

WHAT IS CLAIMED IS:

1. A T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region and a beta chain comprising a variable beta (Vb) region, wherein:
 - 5 the Va region comprises a complementarity determining region 1 (CDR-1), a complementarity determining region 2 (CDR-2), and a complementarity determining region 3 (CDR-3), wherein the Va region CDR-1 comprises an amino acid sequence that is identical to a selected Va region CDR-1 amino acid sequence, the Va region CDR-2 comprises an amino acid sequence that is identical to a selected Va region CDR-2 amino acid sequence, and the Va region
 - 10 CDR-3 comprises an amino acid sequence that is identical to a selected Va region CDR-3 amino acid sequence; and
 - the Vb region comprises a complementarity determining region 1 (CDR-1), a complementarity determining region 2 (CDR-2), and a complementarity determining region 3 (CDR-3), wherein the Vb region CDR-1 comprises an amino acid sequence that is identical to a
 - 15 selected Vb region CDR-1 amino acid sequence, the Vb region CDR-2 comprises an amino acid sequence that is identical to a selected Vb region CDR-2 amino acid sequence, and the Vb region CDR-3 comprises an amino acid sequence that is identical to a selected Vb region CDR-3 amino acid sequence;
 - wherein the selected Va region CDR-1, CDR-2, and CDR-3 amino acid sequences and the
 - 20 selected Vb region CDR-1, CDR-2, and CDR-3 amino acid sequences are one of the following:
 - (1) the selected Va region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in SEQ ID NOs: 5, 6, and 7, respectively, and the selected Vb region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in SEQ ID NOs: 8, 9, and 10, respectively;
 - (2) the selected Va region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in
 - 25 SEQ ID NOs: 27, 28, and 29, respectively, and the selected Vb region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in SEQ ID NOs: 30, 31, and 32, respectively;
 - (3) the selected Va region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in SEQ ID NOs: 33, 34, and 35, respectively, and the selected Vb region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in SEQ ID NOs: 36, 37, and 38, respectively;
 - (4) the selected Va region CDR-1, CDR-2, and CDR-3 amino acid sequences are set forth in
 - 30 SEQ ID NOs: 39, 40, and 41, respectively, and the selected Vb region CDR-1, CDR-2, and

CDR-3 amino acid sequences are set forth in SEQ ID NOs: 42, 43, and 44, respectively.

2. The TCR or antigen-binding fragment thereof of claim 1, wherein the Va region comprises CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 5, 6, and 7, respectively; and the Vb region comprises CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 8, 9, and 10, respectively.

3. The TCR or antigen-binding fragment thereof of claim 2, wherein:
the Va region comprises the amino acid sequence set forth in any of SEQ ID NO: 1, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
the Vb region comprises the amino acid sequence set forth in any of SEQ ID NO: 2, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

4. The TCR or antigen-binding fragment thereof of claim 1, wherein the Va region comprises CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 27, 28, and 29, respectively; and the Vb region comprises CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 30, 31, and 32, respectively.

5. The TCR or antigen-binding fragment thereof of claim 4, wherein:
the Va region comprises the amino acid sequence set forth in any of SEQ ID NO: 45, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and
the Vb region comprises the amino acid sequence set forth in any of SEQ ID NO: 46 or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

6. The TCR or antigen-binding fragment thereof of claim 1, wherein the Va region comprises CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 33, 34 and 35, respectively; and the Vb region comprises CDR-1, CDR-2, and CDR-3 with the amino acid

sequences set forth in SEQ ID NOs: 36, 37, and 38, respectively.

7. The TCR or antigen-binding fragment thereof of claim 6, wherein:

the Va region comprises the amino acid sequence set forth in any of SEQ ID NO: 47, or
5 an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
98%, or 99% sequence identity thereto; and

the Vb region comprises the amino acid sequence set forth in any of SEQ ID NO: 48 or
an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
98%, or 99% sequence identity thereto.

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8. The TCR or antigen-binding fragment thereof of claim 1, wherein the Va region comprises
CDR-1, CDR-2, and CDR-3 with the amino acid sequences set forth in SEQ ID NOs: 39, 40, and
41, respectively; and the Vb region comprises CDR-1, CDR-2, and CDR-3 with the amino acid
sequences set forth in SEQ ID NOs: 42, 43, and 44, respectively.

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9. The TCR or antigen-binding fragment thereof of claim 8, wherein:

the Va region comprises the amino acid sequence set forth in any of SEQ ID NO: 49, or
an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
98%, or 99% sequence identity thereto; and

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the Vb region comprises the amino acid sequence set forth in any of SEQ ID NO: 50 or
an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
98%, or 99% sequence identity thereto.

10. The TCR or antigen-binding fragment thereof of any one of claims 1-9, wherein:

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the alpha chain comprises a mouse alpha chain constant region, and the beta chain
comprises a mouse beta chain constant region.

11. The TCR or antigen-binding fragment thereof of claim 1, wherein:

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the alpha chain comprises the amino acid sequence set forth in any of SEQ ID NO: 15, or
an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
98%, or 99% sequence identity thereto; and

the beta chain comprises the amino acid sequence set forth in any of SEQ ID NO: 16, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

5 12. The TCR or antigen-binding fragment thereof of claim 1, wherein:

the alpha chain comprises the amino acid sequence set forth in any of SEQ ID NO: 51, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and

10 the beta chain comprises the amino acid sequence set forth in any of SEQ ID NO: 52, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

13. The TCR or antigen-binding fragment thereof of claim 1, wherein:

15 the alpha chain comprises the amino acid sequence set forth in any of SEQ ID NO: 53, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and

the beta chain comprises the amino acid sequence set forth in any of SEQ ID NO: 54, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

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14. The TCR or antigen-binding fragment thereof of claim 1, wherein:

the alpha chain comprises the amino acid sequence set forth in any of SEQ ID NO: 55, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and

25 the beta chain comprises the amino acid sequence set forth in any of SEQ ID NO: 56, or an amino acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

15. The TCR or antigen-binding fragment thereof of any of claims 1-14, wherein the TCR or
30 antigen-binding fragment thereof binds to or recognizes a peptide epitope of E6 (SEQ ID NO: 19) that is presented by a major histocompatibility complex (MHC) molecule.

16. The TCR or antigen-binding fragment thereof of claim 15, wherein the MHC molecule is an HLA-A2 molecule.
- 5 17. The TCR or antigen-binding fragment thereof of any of claims 1-16, wherein, the TCR or antigen-binding fragment thereof, when expressed on the surface of a T cell, stimulates cytotoxic activity against a target cancer cell.
18. The TCR or antigen-binding fragment thereof of claim 17, wherein the target cancer cell
10 comprises HPV DNA sequences or expresses E6.
19. A T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region and a beta chain comprising a variable beta (Vb) region, wherein:
- 15 the Va region comprises a complementarity determining region 1 (CDR1), a complementarity determining region 2 (CDR2), and a complementarity determining region 3 (CDR3), and the Vb region comprises a CDR1, a CDR2, and a CDR3, wherein
- (1) the Va region CDR1, CDR2, and CDR3 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 1, respectively, and the Vb region CDR1, CDR2, and CDR3
20 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 2, respectively;
- (2) the Va region CDR1, CDR2, and CDR3 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 45, respectively, and the Vb region CDR1, CDR2, and CDR3 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 46, respectively;
- (3) the Va region CDR1, CDR2, and CDR3 are identical to complementarity determining
25 regions 1, 2, and 3 in SEQ ID NO: 47, respectively, and the Vb region CDR1, CDR2, and CDR3 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 48, respectively;
- or
- (4) the Va region CDR1, CDR2, and CDR3 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 49, respectively, and the Vb region CDR1, CDR2, and CDR3
30 are identical to complementarity determining regions 1, 2, and 3 in SEQ ID NO: 50, respectively.

20. A vector comprising a nucleic acid encoding the TCR or antigen-binding fragment thereof of any of claims 1-19.
21. The vector of claim 20, wherein the vector is an expression vector, a viral vector, a retroviral vector, or a lentiviral vector.
22. A vector comprising:
- a) a first nucleic acid sequence encoding a TCR alpha chain comprising an alpha chain variable region of a human anti-E6 TCR and an alpha chain constant region; and
 - b) a second nucleic acid sequence encoding a TCR beta chain comprising a beta chain variable region of the human anti-E6 TCR and a beta chain constant region.
23. The vector of claim 22, wherein the alpha chain constant region is a human TCR alpha chain constant region and the beta chain constant region is a human TCR beta chain constant region.
24. The vector of claim 22, wherein the alpha chain constant region is a mouse TCR alpha chain constant region and the beta chain constant region is a mouse TCR beta chain constant region.
25. The vector of anyone of claims 22-24, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a linker sequence.
26. The vector of claim 25, wherein the linker sequence is a P2A sequence.
27. The vector of anyone of claims 22-26, wherein
- (1) the first nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 17, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and the second nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 18, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
 - (2) the first nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 57, or a

nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and the second nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 58, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

5 (3) the first nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 59, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and the second nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 60, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or

10 (4) the first nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 61, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and the second nucleic acid sequence comprises a sequence set forth in SEQ ID NO: 62, or a nucleic acid sequence that has at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

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28. The vector of any one of claims 22-27, further comprising a third nucleic acid sequence encoding a checkpoint inhibitor.

29. The vector of claim 28, wherein the checkpoint inhibitor is an antibody.

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30. The vector of claim 28, wherein the checkpoint inhibitor is an anti-PD-1 antibody scFv, or an anti-CTLA4 antibody scFv.

31. The vector of claim 29, wherein the antibody comprises

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a heavy chain variable domain comprising an amino acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 11; and

a light chain variable domain comprising an amino acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:

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12.

32. The vector of any one of claims 28-31, wherein the third nucleic acid sequence comprises
a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, or 99% identical to SEQ ID NO: 13; and
a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
5 96%, 97%, 98%, or 99% identical to SEQ ID NO: 14.
33. The vector of any one of claims 22-32, wherein the vector is an expression vector, a viral
vector, a retroviral vector, or a lentiviral vector.
- 10 34. The vector of claim 33, wherein the retroviral vector is pMP71.
35. The vector of any one of claims 22-34, wherein the vector comprises
(1) a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, or 99% identical to SEQ ID NO: 20;
15 (2) a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, or 99% identical to SEQ ID NO: 63;
(3) a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
96%, 97%, 98%, or 99% identical to SEQ ID NO: 64; or
(4) a nucleic acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,
20 96%, 97%, 98%, or 99% identical to SEQ ID NO: 65.
36. An engineered cell comprising the vector of any of claims 20-35.
37. An engineered cell, comprising the TCR or antigen-binding fragment thereof of any of
25 claims 1-19.
38. The engineered cell of claim 37, wherein the TCR or antigen binding fragment thereof is
heterologous to the cell.
- 30 39. The engineered cell of any of claims 36-38, wherein the engineered cell is a cell line.

40. The engineered cell of any of claims 36-38, wherein the engineered cell is a primary cell obtained from a subject (e.g., a human subject).
41. The engineered cell of any of claims 36-40, wherein the engineered cell is a T cell.
- 5 42. The engineered cell of claim 41, wherein the T-cell is isolated from a human subject.
43. The engineered cell of claim 41, wherein the T cell is CD8+.
- 10 44. The engineered cell of claim 41, wherein the T cell is CD4+.
45. A method for producing the engineered cell, comprising introducing the vector of claims 20-35 into a cell *in vitro* or *ex vivo*.
- 15 46. The method of claim 45, wherein the vector is a viral vector and the introducing is carried out by transduction.
47. A method of treating a disease or a disorder, comprising administering the engineered cell of any of claims 36-44 to a subject having a disease or disorder associated with HPV.
- 20 48. The method of claim 47, wherein the disease or disorder associated with HPV is a cancer.
49. The method of claim 48, wherein the cancer is a cancer of the head and neck, uterine cervix, oropharynx, anus, anal canal, anorectum, vagina, vulva, or penis.
- 25 50. A method of treating a tumor in a subject, the method comprising
administering to the subject in need thereof
(a) an engineered T cell, comprising: a nucleic acid encoding a TCR or antigen-binding
fragment thereof that specifically binds to an HPV antigen; and
30 (b) a checkpoint inhibitor.

51. The method of claim 50, wherein the tumor is an HPV-induced tumor.
52. A TCR or antigen-binding fragment thereof that cross competes with the TCR or antigen-binding fragment thereof of any of claims 1-19.

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