Claims

What is claimed is:

1. An isolated antigen-binding protein that binds specifically to a conformational epitope of an HLA-A2 presented human papillomavirus (HPV) 16 E7 peptide (HPV16E7 peptide), wherein the conformational epitope comprises one or more amino acids of SEQ ID NO: 537 selected from the group consisting of Y11, D14, L15, P17 and E18,

wherein the antigen-binding protein comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3); and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein

(a) the HCDR1 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, and 524;

(b) the HCDR2 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 414, 430, 446, 462, 478, 494, 510, and 526;

(c) the HCDR3 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, and 528;

(d) the LCDR1 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 204, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, and 532;

(e) the LCDR2 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, and 534; and

(f) the LCDR3 domain comprises an amino acid sequence having at least 90% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence

selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 472, 488, 504, 520, and 536.

2. The isolated antigen-binding protein of claim 1, wherein the antigen-binding protein has a property selected from the group consisting of:

(a) binds monomeric HLA-A2:HPV16E7 11-19 (SEQ ID NO:538) peptide with a binding dissociation equilibrium constant (K_D) of less than about 20 nM as measured in a surface plasmon resonance assay at 25°C.;

(b) binds monomeric HLA-A2:HPV16E7 82-90 (SEQ ID NO:539) peptide with a binding dissociation equilibrium constant (K_D) of less than about 25 nM as measured in a surface plasmon resonance assay at 25°C.;

(c) binds to HLA-A2:HPV16E7 11-19 (SEQ ID NO:538) peptide expressing cells with an EC_{50} less than about 6 nM and do not bind to cells expressing predicted off-target peptides as determined by luminescence assay;

(d) binds to HLA-A2:HPV16E7 82-90 (SEQ ID NO:539) peptide expressing cells with an EC_{50} less than about 1 nM and do not substantially bind to cells expressing predicted off-target peptides as determined by luminescence assay;

(e) binds to HLA-A2:HPV16E7 11-19 (SEQ ID NO:538) peptide expressing cells with an EC_{50} less than about 30 nM as determined by flow cytometry assay; and

(f) binds to HLA-A2:HPV16E7 82-90 (SEQ ID NO:539) peptide expressing cells with an EC_{50} less than about 75 nM as determined by flow cytometry assay.

3. The isolated antigen-binding protein of claim 1, wherein the HPV16E7 peptide comprises the amino acid sequence of YMLDLQPET (SEQ ID NO: 538).

4. The isolated antigen-binding protein of claim 1, wherein the antigen-binding protein is a full-length antibody, a Fab, a Fab', a (Fab')2, an Fv, a single chain Fv (scFv), a T-body construct, or a CAR.

5. The isolated antigen-binding protein of claim 1, wherein the antigen-binding protein is a human monoclonal antibody, or antigen-binding fragment thereof.

6. The isolated antigen-binding protein of claim 1, wherein

(a) the HCDR1 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148,

164, 180, 196, 212, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, and 524;

(b) the HCDR2 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 414, 430, 446, 462, 478, 494, 510, and 526;

(c) the HCDR3 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, and 528;

(d) the LCDR1 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 204, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, and 532;

(e) the LCDR2 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, and 534; and

(f) the LCDR3 domain comprises an amino acid sequence having at least 95% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 472, 488, 504, 520, and 536.

7. The isolated antigen-binding protein of claim 6, wherein

(a) the HCDR1 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, and 524;

(b) the HCDR2 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150,

166, 182, 198, 214, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 414, 430, 446, 462, 478, 494, 510, and 526;

(c) the HCDR3 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, and 528;

(d) the LCDR1 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 204, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, and 532;

(e) the LCDR2 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, and 534; and

(f) the LCDR3 domain comprises an amino acid sequence having at least 98% amino acid sequence identity to the entire amino acid sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 472, 488, 504, 520, and 536.

8. The isolated antigen-binding protein of claim 7, wherein

(a) the HCDR1 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, and 524;

(b) the HCDR2 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 414, 430, 446, 462, 478, 494, 510, and 526;

(c) the HCDR3 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 464, 480, 496, 512, and 528;

(d) the LCDR1 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 204, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, and 532;

(e) the LCDR2 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158,174, 190, 206, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, and 534; and

(f) the LCDR3 domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144,160, 176, 192, 208, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 472, 488, 504, 520, and 536.

9. The isolated antigen-binding protein of claim 8, comprising a heavy chain variable region (HCVR)/light chain variable region (LCVR) (HCVR/LCVR) amino acid sequence pair, wherein the amino acid sequence of the HCVR and the amino acid sequence of the LCVR of each HCVR/LCVR pair are each independently at least 90% identical to the amino acid sequences of an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/202, 218/226, 234/242, 250/258, 266/274, 282/290, 298/306, 314/322, 330/338, 346/354, 362/370, 378/386, 394/402, 410/418, 426/434, 442/450, 458/466, 474/482, 490/498, 506/514, and 522/530.

10. The isolated antigen-binding protein of claim 8, wherein the HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 comprise an amino acid sequence set selected from the group consisting of SEQ ID NOs: 4, 6, 8, 12, 14, and 16; 36, 38, 40, 44, 46, and 48; 84, 86, 88, 92, 94, and 96; 196, 198, 200, 204, 206, and 208; 284, 286, 288, 292, 294, and 296; and 508, 510, 512, 516, 518, and 520.

11. The isolated antigen-binding protein of claim 9, wherein the amino acid sequence of the HCVR and the amino acid sequence of the LCVR of each HCVR/LCVR pair are each independently at least 95% identical to the amino acid sequence of an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/202, 218/226, 234/242, 250/258, 266/274, 282/290, 298/306, 314/322, 330/338, 346/354, 362/370, 378/386, 394/402, 410/418, 426/434, 442/450, 458/466, 474/482, 490/498, 506/514, and 522/530.

12. The isolated antigen-binding protein of claim 9, wherein the amino acid sequence of the HCVR and the amino acid sequence of the LCVR of each HCVR/LCVR pair are selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/202, 218/226, 234/242, 250/258, 266/274, 282/290, 298/306, 314/322, 330/338, 346/354, 362/370, 378/386, 394/402, 410/418, 426/434, 442/450, 458/466, 474/482, 490/498, 506/514, and 522/530.

13. The isolated antigen-binding protein of claim 4, wherein the antigen-binding protein is a single chain Fv (scFv).

14. The isolated antigen-binding protein of claim 12, comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 34/42, 82/90, 194/202, 282/290, and 506/514.

15. An isolated antigen-binding protein that binds to the same epitope as an antigen-binding protein of claim 9.

16. The isolated antigen-binding protein of claim 1, further comprising a detectable moiety.

17. A pharmaceutical composition comprising an isolated antigen-binding protein that binds to HLA-A2:HPV16E7 according to claim 11 and a pharmaceutically acceptable carrier or diluent.