

What is claimed is:

1. A T cell receptor (TCR) polypeptide having antigenic specificity for human papillomavirus (HPV) 16 (HPV16), 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-to 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 to -12, 217 or 218.
3. The TCR polypeptide of claim 1 or claim 2, wherein the TCR has antigenic specificity for HPV16 peptides other than E6 and E7, and/or the TCR has antigenic specificity for any one of HPV16 peptides E1, E2, E4, or E5.
- ~~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.~~
- ~~6.4. The TCR polypeptide of claim 43, 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, SEQ ID NOs: 60 and 59 or SEQ ID NOs: 62 and 61.~~
- ~~7. The TCR polypeptide of claim 4, wherein the TCR comprises a TCR_P 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.~~
- ~~8.5. A nucleic acid encoding the TCR polypeptide of any one of claims 1 to 47.~~
- ~~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.~~

~~The nucleic acid of claim 11, wherein the expression vector is a viral vector. The nucleic acid of claim 12, wherein the viral vector is lentiviral expression vector.~~
- ~~12.6. An immune cell comprising one or both of the nucleic acid of any one of claims 8 to 13claim 5 and the TCR polypeptide of any one of claims 1 to 4.~~
- ~~13. An immune cell expressing the TCR polypeptide of any one of claims 1 to 64.~~

- ~~14. The immune cell of claim 14 or 15, wherein the immune cell is a leukocyte.~~
- ~~15. 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.~~
- ~~16.7. The immune cell of any one of claims 14 to 17~~claim 6, 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.
- ~~17.8. The immune cell of claim 6 or claim 17~~8, wherein the immune cell is a cytotoxic T lymphocyte (CTL).
- ~~18. The immune cell of claim 18 or 19, wherein the immune cell is a viral antigen-sensitized CTL.~~
- ~~19.9. The immune cell of any one of claims 18 to 20~~claim 88, 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.
- ~~20. The immune cell of any one of claims 18 to 21, wherein the immune cell is an HPV-sensitized CTL.~~
10. The TCR-expressing cell of any one of claims 15 to 22~~7 to 9~~, wherein the TCR-expressing cell:
 - is genetically modified to no longer express one or more immune checkpoint molecules (e.g., PD-1 and/or CTLA-4); and/or-
- ~~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; and/or-~~
- ~~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; and/or-~~
- ~~21. 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.~~
- ~~22. 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), CD 160, and transforming growth factor b (TGF-b) receptor.~~

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

~~24.11. The use of an adoptive immunotherapy composition for the manufacture of a medicament for A method of treating the treatment of 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 286 to 10.~~

~~25.12. The method use of claim 2911, wherein the HPV-associated cancer is a squamous cell carcinoma.~~

~~26. 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.~~

~~27. 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.~~

~~28.13. The method use of any one of claims 29 to 32 claim 11 and claim 12, wherein the subject has received, is receiving, or will receive an additional anti-cancer therapy (for example, surgery, radiation, chemotherapy, immunotherapy, or hormone therapy), and optionally wherein the subject has received IFN γ prior to administering the adoptive immunotherapy composition.~~

~~29. The method of claim 33, wherein the additional anti-cancer therapy comprises surgery, radiation, chemotherapy, immunotherapy, or hormone therapy.~~

~~30. The method of claim 34, wherein the subject has received IFN γ prior to administering the adoptive immunotherapy composition.~~

~~31. 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.~~

~~32. The method of any one of claims 29 to 36, wherein the subject is human.~~

~~33. The method use of any one of claims 3711 to 13, wherein the TCR-expressing cells of the adoptive immunotherapy composition are derived from the subject or.~~

~~34.14. 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.~~

- ~~35.15.~~ The method use of any one of claims 29~~11~~ to 39~~14~~, further comprising administering at least one immune checkpoint inhibitor.
- ~~36.16.~~ The method use of claim 40~~15~~, 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.
- ~~37.17.~~ The method use of claim 40~~15~~, 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).
- ~~38.18.~~ The method use of claim 40~~15~~, wherein the immune checkpoint inhibitor comprises a CRISPR RNA (crRNA) molecule, or a dominant negative form of an immune checkpoint molecule, or a recombinant switch receptor.
- ~~39.~~ The method of claim 40, wherein the immune checkpoint inhibitor comprises a dominant negative form of an immune checkpoint molecule.
- ~~40.~~ The method of claim 40, wherein the immune checkpoint inhibitor comprises a recombinant switch receptor.
- ~~41.~~ 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.
- ~~42.~~ 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.
- ~~43.19.~~ A cell bank of comprising cells for adoptive immunotherapy, wherein the cells are the TCR-expressing cells of any one of claims 14~~6~~ to 28~~9~~, and wherein the HLA restriction of the TCR-expressing cells is known.
- ~~44.~~ 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.