protoplasmic

10 astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; malignant meningioma; neurofibrosarcoma; malignant neurilemmoma; malignant granular cell tumor; malignant lymphoma; Hodgkin's disease; Hodgkin's lymphoma; paragranuloma; small lymphocytic malignant lymphoma;

15 diffuse large cell malignant lymphoma; follicular malignant lymphoma; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia;

20 myeloid sarcoma; and hairy cell leukemia.

The disclosed TCR-modified immune effector cells (*e.g.*, TCR-T cells) can be used in combination with any compound, moiety or group that has a cytotoxic or cytostatic effect. Drug moieties include chemotherapeutic agents, which may function as microtubulin inhibitors, mitosis inhibitors, topoisomerase inhibitors, or DNA intercalators, and particularly those which are used for

25 cancer therapy. Exemplary anti-cancer compounds include, but are not limited to, Alemtuzumab (Campath®), Alitretinoin (Panretin®), Anastrozole (Arimidex®), Bevacizumab (Avastin®), Bexarotene (Targretin®), Bortezomib (Velcade®), Bosutinib (Bosulif®), Brentuximab vedotin (Adcetris®), Cabozantinib (Cometriq™), Carfilzomib (Kyprolis™), Cetuximab (Erbix®), Crizotinib (Xalkori®), Dasatinib (Sprycel®), Denileukin diftitox (Ontak®), Erlotinib hydrochloride

(Tarceva®), Everolimus (Afinitor®), Exemestane (Aromasin®), Fulvestrant (Faslodex®), Gefitinib (Iressa®), Ibritumomab tiuxetan (Zevalin®), Imatinib mesylate (Gleevec®), Ipilimumab (Yervoy™), Lapatinib ditosylate (Tykerb®), Letrozole (Femara®), Nilotinib (Tasigna®), Ofatumumab (Arzerra®), Panitumumab (Vectibix®), Pazopanib hydrochloride (Votrient®),

5 Pertuzumab (Perjeta™), Pralatrexate (Folotyn®), Regorafenib (Stivarga®), Rituximab (Rituxan®), Romidepsin (Istodax®), Sorafenib tosylate (Nexavar®), Sunitinib malate (Sutent®), Tamoxifen, Temsirolimus (Torisel®), Toremifene (Fareston®), Tositumomab and ¹³¹I-tositumomab (Bexxar®), Trastuzumab (Herceptin®), Tretinoin (Vesanoid®), Vandetanib (Caprelsa®), Vemurafenib (Zelboraf®), Vorinostat (Zolinza®), and Ziv-aflibercept (Zaltrap®). Examples of

10 further chemotherapeutic agents include Examples of such chemotherapeutic agents include, but are not limited to, alkylating agents such as thiopeta and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; acetogenins

15 (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine,

20 cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammall and calicheamicin omegall; dynemicin, including dynemicin A; bisphosphonates, such as

25 clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabacin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin),

epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (*e.g.*, CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

In some embodiments, the subject is also administered an immunotherapeutic agent. Immunotherapy refers to a treatment that uses a subject's immune system to treat cancer, *e.g.*, cancer vaccines, cytokines, use of cancer-specific antibodies, T cell therapy, and dendritic cell therapy.

In some embodiments, the subject is also administered an immune modulatory protein. Examples of immune modulatory proteins include, but are not limited to, B lymphocyte chemoattractant ("BLC"), C-C motif chemokine 11 ("Eotaxin-1"), Eosinophil chemotactic protein 2 ("Eotaxin-2"), Granulocyte colony-stimulating factor ("G-CSF"), Granulocyte macrophage colony-stimulating factor ("GM-CSF"), 1-309, Intercellular Adhesion Molecule 1 ("ICAM-1"), Interferon gamma ("IFN-gamma"), Interlukin-1 alpha ("IL-1 alpha"), Interleukin-1 beta ("IL-1 beta"), Interleukin 1 receptor antagonist ("IL-1 ra"), Interleukin-2 ("IL-2"), Interleukin-4 ("IL-4"), Interleukin-5 ("IL-5"), Interleukin-6 ("IL-6"), Interleukin-6 soluble receptor ("IL-6 sR"), Interleukin-7 ("IL-7"), Interleukin-8 ("IL-8"), Interleukin-10 ("IL-10"), Interleukin- 11 ("IL-11"), Subunit beta of Interleukin-12 ("IL-12 p40" or "IL-12 p70"), Interleukin-13 ("IL-13"), Interleukin-15 ("IL-15"), Interleukin-16 ("IL-16"), Interleukin-17 ("IL-17"), Chemokine (C-C motif) Ligand 2 ("MCP-1"), Macrophage colony-stimulating factor ("M-CSF"), Monokine induced by gamma interferon ("MIG"), Chemokine (C-C motif) ligand 2 ("MIP-1 alpha"), Chemokine (C-C motif) ligand 4 ("MIP-1 beta"), Macrophase inflammatory protein-1-delta ("MIP-1 delta"), Platelet-derived growth factor subunit B ("PDGF-BB"), Chemokine (C-C motif) ligand 5, Regulated on Activation, Normal T cell Expressed and Secreted ("RANTES"), TIMP metalloproteinase inhibitor 1 ("TIMP-1"), TIMP metalloproteinase inhibitor 2 ("TIMP-2"), Tumor necrosis factor, lymphotoxin-alpha ("TNF alpha"), Tumor necrosis factor, lymphotoxin-beta ("TNF beta"), Soluble TNF receptor type 1 ("sTNFR1"), sTNFR2, Brain-derived neurotrophic factor ("BDNF"), Basic fibroblast growth factor ("bFGF"), Bone morphogenetic protein 4 ("BMP-4"), Bone morphogenetic protein 5 ("BMP-5"), Bone morphogenetic protein 7 ("BMP-7"), Nerve growth factor ("b-NGF"), Epidermal growth factor ("EGF"), Epidermal growth factor receptor ("EGFR"), Endocrine-gland-derived vascular endothelial growth factor ("EG-VEGF"), Fibroblast growth factor 4 ("FGF-4"), Keratinocyte growth factor ("FGF-7"), Growth differentiation factor 15 ("GDF-15"), Glial cell-derived neurotrophic factor ("GDNF"), Growth Hormone, Heparin-binding EGF-like growth factor ("HB-EGF"), Hepatocyte growth factor ("HGF"), Insulin-like growth factor binding protein 1 ("IGFBP-1"), Insulin-like growth factor binding protein 2 ("IGFBP-2"), Insulin-like growth factor binding protein 3 ("IGFBP-3"), Insulin-like growth factor binding protein 4 ("IGFBP-4"), Insulin-like growth factor binding protein 6 ("IGFBP-6"), Insulin-like growth factor 1 ("IGF-1"), Insulin,

Macrophage colony-stimulating factor ("M-CSF R"), Nerve growth factor receptor ("NGF R"), Neurotrophin-3 ("NT-3"), Neurotrophin-4 ("NT-4"), Osteoclastogenesis inhibitory factor ("Osteoprotegerin"), Platelet-derived growth factor receptors ("PDGF-AA"), Phosphatidylinositol-glycan biosynthesis ("PIGF"), Skp, Cullin, F-box containing complex ("SCF"), Stem cell factor receptor ("SCF R"), Transforming growth factor alpha ("TGFA"), Transforming growth factor beta-1 ("TGF beta 1"), Transforming growth factor beta-3 ("TGF beta 3"), Vascular endothelial growth factor ("VEGF"), Vascular endothelial growth factor receptor 2 ("VEGFR2"), Vascular endothelial growth factor receptor 3 ("VEGFR3"), VEGF-D 6Ckine, Tyrosine-protein kinase receptor UFO ("Axl"), Betacellulin ("BTC"), Mucosae-associated epithelial chemokine ("CCL28"), Chemokine (C-C motif) ligand 27 ("CTACK"), Chemokine (C-X-C motif) ligand 16 ("CXCL16"), C-X-C motif chemokine 5 ("ENA-78"), Chemokine (C-C motif) ligand 26 ("Eotaxin-3"), Granulocyte chemotactic protein 2 ("GCP-2"), GRO, Chemokine (C-C motif) ligand 14 ("HCC-1"), Chemokine (C-C motif) ligand 16 ("HCC-4"), Interleukin-9 ("IL-9"), Interleukin-17 F ("IL-17F"), Interleukin-18-binding protein ("IL-18 BP"), Interleukin-28 A ("IL-28A"), Interleukin 29 ("IL-29"), Interleukin 31 ("IL-31"), C-X-C motif chemokine 10 ("IP-10"), Chemokine receptor CXCR3 ("I-TAC"), Leukemia inhibitory factor ("LIF"), Light, Chemokine (C motif) ligand ("Lymphotactin"), Monocyte chemoattractant protein 2 ("MCP-2"), Monocyte chemoattractant protein 3 ("MCP-3"), Monocyte chemoattractant protein 4 ("MCP-4"), Macrophage-derived chemokine ("MDC"), Macrophage migration inhibitory factor ("MIF"), Chemokine (C-C motif) ligand 20 ("MIP-3 alpha"), C-C motif chemokine 19 ("MIP-3 beta"), Chemokine (C-C motif) ligand 23 ("MPIF-1"), Macrophage stimulating protein alpha chain ("MSPalpha"), Nucleosome assembly protein 1-like 4 ("NAP-2"), Secreted phosphoprotein 1 ("Osteopontin"), Pulmonary and activation-regulated cytokine ("PARC"), Platelet factor 4 ("PF4"), Stroma cell-derived factor- 1 alpha ("SDF-1 alpha"), Chemokine (C-C motif) ligand 17 ("TARC"), Thymus-expressed chemokine ("TECK"), Thymic stromal lymphopoietin ("TSLP 4- IBB"), CD 166 antigen ("ALCAM"), Cluster of Differentiation 80 ("B7-1"), Tumor necrosis factor receptor superfamily member 17 ("BCMA"), Cluster of Differentiation 14 ("CD14"), Cluster of Differentiation 30 ("CD30"), Cluster of Differentiation 40 ("CD40 Ligand"), Carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein) ("CEACAM-1"), Death Receptor 6 ("DR6"), Deoxythymidine kinase ("Dtk"),

Type 1 membrane glycoprotein ("Endoglin"), Receptor tyrosine-protein kinase erbB-3 ("ErbB3"), Endothelial-leukocyte adhesion molecule 1 ("E-Selectin"), Apoptosis antigen 1 ("Fas"), Fms-like tyrosine kinase 3 ("Flt-3L"), Tumor necrosis factor receptor superfamily member 1 ("GITR"), Tumor necrosis factor receptor superfamily member 14 ("HVEM"), Intercellular adhesion molecule 3 ("ICAM-3"), IL-1 R4, IL-1 RI, IL-10 Rbeta, IL-17R, IL-2Rgamma, IL-21R, Lysosome membrane protein 2 ("LIMP2"), Neutrophil gelatinase-associated lipocalin ("Lipocalin-2"), CD62L ("L-Selectin"), Lymphatic endothelium ("LYVE-1"), MHC class I polypeptide-related sequence A ("MICA"), MHC class I polypeptide-related sequence B ("MICB"), NRG1-beta1, Beta-type platelet-derived growth factor receptor ("PDGF Rbeta"), Platelet endothelial cell adhesion molecule ("PECAM-1"), RAGE, Hepatitis A virus cellular receptor 1 ("TIM-1"), Tumor necrosis factor receptor superfamily member 10C ("TRAIL R3"), Trappin protein transglutaminase binding domain ("Trappin-2"), Urokinase receptor ("uPAR"), Vascular cell adhesion protein 1 ("VCAM-1"), XEDAR, Activin A, Agouti-related protein ("AgRP"), Ribonuclease 5 ("Angiogenin"), Angiopoietin 1, Angiostatin, Cathepsin S, CD40, Cryptic family protein 1B ("Cripto-1"), DAN, Dickkopf-related protein 1 ("DKK-1"), E-Cadherin, Epithelial cell adhesion molecule ("EpCAM"), Fas Ligand (FasL or CD95L), FcγRIIB/C, FcγRIIIb, Galectin-7, Intercellular adhesion molecule 2 ("ICAM-2"), IL-13 R1, IL-13R2, IL-17B, IL-2 Ra, IL-2 Rb, IL-23, LAP, Neuronal cell adhesion molecule ("NrCAM"), Plasminogen activator inhibitor-1 ("PAI-1"), Platelet derived growth factor receptors ("PDGF-AB"), Resistin, stromal cell-derived factor 1 ("SDF-1 beta"), sgpl30, Secreted frizzled-related protein 2 ("ShhN"), Sialic acid-binding immunoglobulin-type lectins ("Siglec-5"), ST2, Transforming growth factor-beta 2 ("TGF beta 2"), Tie-2, Thrombopoietin ("TPO"), Tumor necrosis factor receptor superfamily member 10D ("TRAIL R4"), Triggering receptor expressed on myeloid cells 1 ("TREM-1"), Vascular endothelial growth factor C ("VEGF-C"), VEGFR1, Adiponectin, Adipsin ("AND"), Alpha-fetoprotein ("AFP"), Angiopoietin-like 4 ("ANGPTL4"), Beta-2-microglobulin ("B2M"), Basal cell adhesion molecule ("BCAM"), Carbohydrate antigen 125 ("CA125"), Cancer Antigen 15-3 ("CA15-3"), Carcinoembryonic antigen ("CEA"), cAMP receptor protein ("CRP"), Human Epidermal Growth Factor Receptor 2 ("ErbB2"), Follistatin, Follicle-stimulating hormone ("FSH"), Chemokine (C-X-C motif) ligand 1 ("GRO alpha"), human chorionic gonadotropin ("beta HCG"), Insulin-like growth factor 1 receptor ("IGF-1 sR"), IL-1 sRII, IL-3, IL-

18 Rb, IL-21, Leptin, Matrix metalloproteinase-1 ("MMP-1"), Matrix metalloproteinase-2 ("MMP-2"), Matrix metalloproteinase-3 ("MMP-3"), Matrix metalloproteinase-8 ("MMP-8"), Matrix metalloproteinase-9 ("MMP-9"), Matrix metalloproteinase-10 ("MMP-10"), Matrix metalloproteinase-13 ("MMP-13"), Neural Cell Adhesion Molecule ("NCAM-1"), Entactin ("Nidogen-1"), Neuron specific enolase ("NSE"), Oncostatin M ("OSM"), Procalcitonin, Prolactin, Prostate specific antigen ("PSA"), Sialic acid-binding Ig-like lectin 9 ("Siglec-9"), ADAM 17 endopeptidase ("TACE"), Thyroglobulin, Metalloproteinase inhibitor 4 ("TIMP-4"), TSH2B4, Disintegrin and metalloproteinase domain-containing protein 9 ("ADAM-9"), Angiopoietin 2, Tumor necrosis factor ligand superfamily member 13/ Acidic leucine-rich nuclear phosphoprotein 32 family member B ("APRIL"), Bone morphogenetic protein 2 ("BMP-2"), Bone morphogenetic protein 9 ("BMP-9"), Complement component 5a ("C5a"), Cathepsin L, CD200, CD97, Chemerin, Tumor necrosis factor receptor superfamily member 6B ("DcR3"), Fatty acid-binding protein 2 ("FABP2"), Fibroblast activation protein, alpha ("FAP"), Fibroblast growth factor 19 ("FGF-19"), Galectin-3, Hepatocyte growth factor receptor ("HGF R"), IFN-alpha/beta R2, Insulin-like growth factor 2 ("IGF-2"), Insulin-like growth factor 2 receptor ("IGF-2 R"), Interleukin-1 receptor 6 ("IL-1R6"), Interleukin 24 ("IL-24"), Interleukin 33 ("IL-33"), Kallikrein 14, Asparaginyl endopeptidase ("Legumain"), Oxidized low-density lipoprotein receptor 1 ("LOX-1"), Mannose-binding lectin ("MBL"), Neprilysin ("NEP"), Notch homolog 1, translocation-associated (Drosophila) ("Notch-1"), Nephroblastoma overexpressed ("NOV"), Osteoactivin, Programmed cell death protein 1 ("PD-1"), N-acetylmuramoyl-L-alanine amidase ("PGRP-5"), Serpin A4, Secreted frizzled related protein 3 ("sFRP-3"), Thrombomodulin, Toll-like receptor 2 ("TLR2"), Tumor necrosis factor receptor superfamily member 10A ("TRAIL R1"), Transferrin ("TRF"), WIF-1ACE-2, Albumin, AMICA, Angiopoietin 4, B-cell activating factor ("BAFF"), Carbohydrate antigen 19-9 ("CA19-9"), CD 163, Clusterin, CRT AM, Chemokine (C-X-C motif) ligand 14 ("CXCL14"), Cystatin C, Decorin ("DCN"), Dickkopf-related protein 3 ("Dkk-3"), Delta-like protein 1 ("DLL1"), Fetuin A, Heparin-binding growth factor 1 ("aFGF"), Folate receptor alpha ("FOLR1"), Furin, GPCR-associated sorting protein 1 ("GASP-1"), GPCR-associated sorting protein 2 ("GASP-2"), Granulocyte colony-stimulating factor receptor ("GCSF R"), Serine protease hepsin ("HAI-2"), Interleukin-17B Receptor ("IL-17B R"), Interleukin 27 ("IL-27"), Lymphocyte-activation gene 3 ("LAG-3"),

Apolipoprotein A-V ("LDL R"), Pepsinogen I, Retinol binding protein 4 ("RBP4"), SOST, Heparan sulfate proteoglycan ("Syndecan-1"), Tumor necrosis factor receptor superfamily member 13B ("TACI"), Tissue factor pathway inhibitor ("TFPI"), TSP-1, Tumor necrosis factor receptor superfamily, member 10b ("TRAIL R2"), TRANCE, Troponin I, Urokinase Plasminogen Activator ("uPA"), Cadherin 5, type 2 or VE-cadherin (vascular endothelial) also known as CD144 ("VE-Cadherin"), WNT1-inducible-signaling pathway protein 1 ("WISP-1"), and Receptor Activator of Nuclear Factor κ B ("RANK"). In certain preferred embodiments, the subject is also administered IFN-gamma (IFN γ). In particularly preferred embodiments, the subject is pretreated with IFN γ , such as with low doses of IFN γ , prior to administering the TCR-modified immune effector cells disclosed herein (*e.g.*, the adoptive immunotherapy compositions disclosed herein comprising the TCR-T cells disclosed herein).

The disclosed TCRs can be used in combination with an immune checkpoint inhibitor. Immune Checkpoint inhibition broadly refers to inhibiting the checkpoints that cancer cells can produce to prevent or downregulate an immune response. Two known immune checkpoint pathways involve signaling through the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed-death 1 (PD-1) receptors. These proteins are members of the CD28-B7 family of co-signaling molecules that play important roles throughout all stages of T cell function. The PD-1 receptor (also known as CD279) is expressed on the surface of activated T cells. Its ligands, PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273), are expressed on the surface of APCs such as dendritic cells or macrophages. PD-L1 is the predominant ligand, while PD-L2 has a much more restricted expression pattern. When the ligands bind to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Checkpoint inhibitors include, but are not limited to aptamers and antibodies that block PD-1 (Nivolumab (BMS-936558 or MDX1106), CT-011, MK-3475, AMP-514), PD-L1 (MDX-1105 (BMS-936559), MPDL3280A, MSB0010718C), PD-L2 (rHIgM12B7, AMP-224), CTLA-4 (Ipilimumab (MDX-010), Tremelimumab (CP-675,206)), IDO, B7-H3 (MGA271), B7-H4, TIM3, LAG-3 (BMS-986016).

Human monoclonal antibodies to programmed death 1 (PD-1) and methods for treating cancer using anti-PD-1 antibodies alone or in combination with other immunotherapeutics are

described in U.S. Patent No. 8,008,449, which is incorporated by reference for these antibodies. Anti-PD-L1 antibodies and uses therefor are described in U.S. Patent No. 8,552,154, which is incorporated by reference for these antibodies. Anticancer agent comprising anti-PD-1 antibody or anti-PD-L1 antibody are described in U.S. Patent No. 8,617,546, which is incorporated by reference
5 for these antibodies.

In some embodiments, the PDL1 inhibitor comprises an antibody that specifically binds PDL1, such as BMS-936559 (Bristol-Myers Squibb) or MPDL3280A (Roche). In some embodiments, the PD-1 inhibitor comprises an antibody that specifically binds PD-1, such as lambrolizumab (Merck), nivolumab (Bristol-Myers Squibb), or MEDI4736 (AstraZeneca). Human
10 monoclonal antibodies to PD-1 and methods for treating cancer using anti-PD-1 antibodies alone or in combination with other immunotherapeutics are described in U.S. Patent No. 8,008,449, which is incorporated by reference for these antibodies. Anti-PD-L1 antibodies and uses therefor are described in U.S. Patent No. 8,552,154, which is incorporated by reference for these antibodies. Anticancer agent comprising anti-PD-1 antibody or anti-PD-L1 antibody are described in U.S.
15 Patent No. 8,617,546, which is incorporated by reference for these antibodies.

The disclosed TCRs can be used in combination with other cancer immunotherapies. There are two distinct types of immunotherapy: passive immunotherapy uses components of the immune system to direct targeted cytotoxic activity against cancer cells, without necessarily initiating an immune response in the patient, while active immunotherapy actively triggers an endogenous
20 immune response. Passive strategies include the use of the monoclonal antibodies (mAbs) produced by B cells in response to a specific antigen. The development of hybridoma technology in the 1970s and the identification of tumor-specific antigens permitted the pharmaceutical development of mAbs that could specifically target tumor cells for destruction by the immune system. Among them is rituximab (Rituxan, Genentech), which binds to the CD20 protein that is highly expressed on the
25 surface of B cell malignancies such as non-Hodgkin's lymphoma (NHL). Rituximab is approved by the FDA for the treatment of NHL and chronic lymphocytic leukemia (CLL) in combination with chemotherapy. Another important mAb is trastuzumab (Herceptin; Genentech), which revolutionized the treatment of HER2 (human epidermal growth factor receptor 2)-positive breast cancer by targeting the expression of HER2.

Generating optimal “killer” CD8 T cell responses also requires T cell receptor activation plus co-stimulation, which can be provided through ligation of tumor necrosis factor receptor family members, including OX40 (CD134) and 4-1BB (CD137). OX40 is of particular interest as treatment with an activating (agonist) anti-OX40 mAb augments T cell differentiation and cytolytic function leading to enhanced anti-tumor immunity against a variety of tumors.

In some embodiments, such an additional therapeutic agent may be selected from an antimetabolite, such as methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, fludarabine, 5-fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine or cladribine.

In some embodiments, such an additional therapeutic agent may be selected from an alkylating agent, such as mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine, mitomycin C, cisplatin and other platinum derivatives, such as carboplatin.

In some embodiments, such an additional therapeutic agent may be selected from an anti-mitotic agent, such as taxanes, for instance docetaxel, and paclitaxel, and vinca alkaloids, for instance vindesine, vincristine, vinblastine, and vinorelbine.

In some embodiments, such an additional therapeutic agent may be selected from a topoisomerase inhibitor, such as topotecan or irinotecan, or a cytostatic drug, such as etoposide and teniposide.

In some embodiments, such an additional therapeutic agent may be selected from a growth factor inhibitor, such as an inhibitor of ErbB1 (EGFR) (such as an EGFR antibody, *e.g.* zalutumumab, cetuximab, panitumumab or nimotuzumab or other EGFR inhibitors, such as gefitinib or erlotinib), another inhibitor of ErbB2 (HER2/neu) (such as a HER2 antibody, *e.g.* trastuzumab, trastuzumab-DM1 or pertuzumab) or an inhibitor of both EGFR and HER2, such as lapatinib).

In some embodiments, such an additional therapeutic agent may be selected from a tyrosine kinase inhibitor, such as imatinib (Glivec, Gleevec STI571) or lapatinib.

Therefore, in some embodiments, a disclosed antibody is used in combination with ofatumumab, zanolimumab, daratumumab, ranibizumab, nimotuzumab, panitumumab, hu806,

daclizumab (Zenapax), basiliximab (Simulect), infliximab (Remicade), adalimumab (Humira), natalizumab (Tysabri), omalizumab (Xolair), efalizumab (Raptiva), and/or rituximab.

In some embodiments, a therapeutic agent for use in combination with a TCRs for treating the disorders as described above may be an anti-cancer cytokine, chemokine, or combination thereof. Examples of suitable cytokines and growth factors include IFN γ , IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-18, IL-23, IL-24, IL-27, IL-28a, IL-28b, IL-29, KGF, IFN α (*e.g.*, INF α 2b), IFN β , GM-CSF, CD40L, Flt3 ligand, stem cell factor, ancestim, and TNFa. Suitable chemokines may include Glu-Leu-Arg (ELR)-negative chemokines such as IP-10, MCP-3, MIG, and SDF-1 α from the human CXC and C-C chemokine families. Suitable cytokines include cytokine derivatives, cytokine variants, cytokine fragments, and cytokine fusion proteins.

In some embodiments, a therapeutic agent for use in combination with a CARs for treating the disorders as described above may be a cell cycle control/apoptosis regulator (or "regulating agent"). A cell cycle control/apoptosis regulator may include molecules that target and modulate cell cycle control/apoptosis regulators such as (i) cdc-25 (such as NSC 663284), (ii) cyclin-dependent kinases that overstimulate the cell cycle (such as flavopiridol (L868275, HMR1275), 7-hydroxystaurosporine (UCN-01, KW-2401), and roscovitine (R-roscovitine, CYC202)), and (iii) telomerase modulators (such as BIBR1532, SOT-095, GRN163 and compositions described in for instance US 6,440,735 and US 6,713,055). Non-limiting examples of molecules that interfere with apoptotic pathways include TNF-related apoptosis-inducing ligand (TRAIL)/apoptosis-2 ligand (Apo-2L), antibodies that activate TRAIL receptors, IFNs, and anti-sense Bcl-2.

In some embodiments, a therapeutic agent for use in combination with a TCRs for treating the disorders as described above may be a hormonal regulating agent (*e.g.*, hormone therapy), such as agents useful for anti-androgen and anti-estrogen therapy. Examples of such hormonal regulating agents are tamoxifen, idoxifene, fulvestrant, droloxifene, toremifene, raloxifene, diethylstilbestrol, ethinyl estradiol/estinyl, an antiandrogen (such as flutaminde/eulexin), a progestin (such as such as hydroxyprogesterone caproate, medroxy-progesterone/provera, megestrol acepate/megace), an adrenocorticosteroid (such as hydrocortisone, prednisone), luteinizing hormone-releasing hormone (and analogs thereof and other LHRH agonists such as buserelin and goserelin), an aromatase

inhibitor (such as anastrozole/arimidex, aminoglutethimide/cytraden, exemestane) or a hormone inhibitor (such as octreotide/sandostatin).

In some embodiments, a therapeutic agent for use conjointly with TCRs for treating the disorders as described above may be an anti-cancer nucleic acid or an anti-cancer inhibitory RNA molecule.

In some embodiments, the disclosed TCRs is administered conjointly with radiotherapy. Radiotherapy may comprise radiation or associated administration of radiopharmaceuticals to a patient is provided. The source of radiation may be either external or internal to the patient being treated (radiation treatment may, for example, be in the form of external beam radiation therapy (EBRT) or brachytherapy (BT)). Radioactive elements that may be used in practicing such methods include, *e.g.*, radium, cesium-137, iridium-192, americium-241, gold-198, cobalt-57, copper-67, technetium-99, iodide-123, iodide-131, and indium-111.

In some embodiments, the disclosed TCRs are administered conjointly with surgery.

Exemplification

Example 1: Generation of HPV-specific T cell lines:

Cryopreserved, HPV⁺ PBMCs from HNSCC patients were washed and re-suspended in complete RPMI medium and incubated overnight (*i.e.*, at 37°C, 6.5% CO₂). Cells (5×10⁶) were stimulated with HPV16 antigen epitope at a concentration of 1 µg/ml and incubated for an hour. The cells were then washed and further grown (*i.e.*, incubated) for 14 days in 24 well plates. The cultures were supplemented with R10 medium containing interleukin-2 (IL-2) at 200 IU/ml on day 2 and then every 3 days thereafter, until 14 days. On day 14, viable T cells were counted by trypan blue exclusion and subsequently cryopreserved in liquid nitrogen.

Example 2: Sorting of antigen-specific CTLs by dual cytokine capture assay:

The cryopreserved T cells (10×10⁶) were rapidly thawed, washed and re-suspended in 10ml complete medium containing 120 IU/ml of IL-2 and incubated overnight. A 1ml aliquot of cells from the overnight culture was used as a “stimulator” (*e.g.*, antigen-presenting) population. To the stimulator culture, 1 µg/ml of the antigenic peptide (*e.g.*, the corresponding peptide selected from

SEQ ID NOs. 1-12, 217, and 218) was added and incubated for 1 hour; followed by three washes with complete medium. The stimulator cells were then added to CTLs (*i.e.*, “responder” cells) at a 1:9 ratio, into 48 wells (approx. $5\text{--}10 \times 10^6$ per well) and incubated for 3 hours. Following incubation, CTLs were washed in ice cold buffer (PBS, 2mM EDTA, and 0.5% BSA) and

5 centrifuged at 400g for 10 minutes at 4°C. Cells were then re-suspended in 80µl of cold complete medium and 10µl of IFN γ and TNF α catch reagent (anti-cytokine antibody conjugated to a cell surface-specific antibody, Miltenyi Biotec; Bergisch Gladbach, Germany) per 10^6 cells and incubate on ice for 5 minutes. Cells were then centrifuged in warm complete medium to dilute cells to 10^5 cells/ml and tubes were gently mixed (*e.g.*, manually turning tubes every five minutes or placing in

10 rotating mixer such as a the Miltenyi MACSmix™, at low rotation setting) in a 37°C incubator for 45mins. After incubation, each tube was topped-up with ice cold buffer and centrifuged (300g, 10 minutes, 4°C) followed by one more wash with cold buffer. The cells were re-suspended in 80µl of cold buffer per 10^6 , containing $\times 2.5\mu\text{l}$ of anti-CD3 BV421, $\times 1\mu\text{l}$ of anti-CD8 perCPCy5.5, $\times 2.5\mu\text{l}$ of anti-CD4 PE, $\times 0.2\mu\text{l}$ NIR live-dead, $\times 10\mu\text{l}$ IFN γ detection antibody PE, $\times 10\mu\text{l}$ of TNF α detection

15 antibody APC and incubated on ice for 10 minutes followed by wash in ice cold buffer. Cells were then re-suspended in 300µl cold buffer and filtered (0.45µm) and used for fluorescence-activated cell sorting (FACS). Single, IFN γ and TNF α double-positive HPV-specific CD8 $^+$ T cells were sorted into individual wells of a 96-well PCR plate (*Figure 1*), the last row of wells remaining empty for use as PCR negative controls. After sorting, plates were stored at –80°C until

20 downstream processing.

Example 3: RT-PCR, multiplex nested PCR, and sequencing:

Complementary DNA (cDNA) was synthesized from single cells in the 96-well PCR plates using the SuperScript™ VILO™ cDNA Synthesis Kit (Invitrogen™, Thermo Fisher Scientific; MA, U.S.A.) in 2.5µl reaction mixes, each containing 0.5µl of 5× VILO reaction mix, 0.25µl of 10×

25 Superscript reverse transcriptase, and 0.1% Triton X-100.

TCR transcripts from each cell were amplified by multiplex nested PCR in 25µl reaction mixes containing 2.5µl of cDNA. Primers of 17- to 23-base pair length were designed to target each family of related V genes and the TRAC and TRBC genes, allowing for up to three degenerate base

pairs. A total of 40 external/internal pairs of sense TRAV, 27 sense TRBV, and 1 each of antisense TRAC and TRBC gene segment-specific primers were generated (Table 12). For inclusion in nested PCR, TRAV and TRBV primers were multiplexed to a concentration of 5 μ M for each primer, and TRAC and TRBC primers were reconstituted to a concentration of 5 μ M. The first-round (external) PCR was performed with 0.75U of *Taq* DNA polymerase, 2.5 μ l of 10 $\times$ PCR Buffer (containing KCl, (NH₄)₂SO₄, and 15mM MgCl₂, 0.5 μ l of 10mM deoxynucleotide triphosphates (dNTPs), 0.1 μ M each of the external sense TRAV (T cell receptor α variable) and TRBV (T cell receptor β variable) primers, and each of the external antisense TRAC (T cell receptor α constant) and TRBC (T cell receptor β constant) primers listed in Table 12. Aliquots (2.5 μ l) of the external PCR products served as templates for two separate second-round (internal) PCRs in 25 μ l reactions that incorporated, respectively, either

- (i) internal sense TRAV primers and internal antisense TRAC primer or
- (ii) internal sense TRBV primers and internal antisense TRBC primer, listed in Table 12.

Instead of 10 $\times$ PCR Buffer, the second-round PCR used CoralLoad[®] PCR Buffer (Qiagen GmbH; Hilden, Germany) containing two marker dyes for gel loading. Internal PCR product (5 μ l) was run on 2% agarose gel at 80V to select the positive wells for further analysis (Figure 2).

Table 12: PCR primers

Gene name	External PCR primer Sequence	SEQ ID NO.	Internal PCR primer Sequence	SEQ ID NO.
TRAV1	AACTGCACGTACCAGACATC	71	GCACCCACATTTCTKTCTTAC	140
TRAV2	GATGTGCACCAAGACTCC	72	CACTCTGTGTCCAATGCTTAC	141
TRAV3	AAGATCAGGTCAACGTTGC	73	ATGCACCTATTCAGTCTCTGG	142
TRAV4	CTCCATGGACTCATATGAAGG	74	ATTATATCACGTGGTACCAACAG	143
TRAV5	CTTTTCCTGAGTGTCCGAG	75	TACACAGACAGCTCCTCCAC	144
TRAV6	CACCCTGACCTGCAACTATAC	76	TGGTACCGACAAGATCCAG	145
TRAV7	AGCTGCACGTACTCTGTCAG	77	ACAATTTGCAGTGGTACAGG	146
TRAV8-1	CTCACTGGAGTTGGGATG	78	GTCAACACCTTCAGCTTCTC	147
TRAV8-2	GCCACCCTGGTTAAAGG	79	AGAGTGAAACCTCCTTCCAC	148
TRAV8-3	CACTGTCTCTGAAGGAGCC	80	TTTGAGGCTGAATTTAAGAGG	149
TRAV8-6	GAGCTGAGGTGCAACTACTC	81	AACCAAGGACTCCAGCTTC	150
TRAV8-7	CTAACAGAGGCCACCCAG	82	ATCAGAGGTTTTGAGGCTG	151
TRAV9-1	TGGTATGTCCAATATCCTGG	83	GAAACCACTTCTTTCCACTTG	152
TRAV10	CAAGTGGAGCAGAGTCCTC	84	GAAAGAACTGCACTCTTCAATG	153

TRAV12-1	CARTGTTCCAGAGGGAGC	85	AAGATGGAAGGTTTACAGCAC	154
TRAV13-1	CATCCTTCAACCTGAGTG	86	TCAGACAGTGCCTCAAACCTAC	155
TRAV13-2	CAGCGCTCAGACTACTTC	87	CAGTGAAACATCTCTCTCTGC	156
TRAV14	AAGATAACTCAAACCCAACCAG	88	AGGCTGTGACTCTGGACTG	157
TRAV16	AGTGGAGCTGAAGTGCAAC	89	GTCCAGTACTCCAGACAACG	158
TRAV17	GGAGAAGAGGATCCTCAGG	90	CCACCATGAACTGCAGTTAC	159
TRAV18	TCCAGTATCTAAACAAAGAGCC	91	TGACAGTTCCTTCCACCTG	160
TRAV19	AGGTAACCTCAAGCGCAGAC	92	TGTGACCTTGGACTGTGTG	161
TRAV20	CACAGTCAGCGGTTTAAGAG	93	TCTGGTATAGGCAAGATCCTG	162
TRAV21	TTCCTGCAGCTCTGAGTG	94	AACTTGGTTCTCAACTGCAG	163
TRAV22	GTCCTCCAGACCTGATTCTC	95	CTGACTCTGTGAACAATTTGC	164
TRAV23	TGCTTATGAGAACTGCG	96	TGCATTATTGATAGCCATACG	165
TRAV24	CTCAGTCACTGCATGTTTCA	97	TGCCTTACACTGGTACAGATG	166
TRAV25	GGACTTCACCACGTACTGC	98	TATAAGCAAAGGCCTGGTG	167
TRAV26-1	GCAAACCTGCCTTGTAATC	99	CGACAGATTCACTCCCAG	168
TRAV26-2	AGCCAAATTCAATGGAGAG	100	TTCATTGCCTTGTAACCAC	169
TRAV27	TCAGTTTCTAAGCATCCAAGAG	101	CTCACTGTGTACTGCAACTCC	170
TRAV29	GCAAGTTAAGCAAAATTCACC	102	CTGCTGAAGGTCCTACATTC	171
TRAV30	CAACAACCACTGCAGAGTC	103	AGAAGCATGGTGAAGCAC	172
TRAV34	AGAACTGGAGCAGAGTCCTC	104	ATCTCACCATAAACTGCACG	173
TRAV35	GGTCAACAGCTGAATCAGAG	105	ACCTGGCTATGGTACAAGC	174
TRAV36	GAAGACAAGGTGGTACAAAGC	106	ATCTCTGGTTGTCCACGAG	175
TRAV38-1	GCACATATGACACCAGTGAG	107	CAGCAGGCAGATGATTCTC	176
TRAV39	CTGTTCTGAGCATGCAG	108	TCAACCACTTCAGACAGACTG	177
TRAV40	GCATCTGTGACTATGAACTGC	109	GGAGGCGGAAATATTAAGAC	178
TRAV41	AATGAAGTGGAGCAGAGTCC	110	TTGTTTATGCTGAGCTCAGG	179
TRAC	GACCAGCTTGACATCACAG	111	TGTTGCTCTTGAAGTCCATAG	180
TRBV2	TCGATGATCAATTCTCAGTTG	112	TTCACCTCTGAAGATCCGGTC	181
TRBV3-1	CAAAATACCTGGTCACACAG	113	AATCTTCACATCAATTCCTTG	182
TRBV4-1	TCGCTTCTCACCTGAATG	114	CCTGCAGCCAGAAGACTC	183
TRBV5-1	GATTCTCAGGKCKCCAGTTC	115	CTTGGAGCTGGRSGACTC	184
TRBV5-5	GTACCAACAGGYCCTGGGT	116	TCTGAGCTGAATGTGAACG	185
TRBV6-1	ACTCAGACCCCAAAATTCC	117	GTGTRCCCAGGATATGAACC	186
TRBV6-4	ACTGGCAAAGGAGAAGTCC	118	TGGTTATAGTGTCTCCAGAGC	187
TRBV7-1	TRTGATCCAATTTTCAGGTCA	119	TCYACTCTGAMGWTCCAGCG	188
TRBV7-4	GSWTCTYTGCAGARAGGCC	120	TGRMGATYCAGCGCACA	189
TRBV9	GATCACAGCAACTGGACAG	121	GTACCAACAGAGCCTGGAC	190
TRBV10-1	TGTWCTGGTATCGACAAGACC	122	TCCYCCTCACTCTGGAGTC	191
TRBV11-1	CGATTTTCTGCAGAGACGC	123	GACTCCACTCTCAAGATCCA	192
TRBV12-3	ARGTGACAGARATGGGACAA	124	CYACTCTGARGATCCAGCC	193
TRBV13	AGCGATAAAGGAAGCATCC	125	CATTCTGAACTGAACATGAGC	194
TRBV14	CCAACAATCGATTCTTAGCTG	126	ATTCTACTCTGAAGGTGCAGC	195
TRBV15	AGTGACCCTGAGTTGTTCTC	127	ATAACTTCCAATCCAGGAGG	196
TRBV16	GTCTTTGATGAAACAGGTATGC	128	GAAAGATTTTCAGCTAAGTGCC	197

TRBV17	CAGACCCCCAGACACAAG	129	TGTTCACTGGTACCGACAG	198
TRBV18	CATAGATGAGTCAGGAATGCC	130	CGATTTTCTGCTGAATTTCC	199
TRBV19	AGTTGTGAACAGAATTTGAACC	131	TTCCTCTCACTGTGACATCG	200
TRBV20-1	AAGTTTCTCATCAACCATGC	132	ACTCTGACAGTGACCAGTGC	201
TRBV23-1	GCGATTCTCATCTCAATGC	133	GCAATCCTGTCCTCAGAAC	202
TRBV24-1	CCTACGGTTGATCTATTACTCC	134	GATGGATACAGTGTCTCTCGA	203
TRBV25-1	ACTACACCTCATCCACTATTCC	135	CAGAGAAGGGAGATCTTTCC	204
TRBV27	TGGTATCGACAAGACCCAG	136	TTCYCCCTGATYCTGGAGTC	205
TRBV29-1	TTCTGGTACCGTCAGCAAC	137	TCTGACTGTGAGCAACATGAG	206
TRBV30	TCCAGCTGCTCTTCTACTCC	138	AGAATCTCTCAGCCTCCAGAC	207
TRBC	TAGAACTGGACTTGACAGCG	139	TTCTGATGGCTCAAACACAG	208

These positive PCR products were purified and used as templates for dye-terminator sequencing. Each reaction mixture, comprising 0.5 μ M of TRAC or TRBC internal primer, was added to a 96-well plate containing $\sim 7\mu$ l purified PCR product ($\sim 20\mu$ l total/well), and the reactions underwent PCR thermocycling. Extension sequencing product was purified by ethanol precipitation and samples were used for capillary electrophoresis sequencing. Sequence from TCR α and TCR β plates were analyzed by IMGT/V-QUEST, an integrated alignment tool for immunoglobulin and T cell receptor nucleotide sequences, available online from the international ImMunoGeneTics information system[®] (IMGT[®]) home page. Briefly, nucleotide sequence from each sequenced well was entered into the IMGT/V-QUEST online tool as a T cell receptor (TR) nucleotide sequence and IMGT/V-QUEST identified the CDR3 region, the V, D, and J genes, and alleles by alignment of the input sequence with the IMGT reference directory. Out of sequenced clones, the maximum co-expressed TCR α and TCR β sequences were selected and used to generate TCR lentivirus constructs.

Results

The identified and sequenced clones (*i.e.*, HPV-specific TCR amino acid sequences), whose expression and functional activity was checked in Jurkat cells (primary screening) and in PBMCs (secondary screening) are represented below in Table 13.

Table 13: HPV-specific TCRs sequences

HPV16 Antigen	Epitope	HLA restriction	TCR α gene	TCR β gene	CDR3 sequence (α/β)
E2	TLQDVSLEVYL (SEQ ID NO. 3)	A*02:01	TRAV38-01*03		CDR3 α sequence: CAFTYGGSQGNLIF

			TRAJ42-01		(SEQ ID NO. 25)
				TRBV2*01	CDR3 β sequence: CASRASVGVGTGELFF (SEQ ID NO. 26)
				TRBJ2-2*01	
				TRBD1*01	
E5	NLDTASTTL (SEQ ID NO. 1)	C*05:01 & C*08:02	TRAV19-01		CDR3 α sequence: CALSEGGSQGNLIF (SEQ ID NO. 13)
			TRAJ42-01		
				TRBV7- 6*01	CDR3 β sequence: CASSPELAGPQETQYF (SEQ ID NO. 14)
				TRBJ2-5*01	
				TRBD2*01	
E6	AFRDLCIVY (SEQ ID NO. 5)	C*07:02	TRAV19*01		CDR3 α sequence: CALGSSGTYKYI (SEQ ID NO. 39)
			TRAJ40*01		
				TRBV25- 1*01	CDR3 β sequence: CASSPGQGHNQPQHF (SEQ ID NO. 40)
				TRBJ1-5*01	
				TRBD1*01	
E6	TIHDILECV (SEQ ID NO. 4)	A*02:01	TRAV1- 2*01		CDR3 α sequence: CAVRDTGYGQNFVF (SEQ ID NO. 31)
			TRAJ26*01		
				TRBV27*01	CDR3 β sequence: CASSPQGRINSPLHF (SEQ ID NO. 32)
				TRBJ1-6*02	
				TRBD1*01	
E6	HDILECVY (SEQ ID NO. 2)	B*18:01 (B44 super family)	TRAV26- 1*01		CDR3 α sequence: CIVRDRSYGQNFVF (SEQ ID NO. 19)
			TRAJ26*01		
				TRBV20- 1*01	CDR3 β sequence: CSAREGYRSYF (SEQ ID NO. 20)
				TRBJ2-1*01	
				TRBD1*01	

E6	KQRFHNIRGRWTGRC (SEQ ID NO. 6)	DQB1*03:01 /DRB1*15:01	TRAV13- 2*01,		CDR3 α sequence: CAETLGLDQGGKLIF (SEQ ID NO. 43)
			TRAJ23*01		
				TRBV20- 1*03	CDR3 β sequence: CSTAGETDTQYF (SEQ ID NO. 44)
				TRBJ2-3*01	
				TRBD2*01	

Example 4: TCR lentivirus constructs:

TCR nucleotide sequences were synthesized and a vector insert was cloned into the pLV
5 lentivirus backbone. The insert sequence was codon optimized for expression in human tissues. For
partial murinization of human constant region, some amino acids were replaced with mouse
constant regions. For the T cell receptor α constant region amino acid Pro91, Glu92, Ser93, Ser94
(see International ImMunoGeneTics information system[®], Accession # X02883|TRAC*01|Homo
sapiens) were replaced with Ser, Asp, Val, Pro amino acid respectively. For T cell receptor β
10 constant region Glu18, Ser22, Phe133, Glu136, Gln139 (see International ImMunoGeneTics
information system[®], Accession #'s M12887|TRBC1*01|Homo sapiens and
M12888|TRBC2*01|Homo sapiens) were replaced with Lys, Ala, Ile, Ala, His amino acid
respectively. For constructs with an additional interchain disulfide bond, cysteine was substituted in
place of Thr48 of the α chain and Ser57 of the β chain. The vector inserts were also designed to
15 encode the α -and β -chains of the identified TCR (with the constant regions of each TCR chain
partially murinized) linked by a furin-2A self-cleaving peptide.

The nucleotide sequence for each TCR lentivirus construct, and its relevant features, are
illustrated in Tables 2 to 11. Similarly, the amino acid sequence of each expressed TCR construct,
and its sequence features, is described, respectively, in Figure 3, Figure 4, and Figures 6-11.

Example 5: Jurkat cells engineered to express 1a HPV-TCR from different HPV antigens (E2, E5, and E6) and displaying antigen recognition (primary screening):

TCR lentivirus supernatants were generated by co-transfection of 293T cells with TCR pLV vector and packaging plasmid (pVSV, pMDL and pREV). Two days after transfection, TCR
5 lentiviral supernatants were harvested.

40,000 Jurkat cells in 40µl were transduced with lentivirus (Multiplicity of infection (MOI) of 50) in 96 well plates. Transduction was checked at day 3, post-transduction, by measuring TCR expression by flow cytometry.

Transduced Jurkat cells were further confirmed to have antigen specificity and HLA
10 restriction of the engineered TCR. Briefly, lymphoblastoid cells (LCLs) were stimulated with peptide (1µg/ml) in R-0 (no FBS) media and incubated for 1 hour. The stimulated, antigen-presenting LCLs were then washed (5x) with complete RPMI medium 2300 rpm for 2 min. The transduced Jurkat cells (2×10^5 /well) were then co-cultured with an equal number of the peptide-pulsed LCLs (either HLA-matched or mismatched) in complete medium in 96-well U-bottom plates
15 and incubated for 24 hours and analyzed by flow cytometry.

For cytometry analysis cells were washed with PBS containing 2% FBS (wash buffer) and the pellet was re-suspended in 50 µL of wash buffer containing FITC-conjugated anti-Vα12.1 (E5-NLD TCR, clone-6D6.6; Thermofisher) or PE-conjugated anti-Vβ2 (E6-HDI, clone- MPB2D5 , Beckman Coulter), anti-Vβ11 (E6-AFR-TCR, C21; Beckman Coulter), anti-Vβ14 (E6-TIH-TCR,
20 clone- REA557; Miltenyi Biotec), or anti-Vβ22 (E2-TLQ-TCR, clone- IMMU 546; Beckman Coulter); and Near IR live-dead exclusion dye, and then incubated at 4°C for 30 minutes. Cells were then washed twice with wash buffer, re-suspended in PBS containing 1% paraformaldehyde prior to analysis.

Results

25 By day 3, post transduction with E2-TLQ-TCR, E5-NLD-TCR, E6-TIH-TCR lentivirus, Jurkat cells showed TCR expression as detected by anti-Vβ22, Vα12.1, and Vβ14 antibodies, respectively (see *Figure 12*).

Similarly, Jurkat cells transduced with E5-NLD-TCR (restricted to HLA-C*05:01 and C*08:02) and E2-TLQ-TCR (restricted to HLA-A*02:01) exhibit CD69 expression (as detected

with anti-human CD69 antibody, Clone-FN50) after co-incubation with peptide pulsed LCL (see *Figure 13*).

Example 6: T cells engineered to express a TCR from E5 antigen (E5-NLD-TCR) displayed multifunctional activity and high functional avidity (secondary screening)

Human peripheral blood mononuclear cells (PBMCs) were isolated from healthy donors. Prior to transduction, PBMCs were cultured in complete media with CD3 and CD28 agonists to provide primary and co-stimulatory signals for optimized and efficient T cell activation and expansion for 2 days.

Transductions were performed by adding lentiviral supernatant (up to 80-90µl/ well) to RetroNectin[®]-coated 96-well plates (Takara Bio USA, Inc.; CA, U.S.A.). The plates were centrifuged for 2 hours at 2,000g and 32°C. The supernatant was discarded and the plates were washed with PBS. PBMCs were added (20,000/ well) and the plates were centrifuged at 1,500rpm for 10 minutes at 32°C. After approximately 16 hours, the cells were transferred to 24-well tissue culture-treated plates and cultured for 7 days in the presence of IL-2 (200IU/ml). At day 8, transduced T cells were re-stimulated with peptide-pulsed autologous PBMCs at a 2:1 effector-to-target ratio and cultured in complete RPMI media. IL-2 was added at 200IU/ml on day 2 and then every 3 days thereafter until 21 days. On days 7 and 14, post re-stimulation, viable T cells were visually counted by Trypan Blue exclusion and used for TCR expression studies and functional assays. Any remaining cells were cryopreserved.

The transduced T cells were incubated with cognate peptide antigen in R10 media containing monensin, brefeldin and anti-CD107a antibody. After 4hrs incubation, the cells were washed with PBS containing 2% FBS (wash buffer) and the pellet was re-suspended in wash buffer containing FITC-conjugated anti-CD4 and PerCP-Cy5.5 conjugated anti-CD8 antibodies for IFN γ analysis, or with PerCP-Cy5.5-conjugated anti-CD8 and PE-Cy7-conjugated anti-CD4 and then incubated at 4°C for 30 minutes. Cells were then washed twice with PBS, fixed and permeabilized for 20 min. Cells were then washed and incubated with PE-conjugated anti-IL-2, Alexa Fluor 700-conjugated anti-IFN γ and APC-conjugated anti-TNF 4°C for 30 minutes. Stained cells were washed

twice with permeablizing wash buffer, resuspended in PBS containing 1% paraformaldehyde and analyzed by flow cytometry.

Results

Data demonstrate successful transduction of E5-NLD-TCR in PBMCs (see *Figure 14*). In addition, transduced CD8⁺ T cells showed higher CD107, IFN γ , TNF α and IL-2 expression compared to nontransduced cells stimulated with the same peptide (see *Figure 15*). Transduced CD4⁺ T cells displayed relatively comparable TNF α and IL-2 expression to CD8⁺ T cells. However, IFN γ and CD107 are notably lower in CD4⁺ T cells, which suggest the contribution of CD8 co-receptor in target binding.

Example 7: T cells engineered to express a TCR from E5 antigen (E5-NLD-TCR) displayed high functional avidity (secondary screening)

Transduced and un-transduced T cells were stimulated with HLA-matched LCL pulsed with different concentrations of cognate antigenic peptide (*i.e.*, (10⁻⁶, 10⁻⁷, 10⁻⁸, 10⁻⁹, 10⁻¹⁰, 10⁻¹¹, 10⁻¹² and 10⁻¹³ mole/L)) for 4 hours in R10 media containing monensin and brefeldin at 37°C, 6.5% CO₂. Cells were then washed and the pellet re-suspended in wash buffer containing FITC-conjugated anti-CD4 and PerCP-Cy5.5-conjugated anti-CD8 antibodies. Following incubation with conjugated antibodies at 4°C for 30 minutes, cells were washed, fixed, and permeabilized for 20 min. Cells were then washed and incubated with PE-anti-IFN γ for 4°C for 30 minutes. The stained cells were further washed and re-suspended in PBS containing 1% paraformaldehyde and analyzed by flow cytometry.

Results

As shown in Figure 16, IFN γ expression was induced in E5-NLD-lenti-transduced PBMC stimulated with HLA-matched (C*05:01 and C*08:02), pulsed LCL. Notably, CD8⁺ T cells showed recognition of LCL pulsed with as little as 10pmol/L NLD peptide (SEQ ID NO. 1); essentially demonstrating functional avidity greater than that of TCR gene-engineered T cells used in other gene therapy trials that have mediated tumor regression (Draper et al., Clin Cancer Res 21: 4431-4439, 2015; Doran et al., Journal of Clinical Oncology 2019 37:30, 2759-2768).

Example 8: T cells engineered to express a TCR from E2 antigen (E5-TLQ-TCR) specifically recognized and killed HLA-A2⁺ HPV-16⁺ tumor cells. (in vitro cytotoxicity)

E2-TLQ-TCR-T cell-mediated cytotoxicity of tumor cell lines at effector-to-target (E/T) ratios of 10:1 and 5:1. Briefly, 2×10^4 target cells per well (CaSki (HPV⁺) and SCC70 (HPV⁻)) were seeded and cultured overnight (17 hours). Effector T cells (E2-TLQ-TCR-T cells) were added at the indicated ratios (see *Figure 17*) when the cell index approached plateau and co-cultured for approximately 4 days to assess cytotoxicity over time. IFN γ treated (100 μ /ml) target cells were also included as control; IFN γ being added to the target cell culture for 24 hours and the culture washed with complete RPMI media prior to assay.

Target cell lysis was evaluated by real time cell analysis through electrical impedance of adherent cells in each well every 15 minutes, until the end of the experiment. Results are reported as a cell index value.

The CaSki cell line (HPV16⁺; HLA-A*02:01⁺) was challenged with E2-TLQ-TCR-T cells (*Figure 17, A*) and with “untransduced” control T cells (*Figure 17, B*). E2-TLQ-TCR-T cells (HLA-A*02:01 restricted) induced cytotoxicity of the HPV16⁺ cancer cell line (CaSki) as indicated by the drop in cell index following addition of E2-TLQ-TCR-T cells. Greater cytotoxicity of IFN γ -treated target (CaSki) cells, relative to untreated, was observed and may be related to enhanced antigen processing and expression of MHC molecules. However untransduced T cells showed no cytotoxicity when added at the same effector-to-target ratio.

Control cell line SCC70 (HPV16⁻ and HLA-A*02:01⁺) was challenged with both E2-TLQ-TCR T cells and untransduced T cells (UT). E2-TLQ-T cells induce antigen-specific cytotoxicity as no cytotoxicity was observed in the HPV16⁻ cell line (SCC70) at 10:1 effector-to-target ratio. (*Figure 17, C*)

INCORPORATION BY REFERENCE

All publications, patents, patent applications and sequence accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as
5 commonly understood by one of skill in the art to which the disclosed invention belongs.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A T cell receptor (TCR) polypeptide having antigenic specificity for human papillomavirus (HPV) 16, wherein the TCR comprises at least one complementary determining region 3 α (CDR3 α) amino acid sequence and at least one CDR3 β amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs. 13 to 52, or 219-226.
2. A TCR polypeptide having antigenic specificity for HPV16, wherein the TCR is specific for antigens comprising at least one epitope having an amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs: 1-12, 217 or 218.
3. The TCR polypeptide of claim 1 or 2, wherein the TCR has antigenic specificity for HPV16 peptides other than E6 and E7.
4. The TCR polypeptide of any one of claims 1 to 3, wherein the TCR has antigenic specificity for any one of HPV16 peptides E1, E2, E4, or E5.
5. The TCR polypeptide of any one of claims 1 to 4, wherein the TCR has antigenic specificity for antigens comprising at least one epitope having an amino acid sequence selected from the amino acid sequences set forth in SEQ ID NOs. 1-7.
6. The TCR polypeptide of claim 4, wherein the TCR comprises a CDR3 α amino acid sequence and CDR3 β amino acid set forth in SEQ ID NOs. 13 and 14, SEQ ID NOs. 25 and 26, or SEQ ID NOs. 51 and 52.
7. The TCR polypeptide of claim 4, wherein the TCR comprises a TCR β amino acid sequence and TCR α chain amino acid set forth in SEQ ID NOs. 59 and 60 or SEQ ID NOs. 61 and 62.
8. A nucleic acid encoding the TCR polypeptide of any one of claims 1 to 7.
9. The nucleic acid of claim 8, comprising any one of the nucleic acid sequences set forth in SEQ ID NOs. 53 to 58, 227, 228, and/or fragments thereof.

10. An isolated nucleic acid comprising a nucleotide sequence encoding one or more polypeptides comprising a TCR comprising an amino acid sequence selected from SEQ ID NOs. 59 to 70, 229-232, or 209 to 216.
11. The nucleic acid of any one of claims 8 to 10, wherein the nucleic acid is an expression vector.
12. The nucleic acid of claim 11, wherein the expression vector is a viral vector.
13. The nucleic acid of claim 12, wherein the viral vector is lentiviral expression vector.
14. An immune cell comprising the nucleic acid of any one of claims 8 to 13.
15. An immune cell expressing the TCR polypeptide of any one of claims 1 to 6.
16. The immune cell of claim 14 or 15, wherein the immune cell is a leukocyte.
17. The immune cell of any one of claims 14 to 16 wherein the immune cell is a lymphocyte, a monocyte, a macrophage, a dendritic cell, a mast cell, a neutrophil, a basophil, or an eosinophil.
18. The immune cell of any one of claims 14 to 17 wherein the immune cell is a lymphocyte selected from an $\alpha\beta$ T cell, $\gamma\delta$ T cell, a Natural Killer (NK) cell, a Natural Killer T (NKT) cell, a B cell, an innate lymphoid cell (ILC), a cytokine induced killer (CIK) cell, a cytotoxic T lymphocyte (CTL), a lymphokine activated killer (LAK) cell, a regulatory T cell, or any combination thereof.
19. The immune cell of claim 18, wherein the immune cell is a cytotoxic T lymphocyte (CTL).
20. The immune cell of claim 18 or 19, wherein the immune cell is a viral antigen-sensitized CTL.
21. The immune cell of any one of claims 18 to 20, wherein the immune cell is a CTL sensitized to a viral antigen from any one of human papilloma virus (HPV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), B.K. virus (BKV), John Cunningham virus (JCV), picornavirus (*e.g.*,

Hepatitis A virus), hepadnavirus (*e.g.*, Hepatitis B virus), hepacivirus (*e.g.*, Hepatitis C virus), deltavirus (*e.g.*, Hepatitis D virus), hepevirus (*e.g.*, Hepatitis E virus), or any combination thereof.

22. The immune cell of any one of claims 18 to 21, wherein the immune cell is an HPV-sensitized CTL.

23. The TCR-expressing cell of any one of claims 15 to 22, wherein the TCR-expressing cell is genetically modified to no longer express one or more immune checkpoint molecules.

24. The TCR-expressing cell of any one of claims 15 to 22, wherein said cell also expresses a dominant-negative form of one or more immune checkpoint molecules.

25. The TCR-expressing cell of any one of claims 15 to 22, wherein said cell also expresses switch receptors specific for one or more immune checkpoint molecules.

26. The TCR-expressing cell of any one of claims 15 to 22, wherein said cell also expresses antibodies, or functional fragments thereof, capable of blocking signaling by one or more checkpoint molecules.

27. The TCR-expressing cell of any one of claims 21 to 26, wherein the immune checkpoint molecules are selected from programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), programmed death-ligand 2 (PD-L2), cytotoxic T lymphocyte antigen-4 (CTLA-4), B- and T-lymphocyte attenuator (BTLA), T cell immunoglobulin mucin-3 (TIM-3), lymphocyte-activation protein 3 (LAG-3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), leukocyte-associated immunoglobulin-like receptor 1 (LAIR1), natural killer cell receptor 2B4 (2B4), CD160, and transforming growth factor β (TGF- β) receptor.

28. The immune cell of any one of claims 23 to 27, wherein the immune checkpoint molecule is PD-1 and/or CTLA-4.

29. A method of treating a HPV-associated cancer or precancerous lesions in a subject, the method comprising administering an effective amount of an adoptive immunotherapy composition comprising the TCR-expressing cells of any one of claims 14 to 28.

30. The method of claim 29, wherein the HPV-associated cancer is a squamous cell carcinoma.
31. The method of claim 29 or 30, wherein the HPV-associated cancer is selected from head and neck cancer (*e.g.*, HNSCCs and the like) and cancers of the cervix, anus, vagina, vulva, penis, tongue base, larynx, and tonsil.
32. The method of claim 28, wherein the HPV-associated precancerous lesion comprises abnormal cell changes and/or precancerous cell changes selected from: cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL), or warts on the cervix.
33. The method of any one of claims 29 to 32, wherein the subject has received, is receiving, or will receive an additional anti-cancer therapy.
34. The method of claim 33, wherein the additional anti-cancer therapy comprises surgery, radiation, chemotherapy, immunotherapy, or hormone therapy.
35. The method of claim 34, wherein the subject has received IFN γ prior to administering the adoptive immunotherapy composition.
36. The method of any one of claims 29 to 35, wherein the adoptive immunotherapy composition is administered intrapleurally, intravenously, subcutaneously, intranodally, intratumorally, intrathecally, intraperitoneally, intracranially, or by direct administration to an organ.
37. The method of any one of claims 29 to 36, wherein the subject is human.
38. The method of claim 37, wherein the TCR-expressing cells of the adoptive immunotherapy composition are derived from the subject.
39. The method of claim 37, wherein the TCR-expressing cells of the adoptive immunotherapy composition are derived from a donor sample, or from a bank or library of donor samples.

40. The method of any one of claims 29 to 39, further comprising administering at least one immune checkpoint inhibitor.
41. The method of claim 40, wherein the immune checkpoint inhibitor comprises an anti-PD-1 antibody, anti-PD-L1 antibody, anti-PD-L2 antibody, anti-CTLA-4 antibody, or a combination thereof.
42. The method of claim 40, wherein the immune checkpoint inhibitor comprises an RNAi molecule such as an antisense RNA molecule (asRNA), micro RNA molecule (miRNA), short hairpin RNA molecule (shRNA), or small interfering RNA molecule (siRNA).
43. The method of claim 40, wherein the immune checkpoint inhibitor comprises a CRISPR RNA (crRNA) molecule.
44. The method of claim 40, wherein the immune checkpoint inhibitor comprises a dominant-negative form of an immune checkpoint molecule.
45. The method of claim 40, wherein the immune checkpoint inhibitor comprises a recombinant switch receptor.
46. The method of any of claims 40 to 45, wherein immune checkpoint inhibitor is expressed by a vector comprising a nucleic acid molecule encoding the immune checkpoint inhibitor, wherein the vector is selected from a DNA vector, an RNA vector, a plasmid, or a viral vector.
47. The method of claim 46, wherein the vector comprising a nucleic acid molecule encoding the immune checkpoint inhibitor is expressed in the TCR-expressing cells of the adoptive immunotherapy composition.
48. A cell bank of comprising cells for adoptive immunotherapy, wherein the cells are the TCR-expressing cells of any one of claims 14 to 28, and wherein the HLA restriction of the TCR-expressing cells is known.

49. A method of treating HPV-associated cancer or precancerous lesions in a subject, the method comprising administering an effective amount of an adoptive immunotherapy composition comprising TCR-expressing cells selected from the cell bank of claim 48.

Figure 1

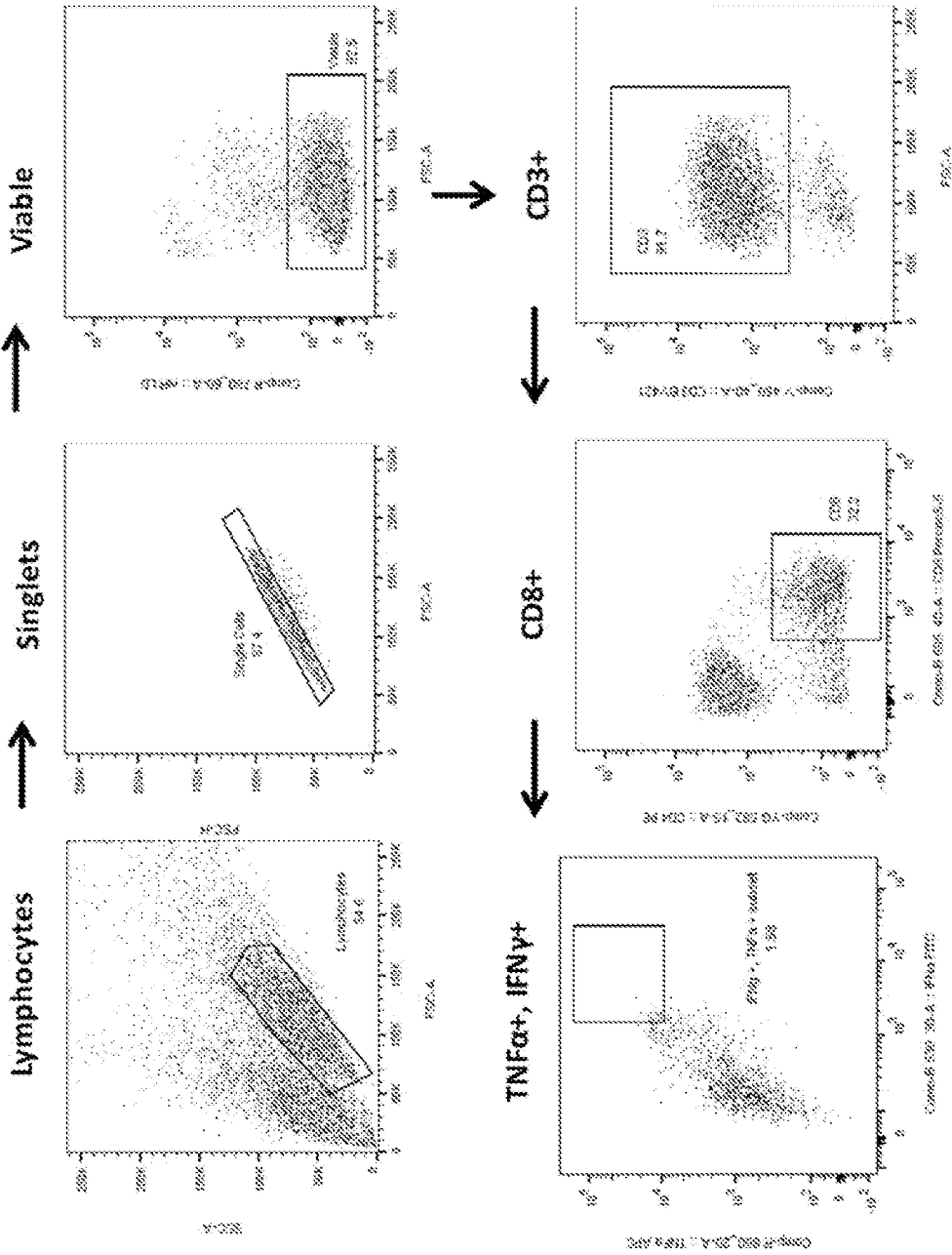


Figure 2

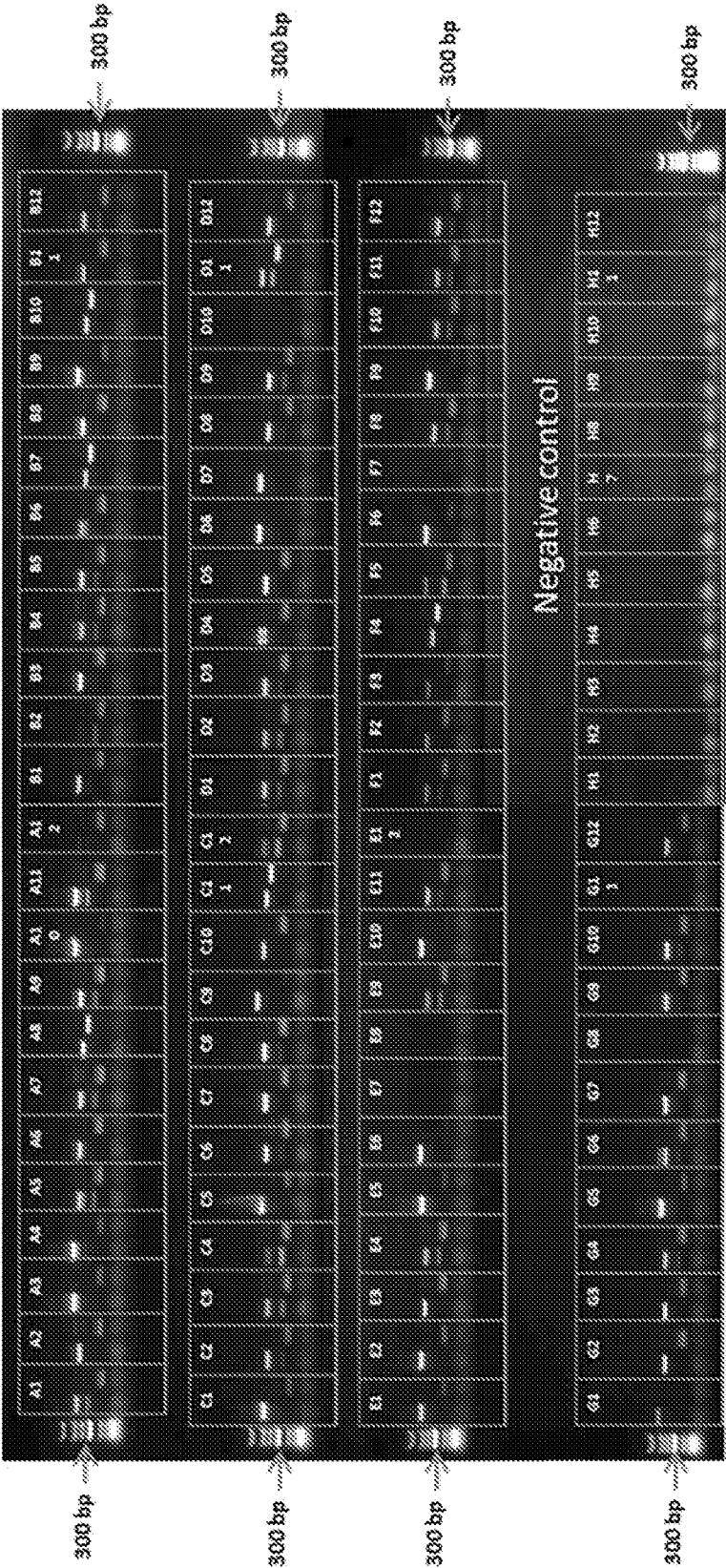


Figure 3

E2-TLQ-TCR amino acid sequence	
<u>TCR β chain</u>	<u>1 ... 314</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 19</u>
<u>TCR β antigen-specific sites</u>	<u>111 ... 126</u>
<u>TCR α chain</u>	<u>347 ... 366</u>
<u>TCR α signal peptide sequence</u>	<u>347 ... 600</u>
<u>TCR α antigen-specific sites</u>	<u>458 ... 471</u>
<u>FURIN cleavage site</u>	<u>315 ... 318</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>319 ... 322</u>
<u>F2A LINKER</u>	<u>323 ... 346</u>
<u>Murinized amino acids</u>	<u>53, 57, 68, 71, 74, 572 ... 575</u>
<u>cysteine bridge changes</u>	<u>192, 529</u>

1 MDTWLVCWAIFSLKAGLTEPEVTQTPSHQVTOMGOEVILRCVPISNHLYFYWYRQILGO
 61 KVEFLVSFYNNIEISEKSEIFDDQFSVERPDGNSFTLKIRSTKLEDSAMYFCASRASVGVG
 121 TGELFFGEGSRLTVLEDLKNVFPPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSW
 181 WVNGKEVHSGVCTDPOPLKEQPALNDSRYCLSSRLRVSATFWQNP RNHFRCOVQFYGLSE
 241 NDEWTQDRAKPVTQIVSAEAWGRADCGITSASYHOGVLSATILYEILLGKATLYAVLVSA
 301 LVLMMVVRKDSRGRKRSGSGAPVKQTLNFDLLKLAGDVESNPGPMTRVSLWAVVST
 361 CLESCMAQTVTOSQPEMSVOEAETVTLSTYDTSESNYLFWYKOPPSROMILVIRQ EAY
 421 KQONATENRFSVNFOKAAKSFSLKISDSQLGDTAMYFCAFTYGGSGGNLIFGKGTKLSVK
 481 PNIQNPDPVAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKCVLDMRSMDFKS
 541 NSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVPCDVKLVEKSFETDTNLNFQNL SVIG
 601 FRILLKLVAGFNLLMTLRLWSS (SEQ ID NO. 209)

Figure 4

E5-NLD-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 312</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 21</u>
<u>TCR β antigen-specific sites</u>	<u>111 ... 126</u>
<u>TCR α chain</u>	<u>347 ... 599</u>
<u>TCR α signal peptide sequence</u>	<u>347 ... 364</u>
<u>TCR α antigen-specific sites</u>	<u>456 ... 470</u>
<u>FURIN cleavage site</u>	<u>313 ... 317</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>318 ... 322</u>
<u>F2A LINKER</u>	<u>323 ... 346</u>
<u>Murinized amino acids</u>	<u>153, 157, 268, 271, 274</u>
<u>cysteine bridge changes</u>	<u>192, 528</u>

1 MGTSLLCWVVLGFLGTDHTGAGVSQSPRYKVTKRGQDVALRCDPISGHVSLYWYRQALGO
 61 GPEFLTYFNYEAQODKSGLPNDRFSAERPEGSISTLTIORTEORDSAMYRCASSPELAGP
 121 QETOYFGPGTRLLVLEDLNKVFPPPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHVELSW
 181 WVNGKEVHSGVCTDPOPLKEQOPALNDSRYCLSSRLRVSATFWONPRNHFRFCQVQFYGLSE
 241 NDEWTQDRAKPVTOIVSAEAWGRADCGITSASYHQGVLSATILYEILLGKATLYAVLVSA
 301 LVLAMAMVKRKDFRAKRS GSGAPVKQTLNFDLLKLAGDVESNPGPMLTASLLRAVIASICV
 361 VSSMAOKVTOAOTEISVVEKEDVTLDVCYETRDTTYLFWYKOPPSGELVFLIRRNSFDE
 421 ONEISGRYSWNFQKSTSSFNFTITASQVVD SAVYFCALSEGGSQGNLIFGKGTKLSVKP
 481 NIONPDPVAVYQLRDSKSSDKSVCLFTDFDSQTNVSQKSDSVYITDKCVLDMRSMDFKSN
 541 SAVAWSNKSDFACANAFNNSIIPEDTFFPS SDVPCDVKLVEKSFETDTNLNLFQNL SVIGF
 601 RILLKLVAGFNLLMTLRLWSS (SEQ ID NO.210)

Figure 5

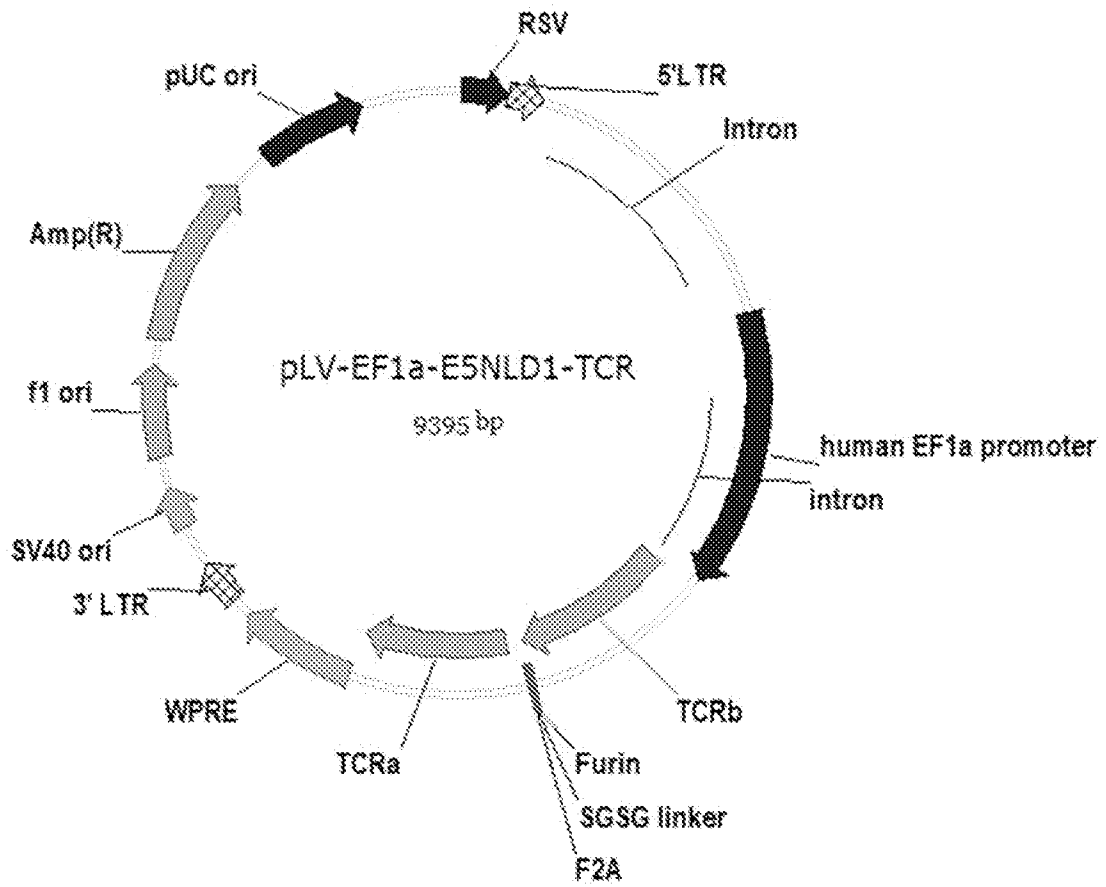


Figure 6

E6-AFR-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 311</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 21</u>
<u>TCR β antigen-specific sites</u>	<u>110 ... 125</u>
<u>TCR α chain</u>	<u>344 ... 596</u>
<u>TCR α signal peptide sequence</u>	<u>344 ... 364</u>
<u>TCR α antigen-specific sites</u>	<u>455 ... 466</u>
<u>FURIN cleavage site</u>	<u>312 ... 315</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>316 ... 319</u>
<u>F2A LINKER</u>	<u>320 ... 343</u>
<u>Murinized amino acids</u>	<u>52, 56, 267, 270, 273, 568 ... 571</u>
<u>cysteine bridge changes</u>	<u>191, 525</u>

1 MTIRLLCYMGPFYFLGAGIMEADYOTPRYLVIGTGKKITLECSQTMGHDKMYWYQODPGM
 61 ELHLIHYSYGVNSTEKGDLSSSESTVSRIRTEHFPLTLESARPSHTSOYLCASSGPGOGHN
 121 OPOHFGDGTRLSILEDLNKVFPPEVAVFEPSSKAEIAHTOKATLVCLATGFFPDHVELSWW
 181 VNGKEVHSGVCTDPOPLKEQPALNDSRYCLSSRLRVSATFWQNP RNHFRCQVQFYGLSEN
 241 DEWTQDRAKPVTOIVSAEAWGRADCGITSAHYHQGVLSATILYEILLGKATLYAVLVSAL
 301 VLMAMVKRKDFRAKRSGSGAPVKQTLNFDLLKLAGDVESNPGPMLTASLLRAVIASICVV
 361 SSMAQKVTOAQTEISVVEKEDVTLDCVYETRDTTYLFWYKOPPSGELVFLIRNSFDEQ
 421 NEISGRYSWNFOKSTSSFNFTITASQVVDASAVYFCALGSSGTYKYIFGTGTRLKVLANIQ
 481 NPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKCVLDMRSMDFKSNSAV
 541 AWSNKSDFACANAFNNSIIPEDTFFPSSDVPCDVKLVEKSFETDTNLNFQNLVIGFRIL
 601 LLKVAGFNLLMTLRLWSS (SEQ ID NO.211)

Figure 7

E6-TIH-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 310</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 21</u>
<u>TCR β antigen-specific sites</u>	<u>110 ... 124</u>
<u>TCR α chain</u>	<u>343 ... 589</u>
<u>TCR α signal peptide sequence</u>	<u>343 ... 360</u>
<u>TCR α antigen-specific sites</u>	<u>447 ... 460</u>
<u>FURIN cleavage site</u>	<u>311 ... 314</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>315 ... 318</u>
<u>F2A LINKER</u>	<u>319 ... 342</u>
Murinized amino acids	151, 155, 266, 269, 272, 561 ... 564
cysteine bridge changes	190, 518

1 MGPOLLGYVVLCLLGAGPLEAQVTQNPRLITVTGKKLTVTCSONMNHEYMSWYRQDPGL
 61 GLRQIYYSMNVEVTDKGDVPEGYKVS RKEKRNFP LILESPSPNQTSLYFCASSPOGRINS
 121 PLHFGNGTRLTVTEDLNKVFPPEVAVFEPSKAEIAHTOKATLVCLATGFFPDHVELSWWV
 181 NGKEVHSGVCTDPOPLKEQPALNDSRYCLSSRLRVSATFWQNP RNHFRCOVQFYGLSEND
 241 EWTDRAKPVTOIVSAEAWGRADCGITSA SYHQGVLSATILYEILLGKATLYAVLVSAIV
 301 LMAMV KRKDFRAKRS GSGAPVKQTLNFDLLKLAGDVESNPGPMQGVFLLYVSMKMGQTG
 361 ONIDOPTEMTATEGAIVQINCTYQTS GFNGLFWYQOHAGEAPTFLSYNVLDGLEEKGRFS
 421 SFLSRSKGYSYLLKELQMKDSASYLC AVRDTGYGQNFVFGPGTRL SVLPYIQNPDPVAVY
 481 QLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCVLDMRSMDFKSNSAVAWSNKSD
 541 FACANAFNNSIIPEDTFFPS SDVPCDKLVEKSFETDTNLNFQNL SVIGFRILLKLVAGE
 601 NLLMTLRLWSS (SEQ ID NO.212)

Figure 8

E6-HDI-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 317</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 21</u>
<u>TCR β antigen-specific sites</u>	<u>119 ... 129</u>
<u>TCR α chain</u>	<u>350 ... 596</u>
<u>TCR α signal peptide sequence</u>	<u>350 ... 368</u>
<u>TCR α antigen-specific sites</u>	<u>454 ... 467</u>
<u>FURIN cleavage site</u>	<u>318 ... 321</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>322 ... 325</u>
<u>F2A LINKER</u>	<u>326 ... 349</u>
<u>Murinized amino acids</u>	<u>155, 159, 271, 274, 277, 568 ... 571</u>
<u>cysteine bridge changes</u>	<u>195, 525</u>

1 MLLLLLLLGPGISLLLPGLAGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFW
 61 YRQFPKQSLMLMATSNEGSKATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYICS
 121 AREGYRSYFGPGTRLTVLEDLKNVFPPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHVE
 181 LSWWVNGKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFRСQVQFYG
 241 LSENDEWTQDRAKPVTQIVSAEAWGRADCGITSASYHQGVLSATILYEILLGKATLYAVL
 301 VSALVLMAMVKRKDSRGRKRS GSGAPVKQTLNFDLLKLAGDVESNPGPMRLVAFVTVFL
 361 TFGTLLIDAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNN
 421 ETNEMASLIITEDRKSSTLILPHATLRDTAVYYCIVRDRSYGQNFVFGPGTRL SVLPYIQ
 481 NPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCVLDMRSMDFKSNSAV
 541 AWSNKSDFACANAFNNSIIPEDTFFPSSDVPСDVKLVKESFETDTNLNFQNL SVIGFRIL
 601 LLKVAGFNLLMTLRLWSS (SEQ ID NO.213)

Figure 9

E6-KQR-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 318</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 21</u>
<u>TCR β antigen-specific sites</u>	<u>119 ... 130</u>
<u>TCR α chain</u>	<u>351 ... 608</u>
<u>TCR α signal peptide sequence</u>	<u>351 ... 371</u>
<u>TCR α antigen-specific sites</u>	<u>460 ... 474</u>
<u>FURIN cleavage site</u>	<u>319 ... 322</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>323 ... 326</u>
<u>F2A LINKER</u>	<u>327 ... 350</u>
<u>Murinized amino acids</u>	<u>137, 141, 272, 275, 278, 580 ... 583</u>
<u>cysteine bridge changes</u>	<u>196, 537</u>

1 MLLLLLLLGPGISLLLPGLAGSGLGAVVSQHPSWVICKSGTSVKIECRSLDFQATTMFW
 61 YRQFPKQSLMLMATSNEGCKATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYICS
 121 TAGETD~~TOY~~FGPGTRLTVLEDLKNVFPPEVAVFEPSKAEIAHTQKATLVCLATGFFPDHV
 181 ELSWVNGKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFRСQVQFY
 241 GLSENDEWTQDRAKPVTQIVSAEAWGRADCGITSASYHQGVLSATILYEILLGKATLYAV
 301 LVSALVLMAMVKRKDSRGRAKRSGSGAPVKQTLNFDLLKLAGDVESNPGPMAGIFALEMY
 361 LWLQLDWVSEGESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPOFIIDI
 421 RSNMDKRQGORVTVLLNKTVKHLSLQIAATQPGDSAVYFCAETLGLDQGGKLIFGQGTTEL
 481 SVKPNIQNPD~~SV~~KPNPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKCVLD
 541 MRSMDFKSNSAVAWSNKSDFACANAFNNSIIPEDTFFPSSDVP~~CD~~VKLVEKSFETDTNLN
 601 FQNL~~SV~~IGFRILLKLVAGFNLLMTLRLWSS (SEQ ID NO.214)

Figure 10

E7-TPT-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 311</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 19</u>
<u>TCR α chain</u>	<u>344 ... 614</u>
<u>TCR α signal peptide sequence</u>	<u>344 ... 360</u>
<u>FURIN cleavage site</u>	<u>312 ... 315</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>316 ... 319</u>
<u>F2A LINKER</u>	<u>320 ... 343</u>
<u>Murinized amino acids</u>	<u>152, 156, 267, 270, 273, 564 ... 567</u>
<u>cysteine bridge changes</u>	<u>191, 521</u>

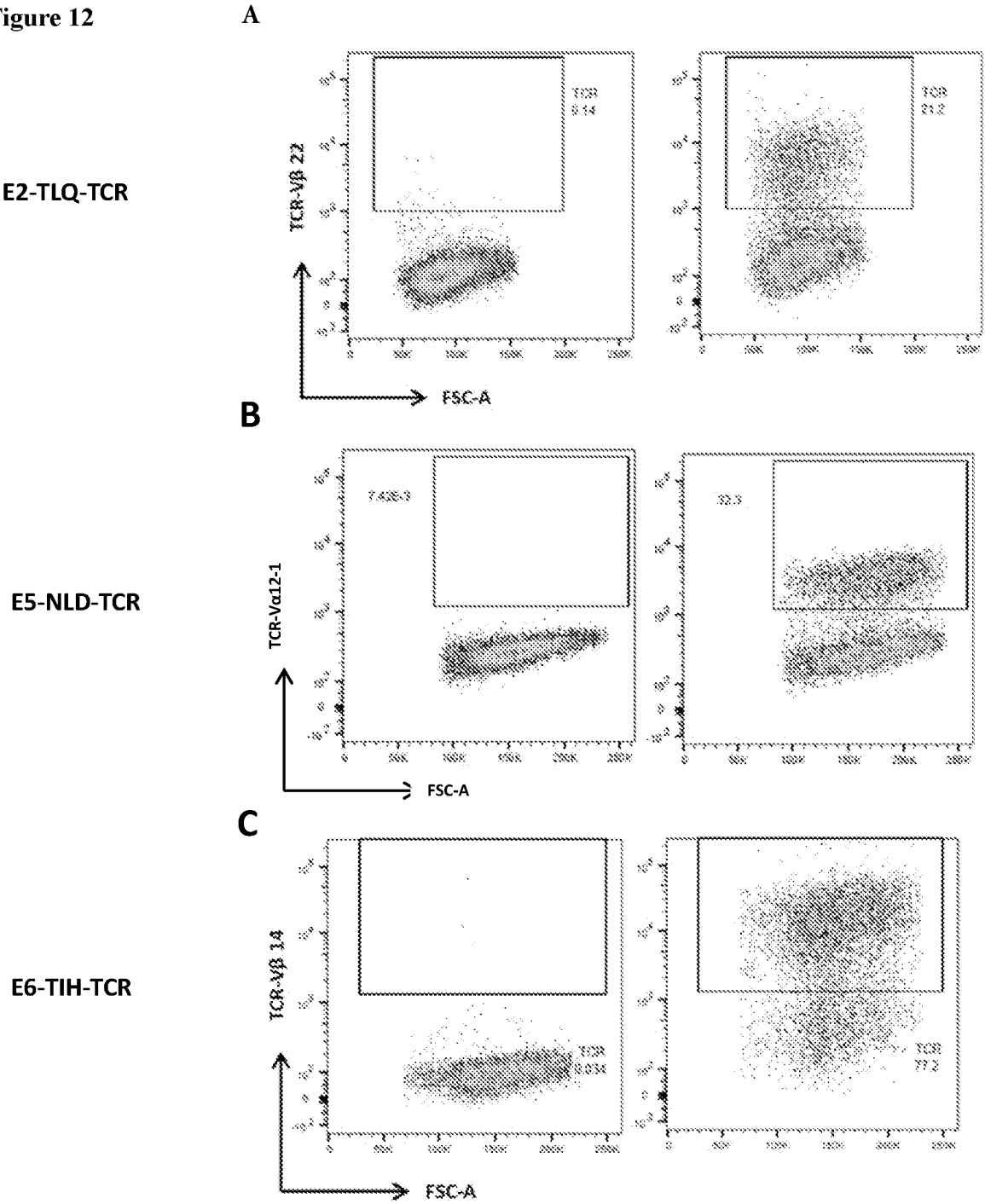
1 MGCRIILCCVVFCLLQAGPLDTAVSOTPKYLVTO MGNDKSIKCEQNLGHDTMYWYKQDSKK
 61 FLKIMFSYNNKELINETVPNRFSPKSPDKAHLNLHINSLELGDSAVYFCASSOGTGRGN
 121 TEAFFGQGTRLTVVEDLNKVFPEVAVFEP SKAEIAHTQKATLVCLATGFYPDHVELSWW
 181 VNGKEVHSGVCTDPOPLKEQPALNDSRYCLSSRLRVSATFWONPRNHFERCQVQFYGLSEN
 241 DEWTQDRAKPVTQIVSAEAWGRADCGITSA SYHQGVLSATILYEILLGKATLYAVLVSAL
 301 VLAMVKKRDFRAKRSGSGAPVKQTLNFDLLKLAGDVESNPGPMFOVARVIVFELTSLTSL
 361 LAKTTOPI SMDSYEGQEVNITCSHNNIATNDYITWYQOFPSOGPRFIIQGYKTKVTNEVA
 421 SLFIPADRKSSTLSLPRVSLSDTAVYYCLVGPYFGGGSYQLTFGKGTKLSVIPNIONPDP
 481 AVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKC VLDMRSMDFKSNSAVAWSN
 541 KSDFACANAFNN SIIPEDTFFPSSDVP CDVKLVEKSFETDTNLFQNL SVIGFRILLKLV
 601 AGFNLLMTLRLWSS (SEQ ID NO.215)

Figure 11

E5-SAF-TCR amino acid sequences	
<u>TCR β chain</u>	<u>1 ... 318</u>
<u>TCR β signal peptide sequence</u>	<u>1 ... 19</u>
<u>TCR α chain</u>	<u>351 ... 629</u>
<u>TCR α signal peptide sequence</u>	<u>351 ... 370</u>
<u>FURIN cleavage site</u>	<u>319 ... 322</u>
<u>SGSG LINKER (SEQ ID NO: 233)</u>	<u>323 ... 326</u>
<u>F2A LINKER</u>	<u>327 ... 350</u>
<u>Murinized amino acids</u>	<u>157, 161, 272, 275, 278, 579 ... 582</u>
<u>cysteine bridge changes</u>	<u>196, 536</u>

1 MGTRLLFWVAFCLLGADHTGAGVSQSPSNKVTEKGKDVELRCDPISGHTALYWYRQSLGO
 61 GLEFLIYFQNSAPDKSGLPSDRFSAERTGGSVSTLTIQRTQQEDSAVYLCASSLGQGAV
 121 GTDTOYFGPGTRLTVLEDRKTLKNVFPPEVAVFEPSKAEIAHTQKATLVCLATGFYPDHV
 181 ELSWVNGKEVHSGVCTDPQPLKEQPALNDSRYCLSSRLRVSATFWQNPРНHFCQVQFY
 241 GLSENDEWTQDRAKPVTOIVSAEAWGRADCGITSASYHQGVLSATILYEILLGKATLYAV
 301 LVSALVLMAMVKRKDSRGRAKRSGSGAPVKOTLNFDLLKLAGDVESNPGPMTEVSLWAV
 361 VVSTCLESQMAQTVTOSQPEMSVQEAETVTLSCTYDTSENNYYLFWYKOPPSRQMLVIR
 421 QEAYKQONATENRFSVNFQKAASFSLKISDSQLGDTAMYFCAFMKPDGSGNTGKLIFGO
 481 GTTLOVKPNIQNPDAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKSDVYITDKCVLDM
 541 RSMDFKNSAVAWSNKSDFACANAFNNSIIPEDTEFFPSSDVPCDVKLVEKSFETDTNLNF
 601 QNLVIGFRILLKLVAGFNLLMTLRLWSS (SEQ ID NO.216)

Figure 12



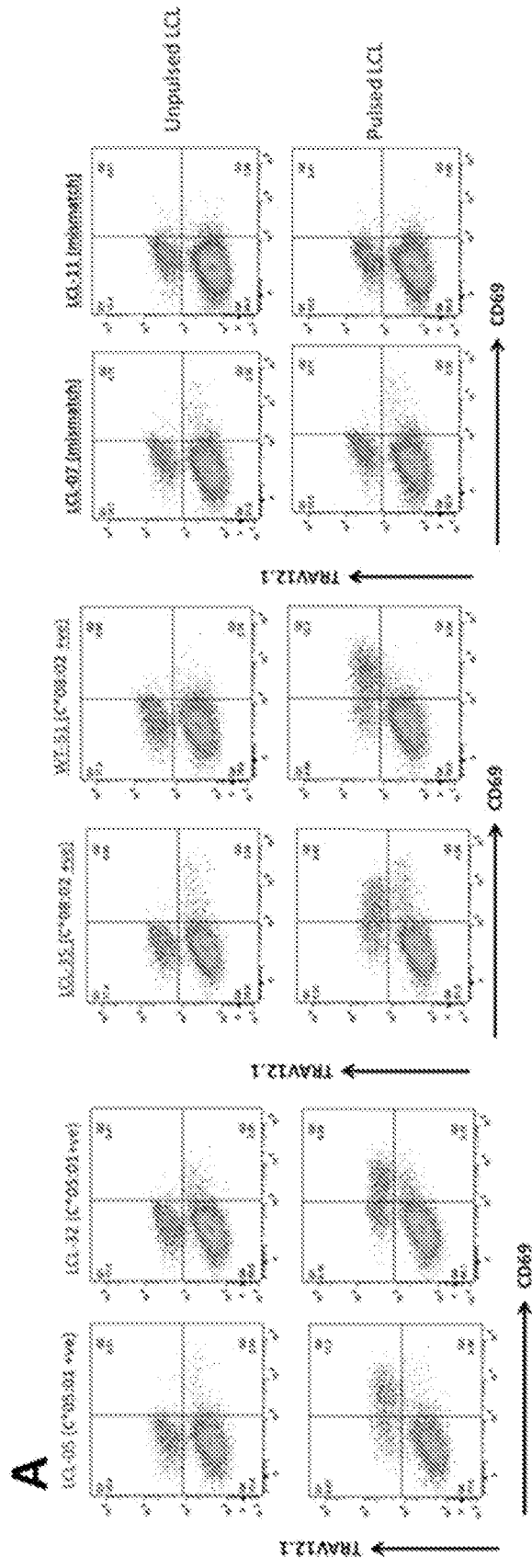


Figure 13

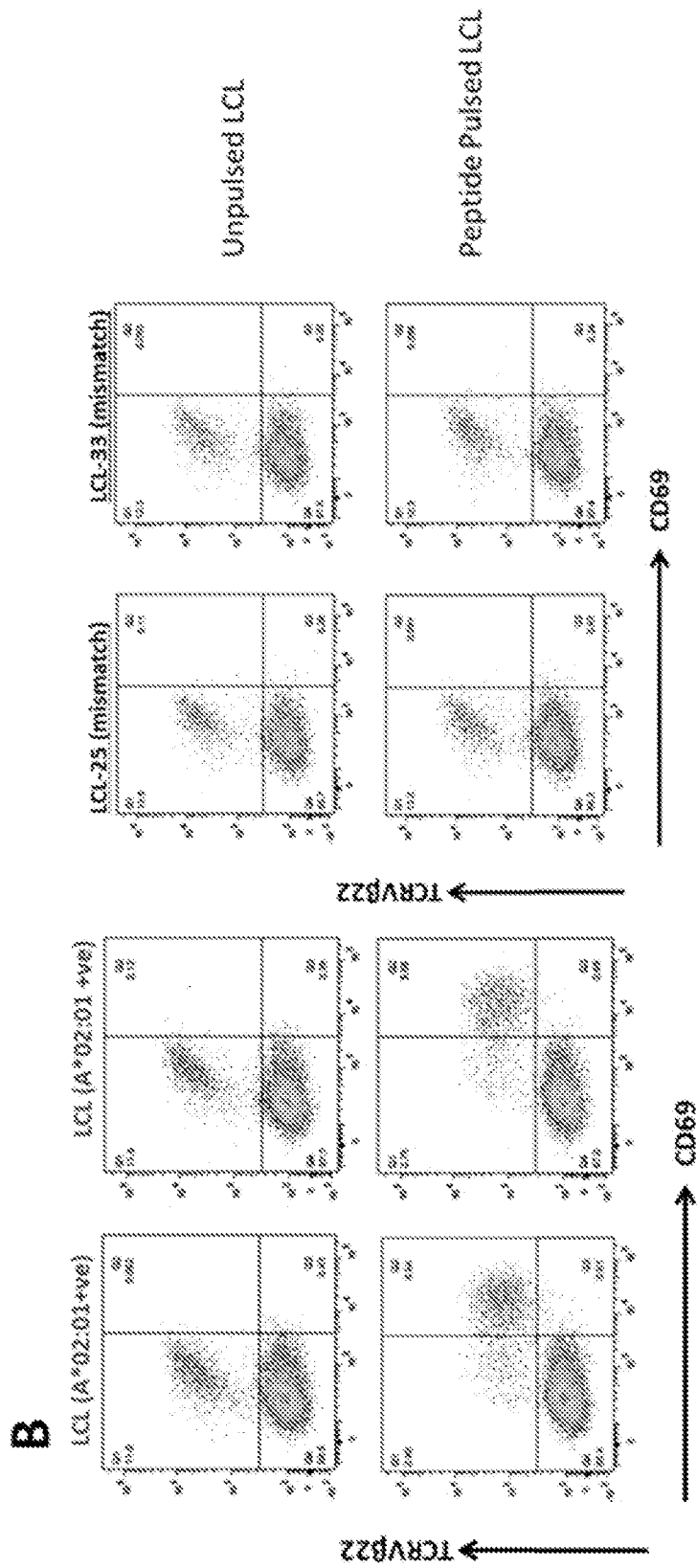


Figure 13 cont.

Figure 14

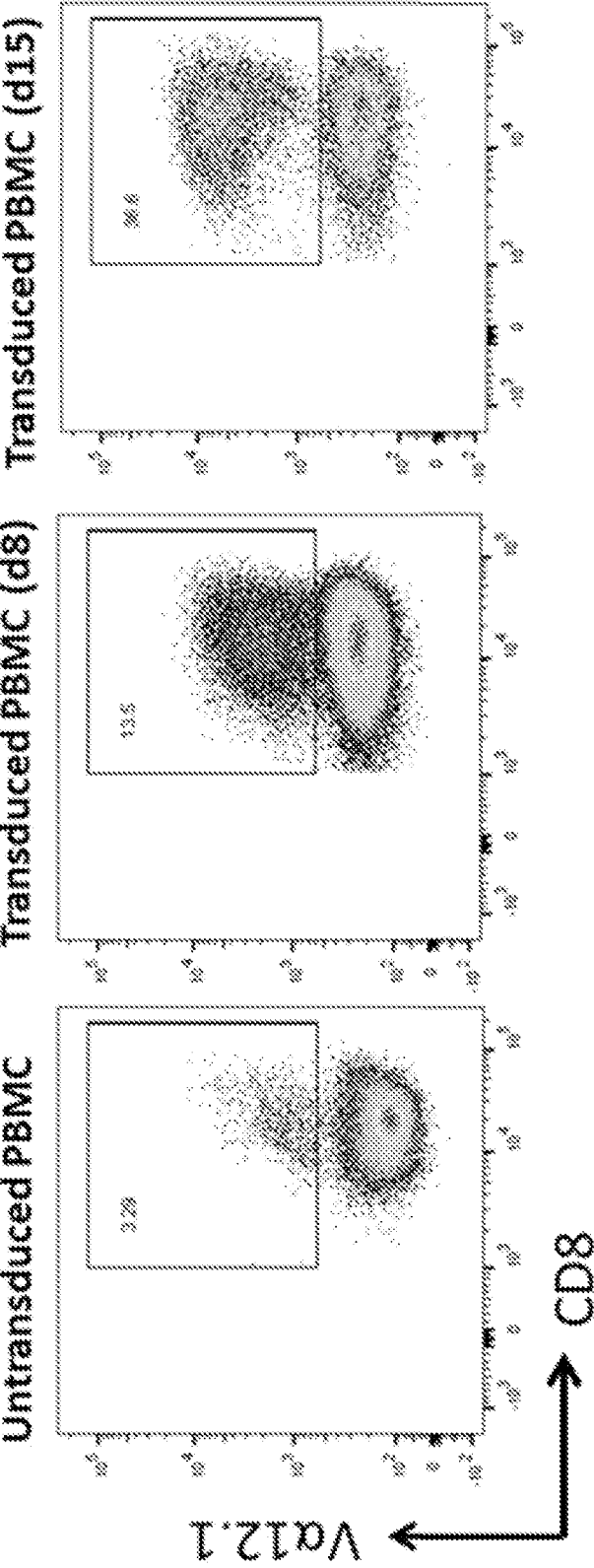


Figure 15

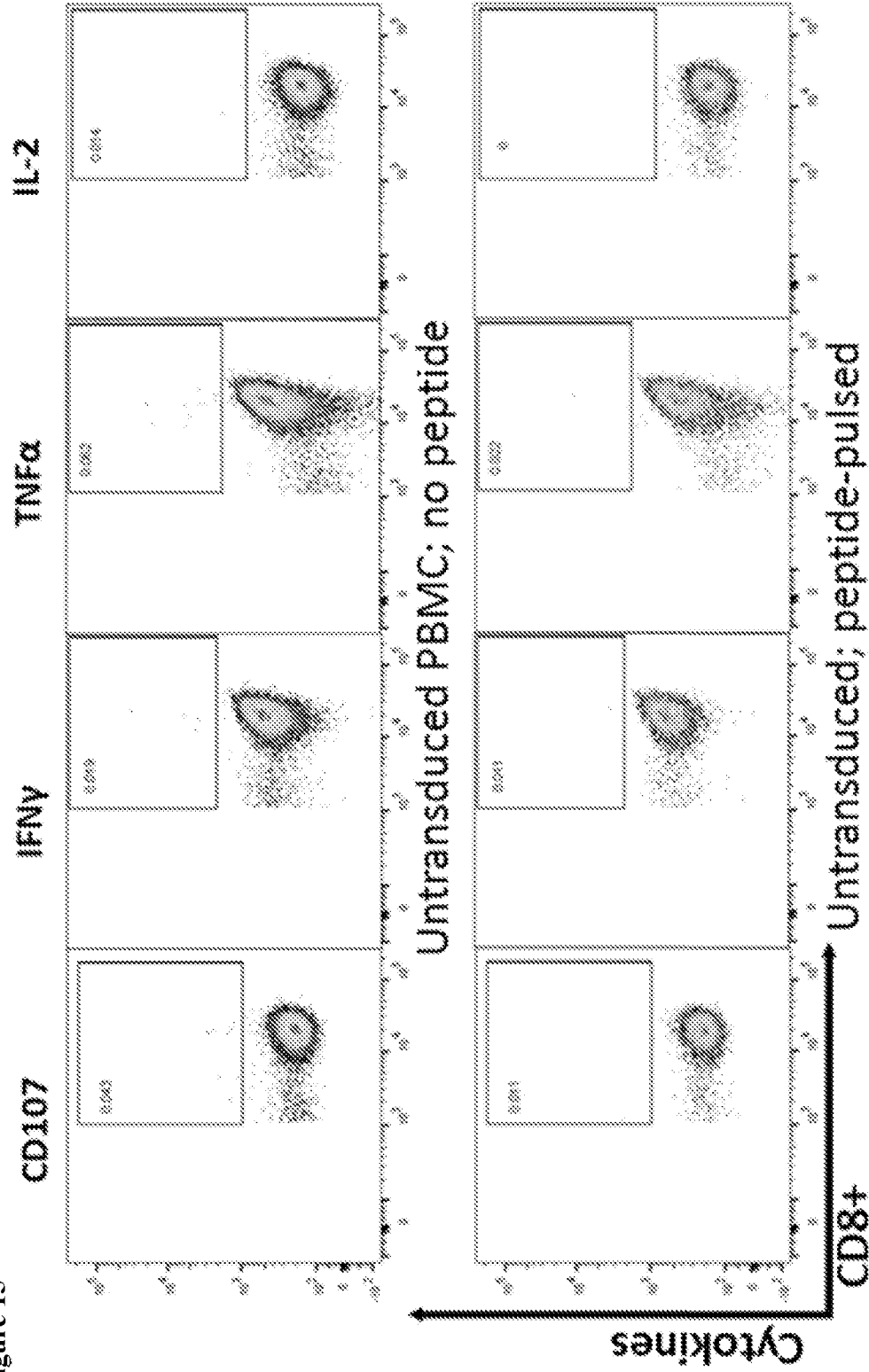


Figure 15 cont.

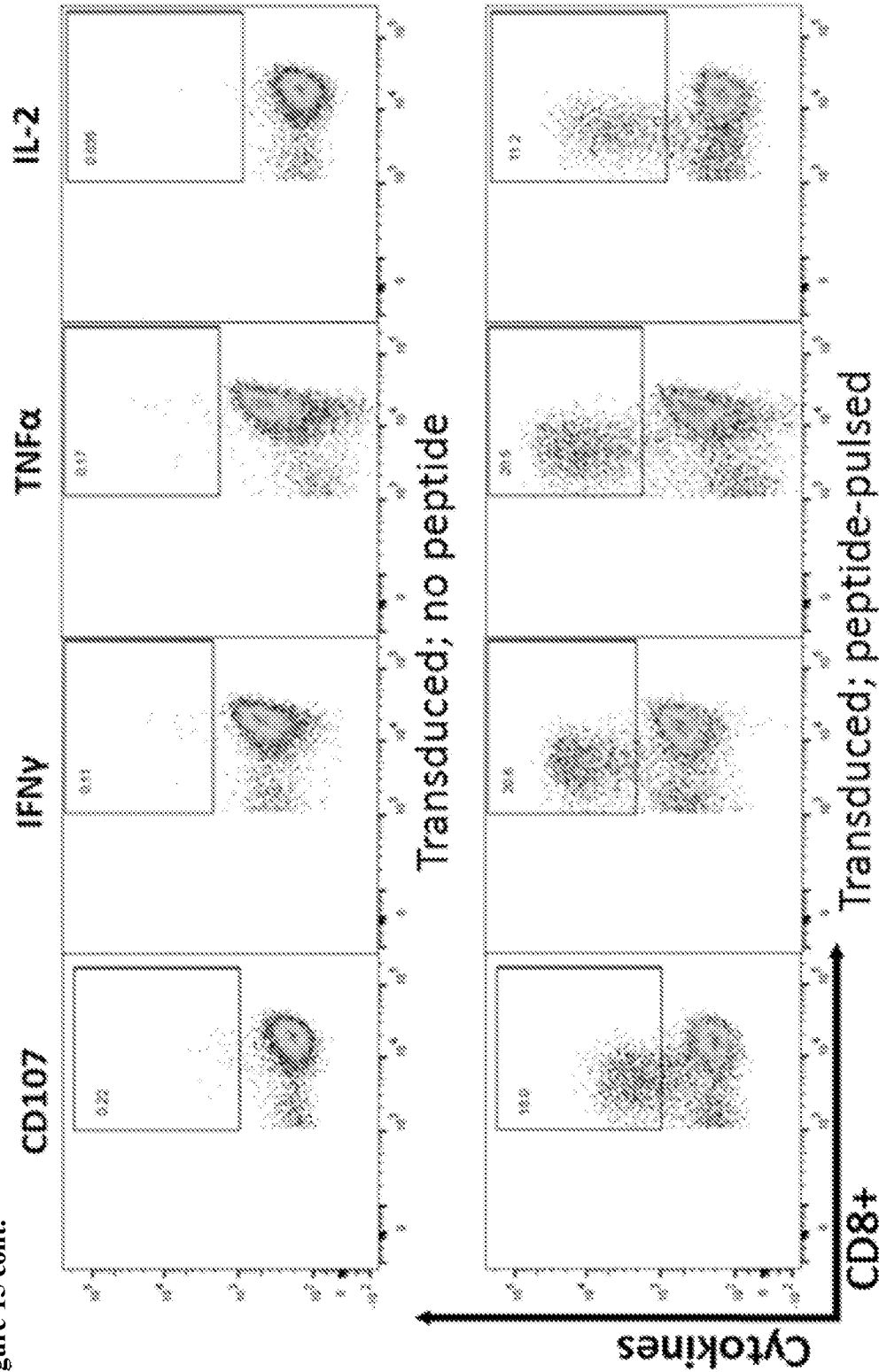


Figure 15 cont.

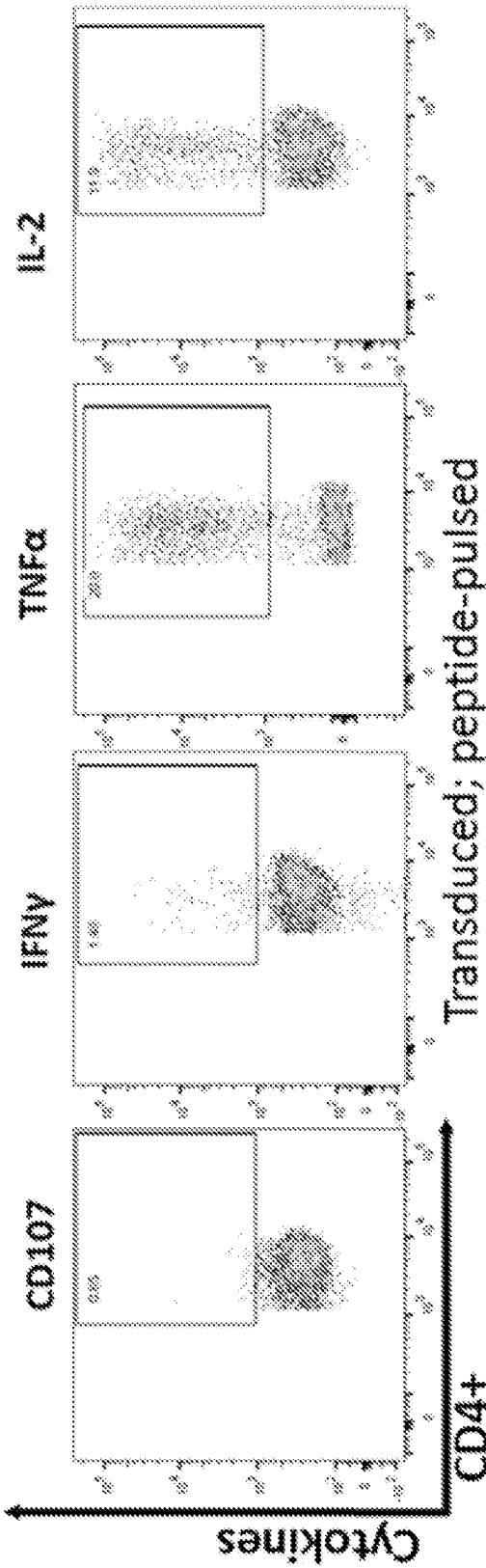


Figure 16

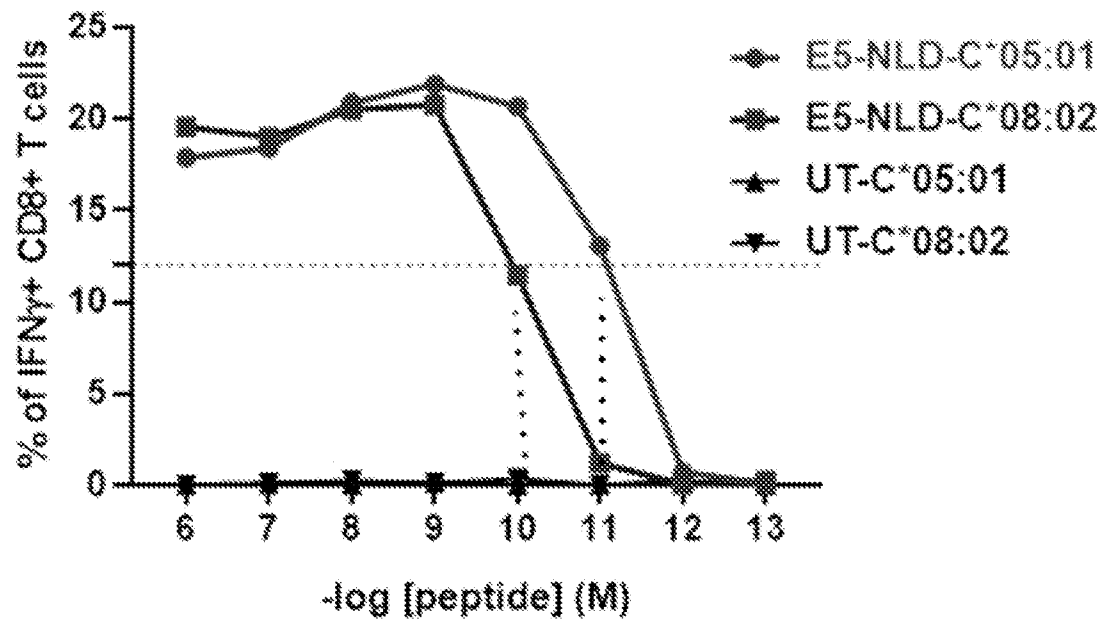


Figure 17

A

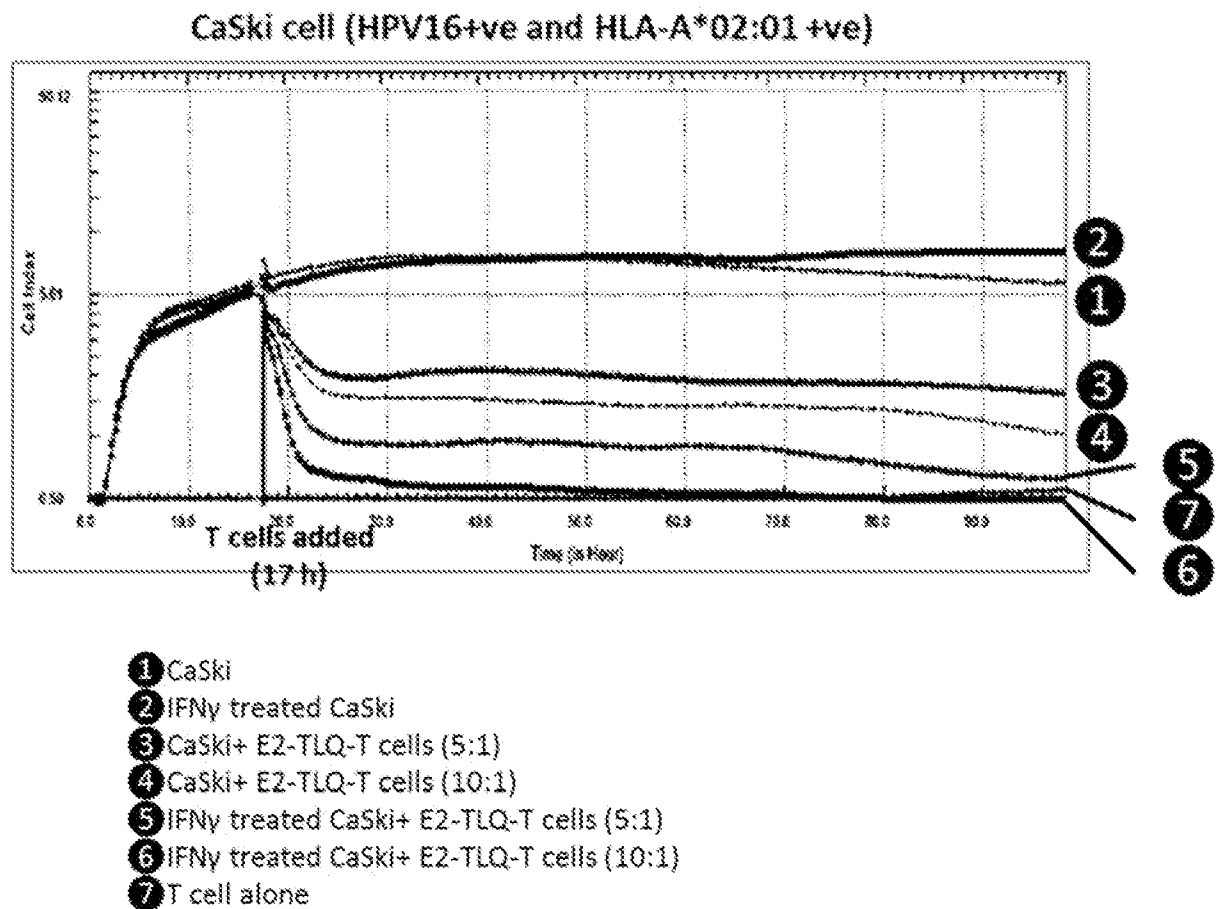
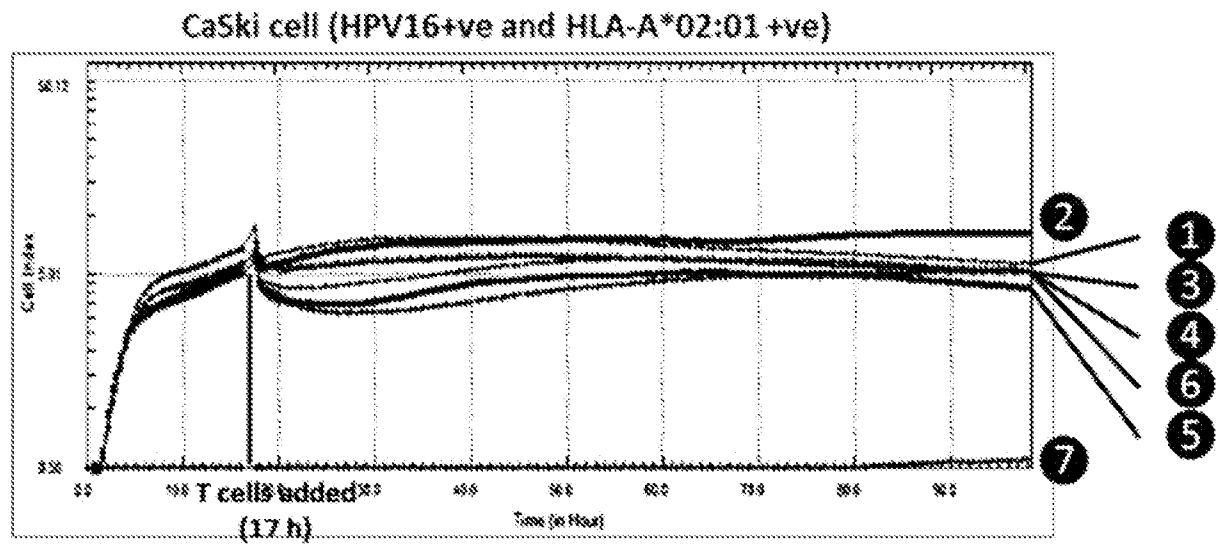


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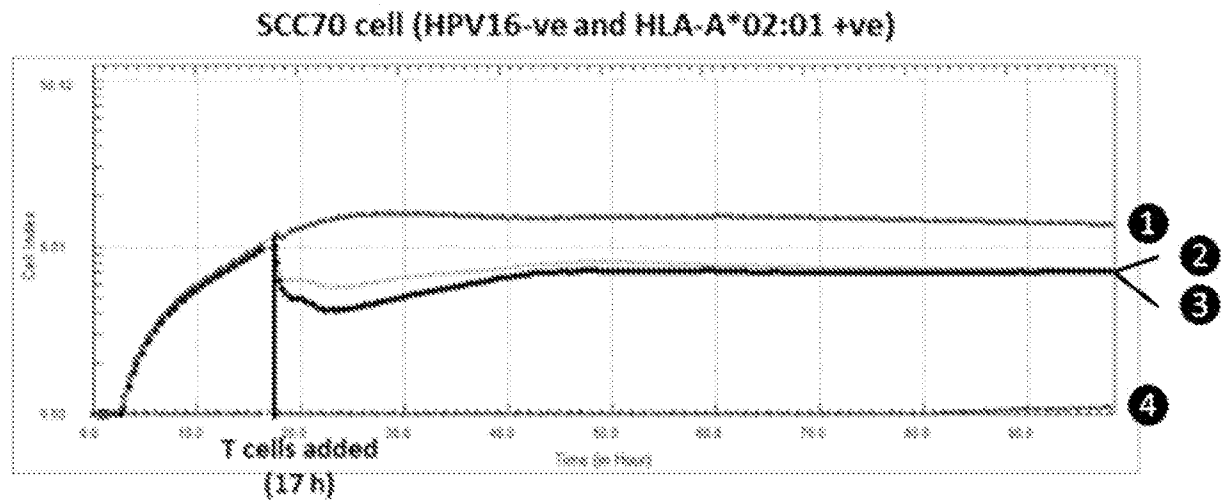
B



- ① Caski
- ② IFN γ treated CaSki
- ③ CaSki+ UT-T cells (5:1)
- ④ CaSki+ UT-T cells (10:1)
- ⑤ IFN γ treated CaSki+ UT-T cells (5:1)
- ⑥ IFN γ treated CaSki+ UT-T cells (10:1)
- ⑦ T cell alone

Figure 17 cont.

C



- ① IFN γ treated SCC70
- ② IFN γ treated SCC70+ UT-T cells (10:1)
- ③ IFN γ treated SCC70+ E2-TLQ-T cells (10:1)
- ④ T cell alone

SEQUENCE LISTING

<110> THE COUNCIL OF THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH

<120> COMPOSITIONS AND METHODS FOR TARGETING HPV-INFECTED CELLS

<130> QAH-02325

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<400> 9
Ala Leu Asp Gly Asn Leu Val Ser Met Asp Val
1 5 10

<210> 10
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<212> PRT
<213> Human papillomavirus 18

<400> 10
Thr Val Leu Glu Leu Thr Glu Val Phe Glu Phe
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<400> 11
Ser Pro Ala Thr Ala Phe Thr Val Tyr
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<210> 12
<211> 19
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Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu Asp Leu Leu Met
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<223> Description of Artificial Sequence: Synthetic
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<210> 14
<211> 16
<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 14

Cys Ala Ser Ser Pro Glu Leu Ala Gly Pro Gln Glu Thr Gln Tyr Phe
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<210> 15

<211> 11

<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 15

Cys Ala Val Ser Asp Arg His Asp Met Arg Phe
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<210> 16

<211> 14

<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 16

Cys Ala Ser Ser Tyr Ser Pro Glu Arg His Glu Gln Phe Phe
1 5 10

<210> 17

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 17

Cys Ala Ser Glu Gly His Asp Met Arg Phe
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<210> 18

<211> 16

<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 18

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<210> 19

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 19

Cys	Ile	Val	Arg	Asp	Arg	Ser	Tyr	Gly	Gln	Asn	Phe	Val	Phe
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<210> 20

<211> 11

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 20

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<210> 21

<211> 14

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 21

Cys	Ala	Arg	Gly	Leu	Glu	Asn	Ala	Gly	Asn	Met	Leu	Thr	Phe
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<210> 22

<211> 14

<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 22

Cys	Ala	Thr	Ser	Val	Arg	Gly	Thr	Gln	Pro	Gln	His	Phe	Phe
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<210> 23

<211> 15

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 23

Cys	Ala	Leu	Ser	Glu	Arg	Gly	Ser	Gly	Gly	Phe	Lys	Thr	Ile	Phe
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<210> 24

<211> 22

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 24

Cys	Ala	Ser	Ser	Ser	Gly	Glu	Lys	Gly	Gln	Gly	Ala	Pro	Val	Ser	Ser
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Tyr	Glu	Gln	Tyr	Phe	Phe
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<210> 25

<211> 14

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 25

Cys Ala Phe Thr Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe
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<210> 26

<211> 16

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 26

Cys Ala Ser Arg Ala Ser Val Gly Val Gly Thr Gly Glu Leu Phe Phe
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<210> 27

<211> 10

<212> PRT

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 27

Cys Ala Leu Ser Gly Asn Met Leu Thr Phe
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<223> Description of Artificial Sequence: Synthetic
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<400> 28

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<210> 29

<211> 15

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<223> Description of Artificial Sequence: Synthetic
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<400> 29

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<211> 18

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<223> Description of Artificial Sequence: Synthetic
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<400> 30

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Phe Phe

<210> 31

<211> 14

<212> PRT

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<223> Description of Artificial Sequence: Synthetic
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<400> 31

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<210> 32

<211> 15

<212> PRT

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<223> Description of Artificial Sequence: Synthetic
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<400> 32

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<210> 33

<211> 12

<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 33

Cys	Ile	Leu	Ser	Ala	His	Asp	Tyr	Lys	Leu	Ser	Phe
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<210> 34

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 34

Cys	Ala	Ser	Ser	Gln	Gly	Gly	Leu	Asn	Ser	Pro	Leu	His	Phe
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<400> 35

Cys	Ala	Met	Arg	Val	Ala	Glu	Gly	Ser	Gln	Gly	Asn	Leu	Ile	Phe
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<210> 36

<211> 15

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 36

Cys	Ala	Ser	Ser	Pro	Trp	Gly	Arg	Gly	Gly	Ser	Pro	Leu	His	Phe
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<210> 37
<211> 15
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 37
Cys Ala Val Lys Phe Asn Thr Asp Gln Gly Gly Lys Leu Ile Phe
1 5 10 15

<210> 38
<211> 15
<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 38
Cys Ala Ser Ser Pro Gln Gly Arg Ile Asn Ser Pro Leu His Phe
1 5 10 15

<210> 39
<211> 12
<212> PRT
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<400> 39
Cys Ala Leu Gly Ser Ser Gly Thr Tyr Lys Tyr Ile
1 5 10

<210> 40
<211> 16
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 40
Cys Ala Ser Ser Gly Pro Gly Gln Gly His Asn Gln Pro Gln His Phe
1 5 10 15

<210> 41
<211> 11
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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 41
Cys Ala Met Arg Glu Ala Asn Asp Met Arg Phe
1 5 10

<210> 42
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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 42
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1 5 10 15

Phe

<210> 43
<211> 15
<212> PRT
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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 43
Cys Ala Glu Thr Leu Gly Leu Asp Gln Gly Gly Lys Leu Ile Phe
1 5 10 15

<210> 44
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<400> 44

Cys Ser Thr Ala Gly Glu Thr Asp Thr Gln Tyr Phe
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<210> 45

<211> 13

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 45

Cys Ala Thr Asp Glu Gly Thr Ala Ser Lys Leu Thr Phe
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<210> 46

<211> 15

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 46

Cys Ser Val Glu Trp Thr Ser Gly Ser Gly Glu Thr Gln Tyr Phe
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<210> 47

<211> 13

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 47

Cys Ala Thr Asp Ala Gly Ser Asp Tyr Lys Leu Ser Phe
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<210> 48

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 48

Cys Ala Ser Ser Leu Glu Pro Gln Tyr Phe
1 5 10

<210> 49

<211> 13

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 49

Cys Ala Thr Asp Glu Gly Thr Gly Asn Gln Phe Tyr Phe
1 5 10

<210> 50

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 50

Cys Ala Ser Ser Trp Asp Thr Gly Thr Glu Thr Gln Tyr Phe
1 5 10

<210> 51

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 51

Cys Ala Phe Pro Ser Ser Gly Thr Tyr Lys Tyr Ile Phe
1 5 10

<210> 52

<211> 12

<212> PRT
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 52

Cys Ala Ser Thr Ala Gly Thr Asp Thr Gln Tyr Phe
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<210> 53

<211> 9395

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic polynucleotide

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<220>

<223> Description of Artificial Sequence: Synthetic
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<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

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<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

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<211> 295

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 59

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Gln Glu Val Ile Leu Arg Cys Val Pro Ile Ser Asn His Leu Tyr Phe
          20           25           30

```

```

Tyr Trp Tyr Arg Gln Ile Leu Gly Gln Lys Val Glu Phe Leu Val Ser
      35           40           45

```

```

Phe Tyr Asn Asn Glu Ile Ser Glu Lys Ser Glu Ile Phe Asp Asp Gln
      50           55           60

```

```

Phe Ser Val Glu Arg Pro Asp Gly Ser Asn Phe Thr Leu Lys Ile Arg
      65           70           75           80

```

```

Ser Thr Lys Leu Glu Asp Ser Ala Met Tyr Phe Cys Ala Ser Arg Ala
          85           90           95

```

```

Ser Val Gly Val Gly Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
      100           105           110

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Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
115 120 125

Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr
130 135 140

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
145 150 155 160

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro
165 170 175

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
180 185 190

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
195 200 205

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
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Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
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Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln
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Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
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Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
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Lys Arg Lys Asp Ser Arg Gly
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<210> 60

<211> 256

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 60

Ala Gln Thr Val Thr Gln Ser Gln Pro Glu Met Ser Val Gln Glu Ala
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Glu Thr Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser Glu Ser Asn Tyr
20 25 30

Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln Met Ile Leu Val
35 40 45

Ile Arg Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr Glu Asn Arg Phe
50 55 60

Ser Val Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser Leu Lys Ile Ser
65 70 75 80

Asp Ser Gln Leu Gly Asp Thr Ala Met Tyr Phe Cys Ala Phe Thr Tyr
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Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu Ser
100 105 110

Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg
115 120 125

Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp
130 135 140

Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr
145 150 155 160

Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser
165 170 175

Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe
180 185 190

Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val
195 200 205

Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn
210 215 220

Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu
225 230 235 240

Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
245 250 255

<210> 61

<211> 291

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 61

Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Thr Lys Arg Gly Gln Asp
1 5 10 15

Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His Val Ser Leu Tyr Trp
20 25 30

Tyr Arg Gln Ala Leu Gly Gln Gly Pro Glu Phe Leu Thr Tyr Phe Asn
35 40 45

Tyr Glu Ala Gln Gln Asp Lys Ser Gly Leu Pro Asn Asp Arg Phe Ser
50 55 60

Ala Glu Arg Pro Glu Gly Ser Ile Ser Thr Leu Thr Ile Gln Arg Thr
65 70 75 80

Glu Gln Arg Asp Ser Ala Met Tyr Arg Cys Ala Ser Ser Pro Glu Leu
85 90 95

Ala Gly Pro Gln Glu Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Leu
100 105 110

Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe
115 120 125

Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu Val
130 135 140

Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp
145 150 155 160

Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln Pro
165 170 175

Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser
180 185 190

Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe
195 200 205

Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr
210 215 220

Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp
225 230 235 240

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly Val
245 250 255

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
260 265 270

Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg
275 280 285

Lys Asp Phe
290

<210> 62

<211> 257

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 62

Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser Val Val Glu Lys
1 5 10 15

Glu Asp Val Thr Leu Asp Cys Val Tyr Glu Thr Arg Asp Thr Thr Tyr
20 25 30

Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Gly Glu Leu Val Phe Leu
35 40 45

Ile Arg Arg Asn Ser Phe Asp Glu Gln Asn Glu Ile Ser Gly Arg Tyr
50 55 60

Ser Trp Asn Phe Gln Lys Ser Thr Ser Ser Phe Asn Phe Thr Ile Thr
65 70 75 80

Ala Ser Gln Val Val Asp Ser Ala Val Tyr Phe Cys Ala Leu Ser Glu
85 90 95

Gly Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
100 105 110

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
115 120 125

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
130 135 140

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
145 150 155 160

Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
165 170 175

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
180 185 190

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
195 200 205

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
210 215 220

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
225 230 235 240

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
245 250 255

Ser

<210> 63

<211> 311

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 63

Met Thr Ile Arg Leu Leu Cys Tyr Met Gly Phe Tyr Phe Leu Gly Ala
1 5 10 15

Gly Leu Met Glu Ala Asp Ile Tyr Gln Thr Pro Arg Tyr Leu Val Ile
20 25 30

Gly Thr Gly Lys Lys Ile Thr Leu Glu Cys Ser Gln Thr Met Gly His
35 40 45

Asp Lys Met Tyr Trp Tyr Gln Gln Asp Pro Gly Met Glu Leu His Leu
50 55 60

Ile His Tyr Ser Tyr Gly Val Asn Ser Thr Glu Lys Gly Asp Leu Ser
65 70 75 80

Ser Glu Ser Thr Val Ser Arg Ile Arg Thr Glu His Phe Pro Leu Thr
85 90 95

Leu Glu Ser Ala Arg Pro Ser His Thr Ser Gln Tyr Leu Cys Ala Ser
100 105 110

Ser Gly Pro Gly Gln Gly His Asn Gln Pro Gln His Phe Gly Asp Gly
115 120 125

Thr Arg Leu Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 64
<211> 254
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 64

Gln	Lys	Val	Thr	Gln	Ala	Gln	Thr	Glu	Ile	Ser	Val	Val	Glu	Lys	Glu
1				5				10					15		

Asp	Val	Thr	Leu	Asp	Cys	Val	Tyr	Glu	Thr	Arg	Asp	Thr	Thr	Tyr	Tyr
			20					25					30		

Leu	Phe	Trp	Tyr	Lys	Gln	Pro	Pro	Ser	Gly	Glu	Leu	Val	Phe	Leu	Ile
		35					40					45			

Arg	Arg	Asn	Ser	Phe	Asp	Glu	Gln	Asn	Glu	Ile	Ser	Gly	Arg	Tyr	Ser
	50					55					60				

Trp	Asn	Phe	Gln	Lys	Ser	Thr	Ser	Ser	Phe	Asn	Phe	Thr	Ile	Thr	Ala
65				70						75					80

Ser	Gln	Val	Val	Asp	Ser	Ala	Val	Tyr	Phe	Cys	Ala	Leu	Gly	Ser	Ser
			85						90					95	

Gly	Thr	Tyr	Lys	Tyr	Ile	Phe	Gly	Thr	Gly	Thr	Arg	Leu	Lys	Val	Leu
			100					105					110		

Ala	Asn	Ile	Gln	Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser
		115					120					125			

Lys	Ser	Ser	Asp	Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln
	130					135					140				

Thr	Asn	Val	Ser	Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys
145					150					155					160

Cys	Val	Leu	Asp	Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val
				165					170					175	

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
180 185 190

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys
195 200 205

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
210 215 220

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
225 230 235 240

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
245 250

<210> 65
<211> 289
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 65
Gln Val Thr Gln Asn Pro Arg Tyr Leu Ile Thr Val Thr Gly Lys Lys
1 5 10 15

Leu Thr Val Thr Cys Ser Gln Asn Met Asn His Glu Tyr Met Ser Trp
20 25 30

Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Gln Ile Tyr Tyr Ser Met
35 40 45

Asn Val Glu Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Lys Val
50 55 60

Ser Arg Lys Glu Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser
65 70 75 80

Pro Asn Gln Thr Ser Leu Tyr Phe Cys Ala Ser Ser Pro Gln Gly Arg
85 90 95

Ile Asn Ser Pro Leu His Phe Gly Asn Gly Thr Arg Leu Thr Val Thr
100 105 110

Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro
115 120 125

Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu Val Cys Leu
130 135 140

Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
145 150 155 160

Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln Pro Leu Lys
165 170 175

Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu
180 185 190

Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys
195 200 205

Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp
210 215 220

Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg
225 230 235 240

Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly Val Leu Ser
245 250 255

Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala
260 265 270

Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg Lys Asp
275 280 285

Phe

<210> 66
<211> 251

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 66

Gln Asn Ile Asp Gln Pro Thr Glu Met Thr Ala Thr Glu Gly Ala Ile
1 5 10 15

Val Gln Ile Asn Cys Thr Tyr Gln Thr Ser Gly Phe Asn Gly Leu Phe
20 25 30

Trp Tyr Gln Gln His Ala Gly Glu Ala Pro Thr Phe Leu Ser Tyr Asn
35 40 45

Val Leu Asp Gly Leu Glu Glu Lys Gly Arg Phe Ser Ser Phe Leu Ser
50 55 60

Arg Ser Lys Gly Tyr Ser Tyr Leu Leu Leu Lys Glu Leu Gln Met Lys
65 70 75 80

Asp Ser Ala Ser Tyr Leu Cys Ala Val Arg Asp Thr Gly Tyr Gly Gln
85 90 95

Asn Phe Val Phe Gly Pro Gly Thr Arg Leu Ser Val Leu Pro Tyr Ile
100 105 110

Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser
115 120 125

Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val
130 135 140

Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu
145 150 155 160

Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser
165 170 175

Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile
180 185 190

Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys
195 200 205

Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn
210 215 220

Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe
225 230 235 240

Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
245 250

<210> 67

<211> 296

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 67

Gly Ser Gly Leu Gly Ala Val Val Ser Gln His Pro Ser Trp Val Ile
1 5 10 15

Cys Lys Ser Gly Thr Ser Val Lys Ile Glu Cys Arg Ser Leu Asp Phe
20 25 30

Gln Ala Thr Thr Met Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu
35 40 45

Met Leu Met Ala Thr Ser Asn Glu Gly Ser Lys Ala Thr Tyr Glu Gln
50 55 60

Gly Val Glu Lys Asp Lys Phe Leu Ile Asn His Ala Ser Leu Thr Leu
65 70 75 80

Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu Asp Ser Ser Phe Tyr
85 90 95

Ile Cys Ser Ala Arg Glu Gly Tyr Arg Ser Tyr Phe Gly Pro Gly Thr
100 105 110

Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val
115 120 125

Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala
130 135 140

Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu
145 150 155 160

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp
165 170 175

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
180 185 190

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
195 200 205

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
210 215 220

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
225 230 235 240

Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His
245 250 255

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
260 265 270

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
275 280 285

Val Lys Arg Lys Asp Ser Arg Gly
290 295

<210> 68

<211> 250

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 68

Lys Thr Thr Gln Pro Pro Ser Met Asp Cys Ala Glu Gly Arg Ala Ala
1 5 10 15

Asn Leu Pro Cys Asn His Ser Thr Ile Ser Gly Asn Glu Tyr Val Tyr
20 25 30

Trp Tyr Arg Gln Ile His Ser Gln Gly Pro Gln Tyr Ile Ile His Gly
35 40 45

Leu Lys Asn Asn Glu Thr Asn Glu Met Ala Ser Leu Ile Ile Thr Glu
50 55 60

Asp Arg Lys Ser Ser Thr Leu Ile Leu Pro His Ala Thr Leu Arg Asp
65 70 75 80

Thr Ala Val Tyr Tyr Cys Ile Val Arg Asp Arg Ser Tyr Gly Gln Asn
85 90 95

Phe Val Phe Gly Pro Gly Thr Arg Leu Ser Val Leu Pro Tyr Ile Gln
100 105 110

Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp
115 120 125

Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser
130 135 140

Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp
145 150 155 160

Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn
165 170 175

Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro
180 185 190

Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu
195 200 205

Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu
210 215 220

Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
225 230 235 240

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
245 250

<210> 69

<211> 297

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 69

Gly Ser Gly Leu Gly Ala Val Val Ser Gln His Pro Ser Trp Val Ile
1 5 10 15

Cys Lys Ser Gly Thr Ser Val Lys Ile Glu Cys Arg Ser Leu Asp Phe
20 25 30

Gln Ala Thr Thr Met Phe Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu
35 40 45

Met Leu Met Ala Thr Ser Asn Glu Gly Cys Lys Ala Thr Tyr Glu Gln
50 55 60

Gly Val Glu Lys Asp Lys Phe Leu Ile Asn His Ala Ser Leu Thr Leu
65 70 75 80

Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu Asp Ser Ser Phe Tyr
85 90 95

Ile Cys Ser Thr Ala Gly Glu Thr Asp Thr Gln Tyr Phe Gly Pro Gly
100 105 110

Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
115 120 125

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
130 135 140

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
145 150 155 160

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
165 170 175

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
180 185 190

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
195 200 205

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
210 215 220

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
225 230 235 240

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
245 250 255

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
260 265 270

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
275 280 285

Met Val Lys Arg Lys Asp Ser Arg Gly
290 295

<210> 70

<211> 259

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 70

Glu Ser Val Gly Leu His Leu Pro Thr Leu Ser Val Gln Glu Gly Asp
1 5 10 15

Asn Ser Ile Ile Asn Cys Ala Tyr Ser Asn Ser Ala Ser Asp Tyr Phe
20 25 30

Ile Trp Tyr Lys Gln Glu Ser Gly Lys Gly Pro Gln Phe Ile Ile Asp
35 40 45

Ile Arg Ser Asn Met Asp Lys Arg Gln Gly Gln Arg Val Thr Val Leu
50 55 60

Leu Asn Lys Thr Val Lys His Leu Ser Leu Gln Ile Ala Ala Thr Gln
65 70 75 80

Pro Gly Asp Ser Ala Val Tyr Phe Cys Ala Glu Thr Leu Gly Leu Asp
85 90 95

Gln Gly Gly Lys Leu Ile Phe Gly Gln Gly Thr Glu Leu Ser Val Lys
100 105 110

Pro Asn Ile Gln Asn Pro Asp Ser Val Lys Pro Asn Pro Ala Val Tyr
115 120 125

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
130 135 140

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
145 150 155 160

Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys
165 170 175

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
180 185 190

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
195 200 205

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
210 215 220

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
225 230 235 240

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
245 250 255

Trp Ser Ser

<210> 71

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
primer

<400> 71

aactgcacgt accagacatc

20

<210> 72

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
primer

<400> 72

gatgtgcacc aagactcc

18

<210> 73

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
primer

<400> 73

aagatcaggt caacgttgc 19

<210> 74
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 74
ctccatggac tcatatgaag g 21

<210> 75
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 75
cttttcctga gtgtccgag 19

<210> 76
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 76
cacctgacc tgcaactata c 21

<210> 77
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 77
agctgcacgt actctgtcag 20

<210> 78
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 78
ctcactggag ttgggatg 18

<210> 79
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 79
gccaccctgg ttaaagg 17

<210> 80
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 80
cactgtctct gaaggagcc 19

<210> 81
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 81
gagctgaggt gcaactactc 20

<210> 82

<211> 18
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 primer

 <400> 82
 ctaacagagg ccacccag 18

 <210> 83
 <211> 20
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 primer

 <400> 83
 tggatatgtcc aatatacctgg 20

 <210> 84
 <211> 19
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 primer

 <400> 84
 caagtggagc agagtcctc 19

 <210> 85
 <211> 18
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 primer

 <400> 85
 cartgttcca gagggagc 18

 <210> 86
 <211> 19
 <212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 86

catccttcaa ccctgagtg

19

<210> 87

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 87

cagcgcctca gactacttc

19

<210> 88

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 88

aagataactc aaaccaacc ag

22

<210> 89

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 89

agtggagctg aagtgaac

19

<210> 90

<211> 19

<212> DNA

<213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic primer

 <400> 90
 ggagaagagg atcctcagg 19

 <210> 91
 <211> 22
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic primer

 <400> 91
 tccagtatct aaacaaagag cc 22

 <210> 92
 <211> 19
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic primer

 <400> 92
 aggtaactca agcgcagac 19

 <210> 93
 <211> 20
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic primer

 <400> 93
 cacagtcagc ggtttaagag 20

 <210> 94
 <211> 18
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic

primer

<400> 94
ttcctgcagc tctgagtg 18

<210> 95
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 95
gtcctccaga cctgattctc 20

<210> 96
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 96
tgcttatgag aacactgcg 19

<210> 97
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 97
ctcagtcact gcatgttcag 20

<210> 98
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 98
ggacttcacc acgtactgc 19

<210> 99
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 99
gcaaacctgc cttgtaatc 19

<210> 100
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 100
agccaaattc aatggagag 19

<210> 101
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 101
tcagtttcta agcatccaag ag 22

<210> 102
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
primer

<400> 102
gcaagttaag caaaattcac c 21

<210> 103	
<211> 19	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> Description of Artificial Sequence: Synthetic primer	
<400> 103	
caacaaccag tgcagagtc	19
<210> 104	
<211> 20	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> Description of Artificial Sequence: Synthetic primer	
<400> 104	
agaactggag cagagtcctc	20
<210> 105	
<211> 20	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> Description of Artificial Sequence: Synthetic primer	
<400> 105	
ggtcaacagc tgaatcagag	20
<210> 106	
<211> 21	
<212> DNA	
<213> Artificial Sequence	
<220>	
<223> Description of Artificial Sequence: Synthetic primer	
<400> 106	
gaagacaagg tggtaaaag c	21

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primer

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21

<210> 141

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19

<210> 175

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<210> 176

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<210> 177

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21

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21

<210> 196

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<400> 196

ataacttcca atccaggagg

20

<210> 197

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<223> Description of Artificial Sequence: Synthetic primer

<400> 197

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 <210> 199
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 <210> 200
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 <210> 201
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 <400> 201
 actctgacag tgaccagtgc 20

 <210> 202
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primer

<400> 202
gcaatcctgt cctcagaac 19

<210> 203
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primer

<400> 203
gatggataca gtgtctctcg a 21

<210> 204
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primer

<400> 204
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<210> 205
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primer

<400> 205
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<210> 206
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primer

<400> 206
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<210> 207
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primer

<400> 207
agaatctctc agcctccaga c 21

<210> 208
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polypeptide

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Gly Leu Thr Glu Pro Glu Val Thr Gln Thr Pro Ser His Gln Val Thr
20 25 30

Gln Met Gly Gln Glu Val Ile Leu Arg Cys Val Pro Ile Ser Asn His
35 40 45

Leu Tyr Phe Tyr Trp Tyr Arg Gln Ile Leu Gly Gln Lys Val Glu Phe
50 55 60

Leu Val Ser Phe Tyr Asn Asn Glu Ile Ser Glu Lys Ser Glu Ile Phe
65 70 75 80

Asp Asp Gln Phe Ser Val Glu Arg Pro Asp Gly Ser Asn Phe Thr Leu
85 90 95

Lys Ile Arg Ser Thr Lys Leu Glu Asp Ser Ala Met Tyr Phe Cys Ala
100 105 110

Ser Arg Ala Ser Val Gly Val Gly Thr Gly Glu Leu Phe Phe Gly Glu
115 120 125

Gly Ser Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
260 265 270

Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Ser Arg Gly Arg Ala Lys Arg Ser Gly
305 310 315 320

Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu
325 330 335

Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Thr Arg Val Ser Leu
340 345 350

Leu Trp Ala Val Val Val Ser Thr Cys Leu Glu Ser Gly Met Ala Gln
355 360 365

Thr Val Thr Gln Ser Gln Pro Glu Met Ser Val Gln Glu Ala Glu Thr
370 375 380

Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser Glu Ser Asn Tyr Tyr Leu
385 390 395 400

Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln Met Ile Leu Val Ile Arg
405 410 415

Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr Glu Asn Arg Phe Ser Val
420 425 430

Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser Leu Lys Ile Ser Asp Ser
435 440 445

Gln Leu Gly Asp Thr Ala Met Tyr Phe Cys Ala Phe Thr Tyr Gly Gly
450 455 460

Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu Ser Val Lys
465 470 475 480

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
485 490 495

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
500 505 510

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
515 520 525

Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
530 535 540

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
545 550 555 560

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys
565 570 575

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
580 585 590

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
595 600 605

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
610 615 620

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<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 210

Met Gly Thr Ser Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Thr
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Tyr Trp Tyr Arg Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

Leu Thr Tyr Phe Asn Tyr Glu Ala Gln Gln Asp Lys Ser Gly Leu Pro
65 70 75 80

Asn Asp Arg Phe Ser Ala Glu Arg Pro Glu Gly Ser Ile Ser Thr Leu
85 90 95

Thr Ile Gln Arg Thr Glu Gln Arg Asp Ser Ala Met Tyr Arg Cys Ala
100 105 110

Ser Ser Pro Glu Leu Ala Gly Pro Gln Glu Thr Gln Tyr Phe Gly Pro
115 120 125

Gly Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
260 265 270

Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe Arg Ala Lys Arg Ser Gly Ser Gly
305 310 315 320

Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly
325 330 335

Asp Val Glu Ser Asn Pro Gly Pro Met Leu Thr Ala Ser Leu Leu Arg
340 345 350

Ala Val Ile Ala Ser Ile Cys Val Val Ser Ser Met Ala Gln Lys Val
355 360 365

Thr Gln Ala Gln Thr Glu Ile Ser Val Val Glu Lys Glu Asp Val Thr
370 375 380

Leu Asp Cys Val Tyr Glu Thr Arg Asp Thr Thr Tyr Tyr Leu Phe Trp
385 390 395 400

Tyr Lys Gln Pro Pro Ser Gly Glu Leu Val Phe Leu Ile Arg Arg Asn
405 410 415

Ser Phe Asp Glu Gln Asn Glu Ile Ser Gly Arg Tyr Ser Trp Asn Phe
420 425 430

Gln Lys Ser Thr Ser Ser Phe Asn Phe Thr Ile Thr Ala Ser Gln Val
435 440 445

Val Asp Ser Ala Val Tyr Phe Cys Ala Leu Ser Glu Gly Gly Gly Ser
450 455 460

Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu Ser Val Lys Pro
465 470 475 480

Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys
485 490 495

Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr
500 505 510

Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Cys
515 520 525

Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala
530 535 540

Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser
545 550 555 560

Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp
565 570 575

Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe
580 585 590

Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala
595 600 605

Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
610 615 620

<210> 211

<211> 618

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 211

Met Thr Ile Arg Leu Leu Cys Tyr Met Gly Phe Tyr Phe Leu Gly Ala
1 5 10 15

Gly Leu Met Glu Ala Asp Ile Tyr Gln Thr Pro Arg Tyr Leu Val Ile
20 25 30

Gly Thr Gly Lys Lys Ile Thr Leu Glu Cys Ser Gln Thr Met Gly His
35 40 45

Asp Lys Met Tyr Trp Tyr Gln Gln Asp Pro Gly Met Glu Leu His Leu
50 55 60

Ile His Tyr Ser Tyr Gly Val Asn Ser Thr Glu Lys Gly Asp Leu Ser
65 70 75 80

Ser Glu Ser Thr Val Ser Arg Ile Arg Thr Glu His Phe Pro Leu Thr
85 90 95

Leu Glu Ser Ala Arg Pro Ser His Thr Ser Gln Tyr Leu Cys Ala Ser
100 105 110

Ser Gly Pro Gly Gln Gly His Asn Gln Pro Gln His Phe Gly Asp Gly
115 120 125

Thr Arg Leu Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe Arg Ala Lys Arg Ser Gly Ser Gly Ala
305 310 315 320

Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp
325 330 335

Val Glu Ser Asn Pro Gly Pro Met Leu Thr Ala Ser Leu Leu Arg Ala
340 345 350

Val Ile Ala Ser Ile Cys Val Val Ser Ser Met Ala Gln Lys Val Thr
355 360 365

Gln Ala Gln Thr Glu Ile Ser Val Val Glu Lys Glu Asp Val Thr Leu
370 375 380

Asp Cys Val Tyr Glu Thr Arg Asp Thr Thr Tyr Tyr Leu Phe Trp Tyr
385 390 395 400

Lys Gln Pro Pro Ser Gly Glu Leu Val Phe Leu Ile Arg Arg Asn Ser
405 410 415

Phe Asp Glu Gln Asn Glu Ile Ser Gly Arg Tyr Ser Trp Asn Phe Gln
420 425 430

Lys Ser Thr Ser Ser Phe Asn Phe Thr Ile Thr Ala Ser Gln Val Val
435 440 445

Asp Ser Ala Val Tyr Phe Cys Ala Leu Gly Ser Ser Gly Thr Tyr Lys
450 455 460

Tyr Ile Phe Gly Thr Gly Thr Arg Leu Lys Val Leu Ala Asn Ile Gln
465 470 475 480

Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp
485 490 495

Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser
500 505 510

Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp
515 520 525

Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn
530 535 540

Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro
545 550 555 560

Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu
565 570 575

Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu
580 585 590

Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
595 600 605

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
610 615

<210> 212

<211> 611

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 212

Met Gly Pro Gln Leu Leu Gly Tyr Val Val Leu Cys Leu Leu Gly Ala
1 5 10 15

Gly Pro Leu Glu Ala Gln Val Thr Gln Asn Pro Arg Tyr Leu Ile Thr
20 25 30

Val Thr Gly Lys Lys Leu Thr Val Thr Cys Ser Gln Asn Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Gln
50 55 60

Ile Tyr Tyr Ser Met Asn Val Glu Val Thr Asp Lys Gly Asp Val Pro
65 70 75 80

Glu Gly Tyr Lys Val Ser Arg Lys Glu Lys Arg Asn Phe Pro Leu Ile
85 90 95

Leu Glu Ser Pro Ser Pro Asn Gln Thr Ser Leu Tyr Phe Cys Ala Ser
100 105 110

Ser Pro Gln Gly Arg Ile Asn Ser Pro Leu His Phe Gly Asn Gly Thr
115 120 125

Arg Leu Thr Val Thr Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val
130 135 140

Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala
145 150 155 160

Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu
165 170 175

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp
180 185 190

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
195 200 205

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
210 215 220

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
225 230 235 240

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
245 250 255

Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His
260 265 270

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
275 280 285

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
290 295 300

Val Lys Arg Lys Asp Phe Arg Ala Lys Arg Ser Gly Ser Gly Ala Pro
305 310 315 320

Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp Val
325 330 335

Glu Ser Asn Pro Gly Pro Met Trp Gly Val Phe Leu Leu Tyr Val Ser
340 345 350

Met Lys Met Gly Gly Thr Thr Gly Gln Asn Ile Asp Gln Pro Thr Glu
355 360 365

Met Thr Ala Thr Glu Gly Ala Ile Val Gln Ile Asn Cys Thr Tyr Gln
370 375 380

Thr Ser Gly Phe Asn Gly Leu Phe Trp Tyr Gln Gln His Ala Gly Glu
385 390 395 400

Ala Pro Thr Phe Leu Ser Tyr Asn Val Leu Asp Gly Leu Glu Glu Lys
405 410 415

Gly Arg Phe Ser Ser Phe Leu Ser Arg Ser Lys Gly Tyr Ser Tyr Leu
420 425 430

Leu Leu Lys Glu Leu Gln Met Lys Asp Ser Ala Ser Tyr Leu Cys Ala
435 440 445

Val Arg Asp Thr Gly Tyr Gly Gln Asn Phe Val Phe Gly Pro Gly Thr
450 455 460

Arg Leu Ser Val Leu Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr
465 470 475 480

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
485 490 495

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
500 505 510

Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys
515 520 525

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
530 535 540

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
545 550 555 560

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
565 570 575

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
580 585 590

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
595 600 605

Trp Ser Ser
610

<210> 213

<211> 618

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 213

Met Leu Leu Leu Leu Leu Leu Leu Gly Pro Gly Ile Ser Leu Leu Leu
1 5 10 15

Pro Gly Ser Leu Ala Gly Ser Gly Leu Gly Ala Val Val Ser Gln His
20 25 30

Pro Ser Trp Val Ile Cys Lys Ser Gly Thr Ser Val Lys Ile Glu Cys
35 40 45

Arg Ser Leu Asp Phe Gln Ala Thr Thr Met Phe Trp Tyr Arg Gln Phe
50 55 60

Pro Lys Gln Ser Leu Met Leu Met Ala Thr Ser Asn Glu Gly Ser Lys
65 70 75 80

Ala Thr Tyr Glu Gln Gly Val Glu Lys Asp Lys Phe Leu Ile Asn His
85 90 95

Ala Ser Leu Thr Leu Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu
100 105 110

Asp Ser Ser Phe Tyr Ile Cys Ser Ala Arg Glu Gly Tyr Arg Ser Tyr
115 120 125

Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val
130 135 140

Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala
145 150 155 160

His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro
165 170 175

Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser
180 185 190

Gly Val Cys Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn
195 200 205

Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe
210 215 220

Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly
225 230 235 240

Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr
245 250 255

Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr
260 265 270

Ser Ala Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu
275 280 285

Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu
290 295 300

Val Leu Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly Arg Ala Lys
305 310 315 320

Arg Ser Gly Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu
325 330 335

Leu Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Arg Leu
340 345 350

Val Ala Arg Val Thr Val Phe Leu Thr Phe Gly Thr Ile Ile Asp Ala
355 360 365

Lys Thr Thr Gln Pro Pro Ser Met Asp Cys Ala Glu Gly Arg Ala Ala
370 375 380

Asn Leu Pro Cys Asn His Ser Thr Ile Ser Gly Asn Glu Tyr Val Tyr
385 390 395 400

Trp Tyr Arg Gln Ile His Ser Gln Gly Pro Gln Tyr Ile Ile His Gly
405 410 415

Leu Lys Asn Asn Glu Thr Asn Glu Met Ala Ser Leu Ile Ile Thr Glu
420 425 430

Asp Arg Lys Ser Ser Thr Leu Ile Leu Pro His Ala Thr Leu Arg Asp
435 440 445

Thr Ala Val Tyr Tyr Cys Ile Val Arg Asp Arg Ser Tyr Gly Gln Asn
450 455 460

Phe Val Phe Gly Pro Gly Thr Arg Leu Ser Val Leu Pro Tyr Ile Gln
465 470 475 480

Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp
485 490 495

Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser
500 505 510

Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp
515 520 525

Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn
530 535 540

Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro
545 550 555 560

Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu
565 570 575

Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu
580 585 590

Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
595 600 605

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
610 615

<210> 214

<211> 630

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 214

Met Leu Leu Leu Leu Leu Leu Gly Pro Gly Ile Ser Leu Leu Leu
1 5 10 15

Pro Gly Ser Leu Ala Gly Ser Gly Leu Gly Ala Val Val Ser Gln His
20 25 30

Pro Ser Trp Val Ile Cys Lys Ser Gly Thr Ser Val Lys Ile Glu Cys
35 40 45

Arg Ser Leu Asp Phe Gln Ala Thr Thr Met Phe Trp Tyr Arg Gln Phe
50 55 60

Pro Lys Gln Ser Leu Met Leu Met Ala Thr Ser Asn Glu Gly Cys Lys
65 70 75 80

Ala Thr Tyr Glu Gln Gly Val Glu Lys Asp Lys Phe Leu Ile Asn His
85 90 95

Ala Ser Leu Thr Leu Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu
100 105 110

Asp Ser Ser Phe Tyr Ile Cys Ser Thr Ala Gly Glu Thr Asp Thr Gln
115 120 125

Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn
130 135 140

Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile
145 150 155 160

Ala His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe
165 170 175

Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His
180 185 190

Ser Gly Val Cys Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu
195 200 205

Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr
210 215 220

Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr
225 230 235 240

Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val
245 250 255

Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile
260 265 270

Thr Ser Ala Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr
275 280 285

Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala
290 295 300

Leu Val Leu Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly Arg Ala
305 310 315 320

Lys Arg Ser Gly Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe Asp
325 330 335

Leu Leu Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Ala
340 345 350

Gly Ile Arg Ala Leu Phe Met Tyr Leu Trp Leu Gln Leu Asp Trp Val
355 360 365

Ser Arg Gly Glu Ser Val Gly Leu His Leu Pro Thr Leu Ser Val Gln
370 375 380

Glu Gly Asp Asn Ser Ile Ile Asn Cys Ala Tyr Ser Asn Ser Ala Ser
385 390 395 400

Asp Tyr Phe Ile Trp Tyr Lys Gln Glu Ser Gly Lys Gly Pro Gln Phe
405 410 415

Ile Ile Asp Ile Arg Ser Asn Met Asp Lys Arg Gln Gly Gln Arg Val
420 425 430

Thr Val Leu Leu Asn Lys Thr Val Lys His Leu Ser Leu Gln Ile Ala
435 440 445

Ala Thr Gln Pro Gly Asp Ser Ala Val Tyr Phe Cys Ala Glu Thr Leu
450 455 460

Gly Leu Asp Gln Gly Gly Lys Leu Ile Phe Gly Gln Gly Thr Glu Leu
465 470 475 480

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Ser Val Lys Pro Asn Pro
485 490 495

Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys
500 505 510

Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp
515 520 525

Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met
530 535 540

Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe
545 550 555 560

Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe
565 570 575

Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser
580 585 590

Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly
595 600 605

Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr
610 615 620

Leu Arg Leu Trp Ser Ser
625 630

<210> 215
<211> 614
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 215
Met Gly Cys Arg Leu Leu Cys Cys Val Val Phe Cys Leu Leu Gln Ala
1 5 10 15

Gly Pro Leu Asp Thr Ala Val Ser Gln Thr Pro Lys Tyr Leu Val Thr
20 25 30

Gln Met Gly Asn Asp Lys Ser Ile Lys Cys Glu Gln Asn Leu Gly His
35 40 45

Asp Thr Met Tyr Trp Tyr Lys Gln Asp Ser Lys Lys Phe Leu Lys Ile
50 55 60

Met Phe Ser Tyr Asn Asn Lys Glu Leu Ile Ile Asn Glu Thr Val Pro
65 70 75 80

Asn Arg Phe Ser Pro Lys Ser Pro Asp Lys Ala His Leu Asn Leu His
85 90 95

Ile Asn Ser Leu Glu Leu Gly Asp Ser Ala Val Tyr Phe Cys Ala Ser
100 105 110

Ser Gln Gly Thr Gly Arg Gly Asn Thr Glu Ala Phe Phe Gly Gln Gly
115 120 125

Thr Arg Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe Arg Ala Lys Arg Ser Gly Ser Gly Ala
305 310 315 320

Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp
325 330 335

Val Glu Ser Asn Pro Gly Pro Met Arg Gln Val Ala Arg Val Ile Val
340 345 350

Phe Leu Thr Leu Ser Thr Leu Ser Leu Ala Lys Thr Thr Gln Pro Ile
355 360 365

Ser Met Asp Ser Tyr Glu Gly Gln Glu Val Asn Ile Thr Cys Ser His
370 375 380

Asn Asn Ile Ala Thr Asn Asp Tyr Ile Thr Trp Tyr Gln Gln Phe Pro
385 390 395 400

Ser Gln Gly Pro Arg Phe Ile Ile Gln Gly Tyr Lys Thr Lys Val Thr
405 410 415

Asn Glu Val Ala Ser Leu Phe Ile Pro Ala Asp Arg Lys Ser Ser Thr
420 425 430

Leu Ser Leu Pro Arg Val Ser Leu Ser Asp Thr Ala Val Tyr Tyr Cys
435 440 445

Leu Val Gly Pro Tyr Phe Gly Gly Gly Ser Tyr Gln Leu Thr Phe Gly
450 455 460

Lys Gly Thr Lys Leu Ser Val Ile Pro Asn Ile Gln Asn Pro Asp Pro
465 470 475 480

Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys
485 490 495

Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp
500 505 510

Ser Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met
515 520 525

Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe
530 535 540

Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe
545 550 555 560

Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser
565 570 575

Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly
580 585 590

Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr
595 600 605

Leu Arg Leu Trp Ser Ser
610

<210> 216

<211> 629

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 216

Met Gly Thr Arg Leu Leu Phe Trp Val Ala Phe Cys Leu Leu Gly Ala
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Ser Asn Lys Val Thr
20 25 30

Glu Lys Gly Lys Asp Val Glu Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Thr Ala Leu Tyr Trp Tyr Arg Gln Ser Leu Gly Gln Gly Leu Glu Phe
50 55 60

Leu Ile Tyr Phe Gln Gly Asn Ser Ala Pro Asp Lys Ser Gly Leu Pro
65 70 75 80

Ser Asp Arg Phe Ser Ala Glu Arg Thr Gly Gly Ser Val Ser Thr Leu
85 90 95

Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Gly Gln Gly Ala Val Gly Thr Asp Thr Gln Tyr Phe Gly
115 120 125

Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Arg Lys Thr Leu Lys Asn
130 135 140

Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile
145 150 155 160

Ala His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr
165 170 175

Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His
180 185 190

Ser Gly Val Cys Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu
195 200 205

Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr
210 215 220

Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr
225 230 235 240

Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val
245 250 255

Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile
260 265 270

Thr Ser Ala Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr
275 280 285

Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala
290 295 300

Leu Val Leu Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly Arg Ala
305 310 315 320

Lys Arg Ser Gly Ser Gly Ala Pro Val Lys Gln Thr Leu Asn Phe Asp
325 330 335

Leu Leu Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Thr
340 345 350

Arg Val Ser Leu Leu Trp Ala Val Val Val Ser Thr Cys Leu Glu Ser
355 360 365

Gly Met Ala Gln Thr Val Thr Gln Ser Gln Pro Glu Met Ser Val Gln
370 375 380

Glu Ala Glu Thr Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser Glu Asn
385 390 395 400

Asn Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln Met Ile
405 410 415

Leu Val Ile Arg Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr Glu Asn
420 425 430

Arg Phe Ser Val Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser Leu Lys
435 440 445

Ile Ser Asp Ser Gln Leu Gly Asp Thr Ala Met Tyr Phe Cys Ala Phe
450 455 460

Met Lys Pro Asp Gly Ser Gly Asn Thr Gly Lys Leu Ile Phe Gly Gln
465 470 475 480

Gly Thr Thr Leu Gln Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala
485 490 495

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu
500 505 510

Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser
515 520 525

Asp Val Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp
530 535 540

Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala
545 550 555 560

Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe
565 570 575

Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe
580 585 590

Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe
595 600 605

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
610 615 620

Arg Leu Trp Ser Ser
625

<210> 217
<211> 19
<212> PRT
<213> Human papillomavirus 16

<400> 217
Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr
1 5 10 15

Asp Leu Tyr

<210> 218
<211> 9
<212> PRT
<213> Human papillomavirus 16

<400> 218
Ser Ala Phe Arg Cys Phe Ile Val Tyr
1 5

<210> 219
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 219
Cys Leu Val Gly Pro Tyr Phe Gly Gly Gly Ser Tyr Gln Leu Thr Phe
1 5 10 15

<210> 220
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 220
Cys Ala Ser Ser Gln Gly Thr Gly Arg Gly Asn Thr Glu Ala Phe Phe
1 5 10 15

<210> 221
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 221
Cys Ala Val Arg Glu Lys Gly Thr Gly Asn Gln Phe Tyr Phe
1 5 10

<210> 222
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 222
Cys Ala Ser Ser Leu Pro Gln Gly Thr Pro Glu Thr Gln Tyr Phe
1 5 10 15

<210> 223
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 223
Cys Gly Leu Ser Trp Gly Asp Lys Thr Asp Lys Leu Ile Phe
1 5 10

<210> 224
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 224
Cys Ala Ser Ser Pro Ser Leu Ala Gly Val Val Pro Gly Glu Leu Phe
1 5 10 15

Phe

<210> 225
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 225
Cys Ala Phe Met Lys Pro Asp Gly Ser Gly Asn Thr Gly Lys Leu Ile
1 5 10 15

Phe

<210> 226
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 226
Cys Ala Ser Ser Leu Gly Gln Gly Ala Val Gly Thr Asp Thr Gln Tyr
1 5 10 15

Phe

<210> 227
<211> 9374
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 227
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gtacgatcgt gccttattag gaaggcaaca gacgggtctg acatggattg gacgaaccac 180
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9374

<210> 228

<211> 9419

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 228

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9419

<210> 229

<211> 292

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 229

Asp	Thr	Ala	Val	Ser	Gln	Thr	Pro	Lys	Tyr	Leu	Val	Thr	Gln	Met	Gly
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Asn	Asp	Lys	Ser	Ile	Lys	Cys	Glu	Gln	Asn	Leu	Gly	His	Asp	Thr	Met
		20					25					30			

Tyr	Trp	Tyr	Lys	Gln	Asp	Ser	Lys	Lys	Phe	Leu	Lys	Ile	Met	Phe	Ser
	35						40					45			

Tyr	Asn	Asn	Lys	Glu	Leu	Ile	Ile	Asn	Glu	Thr	Val	Pro	Asn	Arg	Phe
50						55					60				

Ser	Pro	Lys	Ser	Pro	Asp	Lys	Ala	His	Leu	Asn	Leu	His	Ile	Asn	Ser
65					70					75				80	

Leu	Glu	Leu	Gly	Asp	Ser	Ala	Val	Tyr	Phe	Cys	Ala	Ser	Ser	Gln	Gly
			85						90					95	

Thr	Gly	Arg	Gly	Asn	Thr	Glu	Ala	Phe	Phe	Gly	Gln	Gly	Thr	Arg	Leu
			100					105					110		

Thr	Val	Val	Glu	Asp	Leu	Asn	Lys	Val	Phe	Pro	Pro	Glu	Val	Ala	Val
		115					120					125			

Phe	Glu	Pro	Ser	Lys	Ala	Glu	Ile	Ala	His	Thr	Gln	Lys	Ala	Thr	Leu
	130					135					140				

Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr	Pro	Asp	His	Val	Glu	Leu	Ser	Trp
145					150					155					160

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln
165 170 175

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
180 185 190

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
195 200 205

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
210 215 220

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
225 230 235 240

Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly
245 250 255

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
260 265 270

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
275 280 285

Arg Lys Asp Phe
290

<210> 230

<211> 254

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 230

Leu Ala Lys Thr Thr Gln Pro Ile Ser Met Asp Ser Tyr Glu Gly Gln
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Glu Val Asn Ile Thr Cys Ser His Asn Asn Ile Ala Thr Asn Asp Tyr
20 25 30

Ile Thr Trp Tyr Gln Gln Phe Pro Ser Gln Gly Pro Arg Phe Ile Ile
35 40 45

Gln Gly Tyr Lys Thr Lys Val Thr Asn Glu Val Ala Ser Leu Phe Ile
50 55 60

Pro Ala Asp Arg Lys Ser Ser Thr Leu Ser Leu Pro Arg Val Ser Leu
65 70 75 80

Ser Asp Thr Ala Val Tyr Tyr Cys Leu Val Gly Pro Tyr Phe Gly Gly
85 90 95

Gly Ser Tyr Gln Leu Thr Phe Gly Lys Gly Thr Lys Leu Ser Val Ile
100 105 110

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
115 120 125

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
130 135 140

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
145 150 155 160

Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
165 170 175

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
180 185 190

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys
195 200 205

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
210 215 220

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
225 230 235 240

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
245 250

<210> 231
<211> 299
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 231
Gly Ala Gly Val Ser Gln Ser Pro Ser Asn Lys Val Thr Glu Lys Gly
1 5 10 15

Lys Asp Val Glu Leu Arg Cys Asp Pro Ile Ser Gly His Thr Ala Leu
20 25 30

Tyr Trp Tyr Arg Gln Ser Leu Gly Gln Gly Leu Glu Phe Leu Ile Tyr
35 40 45

Phe Gln Gly Asn Ser Ala Pro Asp Lys Ser Gly Leu Pro Ser Asp Arg
50 55 60

Phe Ser Ala Glu Arg Thr Gly Gly Ser Val Ser Thr Leu Thr Ile Gln
65 70 75 80

Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala Ser Ser Leu
85 90 95

Gly Gln Gly Ala Val Gly Thr Asp Thr Gln Tyr Phe Gly Pro Gly Thr
100 105 110

Arg Leu Thr Val Leu Glu Asp Arg Lys Thr Leu Lys Asn Val Phe Pro
115 120 125

Pro Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr
130 135 140

Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His
145 150 155 160

Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val
165 170 175

Cys Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser
180 185 190

Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln
195 200 205

Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser
210 215 220

Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile
225 230 235 240

Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala
245 250 255

Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu
260 265 270

Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu
275 280 285

Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly
290 295

<210> 232

<211> 259

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 232

Ala Gln Thr Val Thr Gln Ser Gln Pro Glu Met Ser Val Gln Glu Ala
1 5 10 15

Glu Thr Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser Glu Asn Asn Tyr
20 25 30

Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln Met Ile Leu Val
35 40 45

Ile Arg Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr Glu Asn Arg Phe
50 55 60

Ser Val Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser Leu Lys Ile Ser
65 70 75 80

Asp Ser Gln Leu Gly Asp Thr Ala Met Tyr Phe Cys Ala Phe Met Lys
85 90 95

Pro Asp Gly Ser Gly Asn Thr Gly Lys Leu Ile Phe Gly Gln Gly Thr
100 105 110

Thr Leu Gln Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
115 120 125

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
130 135 140

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
145 150 155 160

Tyr Ile Thr Asp Lys Cys Val Leu Asp Met Arg Ser Met Asp Phe Lys
165 170 175

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
180 185 190

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
195 200 205

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
210 215 220

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
225 230 235 240

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
245 250 255

Trp Ser Ser

<210> 233

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 233

Ser Gly Ser Gly

1