

Adoptive cell transfer (ACT), as a modality of immunotherapy against cancer, has demonstrated remarkable success in treating hematologic malignancies and malignant melanoma. One form of ACT, which uses genetically modified T cells expressing a chimeric antigen receptor (CAR) to specifically target a tumor-associated-antigen (TAA), such as CD19 or GD2, has displayed encouraging results in clinical trials for treating such diseases as B cell malignancies. Despite this documented success of CAR-T cell therapy in patients with hematologic malignancies, only modest responses have been observed against solid tumors. Thus, there is a need for efficacious TCR-T cell therapies targeting EBV-induced cancer.

SUMMARY

The present disclosure provides an engineered T cell, comprising a nucleic acid encoding an anti-LMP2 TCR wherein the anti-LMP2 TCR is a genetically engineered T cell receptor (TCR) that specifically binds to LMP2 in a tumor.

In one ~~aspect~~~~example~~, provided herein is 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. In some ~~embodiment~~~~examples~~, the Va region comprises a complementarity determining region 1 (CDR1), a complementarity determining region 2 (CDR2), and a complementarity determining region 3 (CDR3). In some ~~embodiment~~~~examples~~, the CDR3 of the Va region comprises an amino acid sequence X₁GX₂SGYSTL, wherein the X₁ is a E, T, Q, V, or N; the X₂ is a D, G, N, or E. In some ~~embodiment~~~~examples~~, the Vb region comprises a CDR1, a CDR2, and a CDR3. In some ~~embodiment~~~~examples~~, the CDR3 of the Vb region comprises an amino acid sequence X₃X₄QGGX₅X₆X₇X₈, wherein the X₃ is a S, T, N, or R; the X₄ is a T, R, Y, G, V, Q, F, S, or P; the X₅ is a N, G, H, T, S, A, I, or W; the X₆ is a Y, N, D, E, R, or I; the X₇ is a G, Q, N, Y; the X₈ is a Y, F, or G.

In one aspect, the present disclosure refers to 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

(a) the Va region comprises a complementarity determining region 1 (CDR1), a complementarity determining region 2 (CDR2), and a complementarity determining region 3 (CDR3), wherein the CDR3 of the Va region comprises an amino acid sequence X₁GX₂SGYSTL, wherein

the X₁ is a E, T, Q, V, or N,

the X₂ is a D, G, N, or E ; and

(b) the Vb region comprises a CDR1, a CDR2, and a CDR3, wherein the CDR3 of the Vb region comprises an amino acid sequence X₃X₄QGGX₅X₆X₇X₈, wherein

the X₃ is a S, T, N, or R,

the X₄ is a T, R, Y, G, V, Q, F, S, or P,

the X₅ is a N, G, H, T, S, A, I, or W,

the X₆ is a Y, N, D, E, R, or I,

the X₇ is a G, Q, N, Y,

the X₈ is a Y, F, or G.

In some ~~embodiment~~~~examples~~, the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment. In some ~~embodiment~~~~examples~~, the TRAV gene segment is TRAV17; the TRAJ gene segment is TRAJ11; the TRBV gene segment is TRBV6-5; the TRBD gene segment is TRBD1 or TRBD2; and the TRBJ gene segment is TRBJ2-1 or TRBJ1-2.

In some embodiment examples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to TSINN (SEQ ID NO: 1), the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to IRSNERE (SEQ ID NO: 2), the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to MNHEY (SEQ ID NO: 4), and the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SVGAGI (SEQ ID NO: 5).

In some embodiment examples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence. In some embodiment examples, the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence. In some embodiment examples, the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4-6, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7-9, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10-12, respectively;

(3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16-18, respectively;

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19-21, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22-24, respectively;

In one aspectexample, provided herein is a T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region. In some embodimentexamples, 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). In some embodimentexamples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 55, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 56, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 57. In some embodimentexamples, provided herein is the T cell receptor (TCR) or antigen-binding fragment thereof, further comprising a beta chain comprising a variable beta (Vb) region. In some embodimentexamples, 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). In some embodimentexamples, the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 58, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 59, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 60.

In some embodimentexamples, the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (FLYALALLL) (SEQ ID NO: 139) that is presented by a major histocompatibility complex (MHC) molecule.

In some embodimentexamples, the MHC molecule is an HLA-A2 molecule.

In some embodimentexamples, the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment. In some embodimentexamples, the TRAV gene segment is TRAV21; the TRAJ gene segment is TRAJ33; the TRBV gene segment is TRBV10-2; the TRBD gene segment is TRBD1 or TRBD2; and the TRBJ gene segment is TRBJ2-7.

In some embodimentexamples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 143, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 144, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 145; and in some embodimentexamples, the Vb CDR1 region comprises an amino acid sequence that is at least 80%

identical to SEQ ID NO: 146, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 147, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 148.

In one aspect, the present disclosure refers to a T cell receptor (TCR) or antigen-binding fragment thereof, comprising

an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and

a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence; wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 143, 144, and 145, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 146, 147, and 148, respectively; and

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 73, 74, and 75, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 76, 77, and 78, respectively.

In some embodimentexamples, the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 CLGGLTMTV (SEQ ID NO: 167) and/or SLGGLTMTV (SEQ ID NO: 168) that is presented by a major histocompatibility complex (MHC) molecule.

5 In some embodimentexamples, the MHC molecule is an HLA-A2 molecule.

In one aspectexample, provided herein is a T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region. In some embodimentexamples, 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). In some embodimentexamples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence. In some

15 embodimentexamples, provided herein is the TCR or antigen-binding fragment thereof, further comprising a beta chain comprising a variable beta (Vb) region. In some embodimentexamples, 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). In some embodimentexamples, the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence. In some embodimentexamples, the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

25 (1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 91, 92, 93, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 94, 95, 96, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 97, 98, 99, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 100, 101, 102, respectively;

(3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 103, 104, 105, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 106, 107, 108, respectively; and

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 149, 150, and 151, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 152, 153, and 154, respectively; and

(5) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 155, 156, and 157, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 158, 159, and 160, respectively.

In some embodimentexamples, the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment. In some embodimentexamples, the TRAV gene segment is TRAV4, TRAV25, TRAV22, or TRAV6; the TRAJ gene segment is TRAJ23, TRAJ47, TRAJ29, TRAJ43, or TRAJ11; the TRBV gene segment is TRBV12-4, TRBV12-3, TRBV11-2, TRBV4-1, or TRBV11-2; the TRBD gene segment is TRBD2; and the TRBJ gene segment is TRBJ1-1, TRBJ2-1, TRBJ2-5, or TRBJ2-7.

In some embodimentexamples, the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (SSCSSCPLSK) (SEQ ID NO: 140) that is presented by a major histocompatibility complex (MHC) molecule.

In some embodimentexamples, the MHC molecule is an HLA-A11 molecule.

In one aspectexample, provided herein is a T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region. In some embodimentexamples, 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). In some embodimentexamples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino

acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence. In some [embodimentexamples](#), provided herein is the TCR or antigen-binding fragment thereof, further comprising a beta chain comprising a variable beta (Vb) region. In some [embodimentexamples](#), 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). In some [embodimentexamples](#), the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence. In some [embodimentexamples](#), the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 109, 110, 111, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 112, 113, 114, respectively; or

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 115, 116, 117, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 118, 119, 120, respectively.

In some [embodimentexamples](#), the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment. In some [embodimentexamples](#), the TRAV gene segment is TRAV12-1; the TRAJ gene segment is TRAJ21; the TRBV gene segment is TRBV20-1; the TRBD gene segment is TRBD1; and the TRBJ gene segment is TRBJ2-5 or TRBJ2-3.

In some [embodimentexamples](#), the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (IYVLVMLVL) (SEQ ID NO: 141) that is presented by a major histocompatibility complex (MHC) molecule.

In one [aspectexample](#), provided herein is a T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region. In some [embodimentexamples](#), 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). In some embodimentexamples, the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence. In some embodimentexamples, provided herein is the TCR or antigen-binding fragment thereof, further comprising a beta chain comprising a variable beta (Vb) region. In some embodimentexamples, 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). In some embodimentexamples, the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence. In some embodimentexamples, the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 121, 122, 123, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 124, 125, 126, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 127, 128, 129, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 130, 131, 132, respectively;

(3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 133, 134, 135, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 136, 137, 138, respectively; or

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 161, 162, and 163, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 164, 165, and 166, respectively.

In one aspect, the present disclosure refers to a T cell receptor (TCR) or antigen-binding fragment thereof, comprising:

an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and

a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence; wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 91, 92, and 93, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 94, 95, and 96, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 97, 98, and 99, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 100, 101, and 102, respectively;

(3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 103, 104, and 105, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 106, 107, and 108, respectively;

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 149, 150, and 151, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 152, 153, and 154, respectively;

(5) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 155, 156, and 157, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 158, 159, and 160, respectively;

(6) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 121, 122, and 123, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 124, 125, and 126, respectively;

(7) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 109, 110, and 111, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 112, 113, and 114, respectively;

(8) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 115, 116, and 117, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 118, 119, and 120, respectively;

(9) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 127, 128, and 129, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 130, 131, and 132, respectively;

(10) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 133, 134, and 135, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 136, 137, and 138, respectively; and

(11) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 161, 162, and 163, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 164, 165, and 166, respectively.

In some ~~embodiment~~ examples, the Va region is encoded by a sequence from rearrangement of a TCR alpha variable (TRAV) gene segment and a TCR alpha joining (TRAJ) gene segment, and the Vb region is encoded by a sequence from rearrangement of a TCR beta variable (TRBV)

gene segment, optionally a TCR beta diversity (TRBD) gene segment, and a TCR beta joining (TRBJ) gene segment. In some [embodimentexamples](#), the TRAV gene segment is TRAV25, TRAV12-3, or TRAV21; the TRAJ gene segment is TRAJ16, TRAJ3, TRAJ35; the TRBV gene segment is TRBV6-6, TRBV24-1, or TRBV30; the TRBD gene segment is TRBD1 or TRBD2; and the TRBJ gene segment is TRBJ1-1, TRBJ2-5, TRBJ2-3, or TRBJ2-7.

In some [embodimentexamples](#), the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (TYGPVFMCL) (SEQ ID NO: 142) that is presented by a major histocompatibility complex (MHC) molecule.

In some [embodimentexamples](#), the MHC molecule is an HLA-A24 molecule.

In some [embodimentexamples](#), the alpha chain comprises a mouse alpha chain constant region, and the beta chain comprises a mouse beta chain constant region.

In some [embodimentexamples](#), the alpha chain comprises a human alpha chain constant region, and the beta chain comprises a human beta chain constant region.

In some [embodimentexamples](#), the TCR or antigen-binding fragment thereof, when expressed on the surface of a T cell, stimulates cytotoxic activity against a target cancer cell. In some [embodimentexamples](#), the target cancer cell comprises a nucleic acid sequence encoding LMP2 or expresses LMP2.

In one aspect, provided herein is a vector comprising a nucleic acid encoding TCR or antigen-binding fragment thereof as described herein.

In one [aspectexample](#), provided herein is a vector comprising: a) a first nucleic acid sequence encoding a TCR alpha chain comprising an alpha chain variable region of a human anti-LMP2 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-LMP2 TCR and a beta chain constant region. In some [embodimentexamples](#), the TCR alpha chain and the TCR beta chain form the TCR or antigen-binding fragment thereof as described herein. In one aspect, the present disclosure provides a vector comprising:

a) a first nucleic acid sequence encoding a TCR alpha chain comprising an alpha chain variable region of a human anti-LMP2 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-LMP2 TCR and a beta chain constant region,

wherein the TCR alpha chain and the TCR beta chain form the TCR or antigen-binding fragment thereof as described herein.

In some [embodimentexamples](#), the first nucleic acid sequence and the second nucleic acid sequence is linked by a linker sequence. In some [embodimentexamples](#), the linker sequence is a P2A sequence.

In some [embodimentexamples](#), the vector is an expression vector, a viral vector, a retroviral vector, or a lentiviral vector. In some [embodimentexamples](#), the retroviral vector is pMP71.

In one aspect, provided herein is an engineered cell comprising the vector as described herein.

In one aspect, provided herein is an engineered cell, comprising the TCR or antigen-binding fragment thereof as described herein.

5 In some embodimentexamples, the TCR or antigen binding fragment thereof is heterologous to the cell.

In some embodimentexamples, the engineered cell is a cell line.

In some embodimentexamples, the engineered cell is a primary cell obtained from a subject (e.g., a human subject).

10 In some embodimentexamples, the engineered cell is a T cell. In some embodimentexamples, the T-cell is isolated from a human subject. In some embodimentexamples, the T cell is CD8+. In some embodimentexamples, the T cell is CD4+.

In some embodimentexamples, the engineered cell expresses a bifunctional trap protein. In some embodimentexamples, the bifunctional trap protein targets a checkpoint inhibitor (e.g., PD-1) and a member of the transforming growth factor beta family (e.g., TGF-β).

15 In some embodimentexamples, the engineered cell expresses an antibody or antigen-binding fragment thereof targeting a checkpoint inhibitor (e.g., PD-1).

In some embodimentexamples, the engineered cell expresses a protein that binds to a member of the transforming growth factor beta family (e.g., TGF-β).

20 In one aspect, provided herein is a method for producing the engineered cell, comprising introducing the vector as described herein into the cell *in vitro* or *ex vivo*. In some embodimentexamples, the introducing step is carried out by transduction.

In one aspectexample, provided herein is a method of treating a disease or a disorder, comprising administering the engineered cell as described herein to a subject having a disease or disorder associated with EBV. In one aspect, the present disclosure refers to use of the engineered cell as described herein in the manufacture of a medicament for treating a disease or disorder associated with EBV. In some embodimentexamples, the disease or disorder associated with EBV is a cancer.

25 In one aspectexample, provided herein is a method of treating a tumor in a subject, the method comprising administering to the subject in need thereof an engineered T cell, comprising a nucleic acid encoding the TCR or antigen-binding fragment thereof as described herein that specifically binds to an antigen in the tumor. In one aspect, the present disclosure refers to use of an engineered T cell, comprising a nucleic acid encoding the TCR or antigen-binding fragment thereof as described herein that specifically binds to an antigen in the tumor, in the manufacture of a medicament for treating a tumor in a subject.

In one ~~aspect~~example, provided herein is 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 the TCR or antigen-binding fragment thereof as described herein that specifically binds to an antigen in a tumor; and (b) either one or both of a checkpoint inhibitor and a protein that binds to a member of the transforming growth factor beta family (e.g., TGF- β).

In one ~~aspect~~example, provided herein is a method of treating a tumor in a subject, the method comprising administering to the subject in need thereof an engineered T cell, comprising: a nucleic acid encoding (a) the TCR or antigen-binding fragment thereof as described herein that specifically binds to an antigen in a tumor; and (b) a bifunctional trap protein that targets a checkpoint inhibitor and a member of the transforming growth factor beta family (e.g., TGF- β).

In one aspect, the present disclosure refers to use of:

(a) an engineered T cell, comprising: a nucleic acid encoding the TCR or antigen-binding fragment thereof as described herein that specifically binds to an antigen in a tumor, in the manufacture of a medicament for use in combinatorial therapy for treating a tumor in a subject, wherein said medicament is to be administered in combination with:

(b) either one or both of a checkpoint inhibitor and a protein that binds to a member of the transforming growth factor beta family; or a bifunctional trap protein that targets a checkpoint inhibitor and a member of the transforming growth factor beta family.

In some ~~embodiment~~examples, the tumor is an EBV-associated tumor.

In some ~~embodiment~~examples, the cancer or the EBV-associated tumor as described herein is Burkitt's lymphoma, immunosuppressive lymphoma, diffuse large B-cell lymphoma, diffuse large B-cell lymphoma associated with chronic inflammation, lymphomatoid granulomatosis, plasmablastic lymphoma, primary effusion lymphoma, post-transplant lymphoproliferative disorder, nasopharyngeal carcinoma, gastric adenocarcinoma, lymphoepithelioma-associated carcinoma, immunodeficiency-related leiomyosarcoma, or Hodgkin's lymphoma.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention~~disclosure belongs. Methods and materials are described herein for use in the present ~~invention~~disclosure; other, suitable methods and materials known in the art can also be used.

The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the ~~invention~~disclosure will be apparent from the following detailed description and figures, and from the claims.

WHAT IS CLAIMED IS:

5 1. A T cell receptor (TCR) or antigen-binding fragment thereof, comprising
an alpha chain comprising a variable alpha (Va) region, wherein 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
10 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va
CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at
least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region
comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino
acid sequence; and
a beta chain comprising a variable beta (Vb) region, wherein the Vb region comprises a
15 complementarity determining region 1 (CDR-1), a complementarity determining region 2
(CDR-2), and a complementarity determining region 3 (CDR-3), wherein the Vb CDR1 region
comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino
acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80%
identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an
20 amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence;
wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid
sequences are one of the following:
(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs:
143, 144, and 145, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set
25 forth in SEQ ID NOs: 146, 147, and 148, respectively; and
(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs:
73, 74, and 75, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set
forth in SEQ ID NOs: 76, 77, and 78, respectively.

12. 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

(a) the Va region comprises a complementarity determining region 1 (CDR1), a complementarity determining region 2 (CDR2), and a complementarity determining region 3 (CDR3), wherein the CDR3 of the Va region comprises an amino acid sequence X₁GX₂SGYSTL, wherein

the X₁ is a E, T, Q, V, or N,

the X₂ is a D, G, N, or E ; and

(b) the Vb region comprises a CDR1, a CDR2, and a CDR3, wherein the CDR3 of the Vb region comprises an amino acid sequence X₃X₄QGGX₅X₆X₇X₈, wherein

the X₃ is a S, T, N, or R,

the X₄ is a T, R, Y, G, V, Q, F, S, or P,

the X₅ is a N, G, H, T, S, A, I, or W,

the X₆ is a Y, N, D, E, R, or I,

the X₇ is a G, Q, N, Y,

the X₈ is a Y, F, or G.

23. The T cell receptor (TCR) or antigen-binding fragment thereof of claim **12**, wherein the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment, wherein

the TRAV gene segment is TRAV17;

the TRAJ gene segment is TRAJ11;

the TRBV gene segment is TRBV6-5;

the TRBD gene segment is TRBD1 or TRBD2; and

the TRBJ gene segment is TRBJ2-1 or TRBJ1-2.

34. The T cell receptor (TCR) or antigen-binding fragment thereof of claim **12** or claim **23**, wherein the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to

TSINN (SEQ ID NO: 1), the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to IRSNERE (SEQ ID NO: 2), the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to MNHEY (SEQ ID NO: 4), and the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SVGAGI (SEQ ID NO: 5).

5

45. The T cell receptor (TCR) or antigen-binding fragment thereof of any one of claims ~~1-32~~-4, wherein the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and

10 wherein the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, 15 the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence;

wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1-3, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4-6, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7-9, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10-12, respectively;

25 (3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13-15, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16-18, respectively;

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19-21, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in 30 SEQ ID NOs: 22-24, respectively;

(5) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 25-27, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 28-30, respectively;

5 (6) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 31-33, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 34-36, respectively;

(7) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 37-39, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 40-42, respectively;

10 (8) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 43-45, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 46-48, respectively;

(9) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 49-51, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
15 SEQ ID NOs: 52-54, respectively;

(10) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 55-57, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 58-60, respectively;

20 ~~(1011)~~ the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 61-63, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 64-66, respectively;

~~(1112)~~ the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 67-69, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 70-72, respectively;

25 ~~(12) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 73-75, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 76-78, respectively;~~

(13) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 79-81, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
30 SEQ ID NOs: 82-84, respectively; ~~or~~ and

(14) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 85-87, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 88-90, respectively.

~~5. A T cell receptor (TCR) or antigen-binding fragment thereof, comprising an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 55, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 56, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 57; and a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 58, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 59, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 60.~~

~~6. The TCR or antigen-binding fragment thereof of any one of claims 1-5, wherein the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (FLYALALLL) (SEQ ID NO: 139) that is presented by a major histocompatibility complex (MHC) molecule.~~

~~7. The TCR or antigen-binding fragment thereof of claim 6, wherein the MHC molecule is an HLA-A2 molecule.~~

~~8. The T cell receptor (TCR) or antigen-binding fragment thereof of claim 1, wherein the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of~~

~~a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment, wherein~~

~~the TRAV gene segment is TRAV21;~~

~~the TRAJ gene segment is TRAJ33;~~

~~the TRBV gene segment is TRBV10-2;~~

~~the TRBD gene segment is TRBD1 or TRBD2; and~~

~~the TRBJ gene segment is TRBJ2-7.~~

~~9. The T cell receptor (TCR) or antigen binding fragment thereof of claim 1 or 8,~~

~~wherein the Va CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 143, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 144, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 145; and~~

~~wherein the Vb CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 146, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 147, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 148.~~

~~10. A T cell receptor (TCR) or antigen binding fragment thereof, comprising~~

~~an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 143, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 144, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 145; and~~

~~a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 146, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO:~~

~~147, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to SEQ ID NO: 148.~~

~~11. The TCR or antigen binding fragment thereof of any one of claims 1 and 8-10, wherein the TCR or antigen binding fragment thereof binds to or recognizes a peptide epitope of LMP2 CLGGLTMMV (SEQ ID NO: 167) and/or SLGGLTMMV (SEQ ID NO: 168) that is presented by a major histocompatibility complex (MHC) molecule.~~

~~12. The TCR or antigen binding fragment thereof of claim 11, wherein the MHC molecule is an HLA A2 molecule.~~

~~136.~~ A T cell receptor (TCR) or antigen-binding fragment thereof, comprising:

an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and

a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence;

wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 91, 92, and 93, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 94, 95, and 96, respectively;

(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 97, 98, and 99, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 100, 101, and 102, respectively;

(3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 103, 104, and 105, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 106, 107, and 108, respectively;

(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 149, 150, and 151, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 152, 153, and 154, respectively; ~~and~~

(5) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 155, 156, and 157, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 158, 159, and 160, respectively;

(6) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 121, 122, and 123, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 124, 125, and 126, respectively;

(7) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 109, 110, and 111, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 112, 113, and 114, respectively;

(8) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 115, 116, and 117, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 118, 119, and 120, respectively;

(9) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 127, 128, and 129, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 130, 131, and 132, respectively;

(10) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 133, 134, and 135, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 136, 137, and 138, respectively; and

(11) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 161, 162, and 163, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 164, 165, and 166, respectively.

14. ~~The T-cell receptor (TCR) or antigen-binding fragment thereof of claim 13, wherein the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment, wherein~~

~~the TRAV gene segment is TRAV4, TRAV25, TRAV22, or TRAV6;~~

~~the TRAJ gene segment is TRAJ23, TRAJ47, TRAJ29, TRAJ43, or TRAJ11;~~

~~the TRBV gene segment is TRBV12-4, TRBV12-3, TRBV11-2, TRBV4-1, or TRBV11-2;~~

~~the TRBD gene segment is TRBD2; and~~

~~the TRBJ gene segment is TRBJ1-1, TRBJ2-1, TRBJ2-5, or TRBJ2-7.~~

15. ~~The TCR or antigen-binding fragment thereof of claim 13 or 14, wherein the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (SSCSSCPLSK) (SEQ ID NO: 140) 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-A11 molecule.~~

17. ~~A T cell receptor (TCR) or antigen-binding fragment thereof, comprising:~~

~~an alpha chain comprising a variable alpha (Va) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and~~

a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence; wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are one of the following:

- (1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 109, 110, and 111, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 112, 113, and 114, respectively; or
- (2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 115, 116, and 117, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 118, 119, and 120, respectively.

18. The T cell receptor (TCR) or antigen binding fragment thereof of claim 17, wherein the Va region is encoded by a sequence from rearrangement of a human TRAV gene segment and a human TRAJ gene segment, and the Vb region is encoded by a sequence from rearrangement of a human TRBV gene segment, optionally a human TRBD gene segment, and a human TRBJ gene segment, wherein

- the TRAV gene segment is TRAV12-1;
- the TRAJ gene segment is TRAJ21;
- the TRBV gene segment is TRBV20-1;
- the TRBD gene segment is TRBD1; and
- the TRBJ gene segment is TRBJ2-5 or TRBJ2-3.

19. The TCR or antigen binding fragment thereof of claim 17 or 18, wherein the TCR or antigen binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (IYVLVMLVL) (SEQ ID NO: 141) that is presented by a major histocompatibility complex (MHC) molecule.

20. A T cell receptor (TCR) or antigen-binding fragment thereof, comprising:
an alpha chain comprising a variable alpha (Va) region, wherein the Va region comprises a
complementarity determining region 1 (CDR-1), a complementarity determining region 2
5 (CDR-2), and a complementarity determining region 3 (CDR-3), wherein the Va CDR1 region
comprises an amino acid sequence that is at least 80% identical to a selected Va CDR1 amino
acid sequence, the Va CDR2 region comprises an amino acid sequence that is at least 80%
identical to a selected Va CDR2 amino acid sequence, the Va CDR3 region comprises an amino
acid sequence that is at least 80% identical to a selected Va CDR3 amino acid sequence; and
10 a beta chain comprising a variable beta (Vb) region, wherein 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 CDR1 region
comprises an amino acid sequence that is at least 80% identical to a selected Vb CDR1 amino
acid sequence, the Vb CDR2 region comprises an amino acid sequence that is at least 80%
15 identical to a selected Vb CDR2 amino acid sequence, the Vb CDR3 region comprises an
amino acid sequence that is at least 80% identical to a selected Vb CDR3 amino acid sequence;
wherein the selected Va CDRs 1, 2, and 3 and Vb CDRs 1, 2, and 3 amino acid sequences are
one of the following:
(1) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 121, 122,
20 and 123, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
SEQ ID NOs: 124, 125, and 126, respectively;
(2) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 127, 128,
and 129, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
SEQ ID NOs: 130, 131, and 132, respectively;
25 (3) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 133, 134,
and 135, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
SEQ ID NOs: 136, 137, and 138, respectively; or
(4) the selected Va CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 161, 162,
and 163, respectively, and the selected Vb CDRs 1, 2, 3 amino acid sequences are set forth in
30 SEQ ID NOs: 164, 165, and 166, respectively.

21. The T cell receptor (TCR) or antigen-binding fragment thereof of claim 15, wherein the Va region is encoded by a sequence from rearrangement of a TCR alpha variable (TRAV) gene segment and a TCR alpha joining (TRAJ) gene segment, wherein the Vb region is encoded by a sequence from rearrangement of a TCR beta variable (TRBV) gene segment, optionally a TCR beta diversity (TRBD) gene segment, and a TCR beta joining (TRBJ) gene segment, wherein the TRAV gene segment is TRAV25, TRAV12-3, or TRAV21; the TRAJ gene segment is TRAJ16, TRAJ3, or TRAJ35; the TRBV gene segment is TRBV6-6, TRBV24-1, or TRBV30; the TRBD gene segment is TRBD1 or TRBD2; and the TRBJ gene segment is TRBJ1-1, TRBJ2-5, TRBJ2-3, or TRBJ2-7.

22. The TCR or antigen-binding fragment thereof of claim 20 or 21, wherein the TCR or antigen-binding fragment thereof binds to or recognizes a peptide epitope of LMP2 (TYGPVFMCL) (SEQ ID NO: 142) that is presented by a major histocompatibility complex (MHC) molecule.

23. The TCR or antigen-binding fragment thereof of claim 19 or 22, wherein the MHC molecule is an HLA-A24 molecule.

247. The TCR or antigen-binding fragment thereof of any one of claims 1-236, wherein the alpha chain comprises a mouse or human alpha chain constant region, and the beta chain comprises a mouse or human beta chain constant region.

25. The TCR or antigen-binding fragment thereof of any one of claims 1-23, wherein the alpha chain comprises a human alpha chain constant region, and the beta chain comprises a human beta chain constant region.

268. The TCR or antigen-binding fragment thereof of any of claims 1-257, 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.

~~27. The TCR or antigen-binding fragment thereof of claim 26, wherein the target cancer cell comprises a nucleic acid sequence encoding LMP2 or expresses LMP2.~~

5 ~~289.~~ A vector comprising a nucleic acid encoding TCR or antigen-binding fragment thereof of any one of claims 1-~~278~~.

~~2910.~~ A vector comprising:

10 a) a first nucleic acid sequence encoding a TCR alpha chain comprising an alpha chain variable region of a human anti-LMP2 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-LMP2 TCR and a beta chain constant region,

wherein the TCR alpha chain and the TCR beta chain form the TCR or antigen-binding fragment thereof of any one of claims 1-~~278~~.

15

~~30. The vector of claim 29, wherein the first nucleic acid sequence and the second nucleic acid sequence is linked by a linker sequence.~~

~~31. The vector of claim 30, wherein the linker sequence is a P2A sequence.~~

20

~~32. The vector of any one of claims 28-31, wherein the vector is an expression vector, a viral vector, a retroviral vector, or a lentiviral vector.~~

~~33. The vector of claim 32, wherein the retroviral vector is pMP71.~~

25

~~3411.~~ An engineered cell comprising the vector of ~~any one of claims 28-33~~claim 9 or claim 10.

30

~~3512.~~ An engineered cell, comprising the TCR or antigen-binding fragment thereof of any of claims 1-~~278~~.

36. ~~—The engineered cell of claim 34 or 35, wherein the TCR or antigen binding fragment thereof is heterologous to the cell.~~

3713. The engineered cell of ~~any one of claims 34-36~~claim 11 or claim 12, wherein the engineered cell is a cell line or a primary cell obtained from a subject.

38. ~~—The engineered cell of any one of claims 34-36, wherein the engineered cell is a primary cell obtained from a subject (e.g., a human subject).~~

3914. The engineered cell of any of claims ~~34-38~~11-13, wherein the engineered cell is a T cell.

40. ~~—The engineered cell of claim 39, wherein the T cell is isolated from a human subject.~~

41. ~~—The engineered cell of claim 39, wherein the T cell is CD8+.~~

42. ~~—The engineered cell of claim 39, wherein the T cell is CD4+.~~

4315. The engineered cell of any one of claims ~~34-42~~11-14, wherein the engineered cell expresses a bifunctional trap protein, an antibody or antigen-binding fragment thereof targeting a checkpoint inhibitor, or a protein that binds to a member of the transforming growth factor beta family.

44. ~~—The engineered cell of claim 43, wherein the bifunctional trap protein targets a checkpoint inhibitor (e.g., PD-1) and a member of the transforming growth factor beta family (e.g., TGF- β).~~

45. ~~—The engineered cell of any one of claims 34-42, wherein the engineered cell expresses an antibody or antigen binding fragment thereof targeting a checkpoint inhibitor (e.g., PD-1).~~

~~46. The engineered cell of any one of claims 34-42 and 45, wherein the engineered cell expresses a protein that binds to a member of the transforming growth factor beta family (e.g., TGF- β).~~

5 ~~4716.~~ A method for producing the engineered cell, comprising introducing the vector of ~~any one of claims 28-33~~claim 9 or claim 10 into the cell *in vitro* or *ex vivo*.

~~48. The method of claim 47, wherein the introducing step is carried out by transduction.~~

10 ~~4917. A method of treating a disease or a disorder, comprising administering~~Use of the engineered cell of any one of claims ~~34-46~~11-15 in the manufacture of a medicament for treating to a subject having a disease or disorder associated with EBV.

15 ~~5018.~~ The ~~method-use~~ of claim ~~4917~~, wherein the disease or disorder associated with EBV is a cancer.

~~5119. A method of treating a tumor in a subject, the method comprising administering to the subject in need thereof~~Use of an engineered T cell, comprising a nucleic acid encoding the TCR or antigen-binding fragment thereof of claims 1-~~27-8~~ that specifically binds to an antigen in the tumor, in the manufacture of a medicament for treating a tumor in a subject.

25 ~~5220. A method of treating a tumor in a subject, the method comprising administering to the subject in need thereof~~Use of:
(a) an engineered T cell, comprising: a nucleic acid encoding the TCR or antigen-binding fragment thereof of claims 1-~~27-8~~ that specifically binds to an antigen in a tumor, in the manufacture of a medicament; and for use in combinatorial therapy for treating a tumor in a subject, wherein said medicament is to be administered in combination with:

30 (b) either one or both of a checkpoint inhibitor and a protein that binds to a member of the transforming growth factor beta family; or a bifunctional trap protein that targets a checkpoint inhibitor and a member of the transforming growth factor beta family (e.g., TGF- β).

53. ~~A method of treating a tumor in a subject, the method comprising~~
~~administering to the subject in need thereof~~
~~an engineered T cell, comprising: a nucleic acid encoding~~
5 ~~(a) the TCR or antigen-binding fragment thereof of claims 1-27 that specifically binds~~
~~to an antigen in a tumor; and~~
~~(b) a bifunctional trap protein that targets a checkpoint inhibitor and a member of the~~
~~transforming growth factor beta family (e.g., TGF- β).~~

10 54. ~~The method of any one of claims 51-53, wherein the tumor is an EBV-associated~~
~~tumor.~~

55. ~~The method of claim 50 or 54, wherein the cancer or the EBV-associated tumor is~~
~~Burkitt's lymphoma, immunosuppressive lymphoma, diffuse large B-cell lymphoma, diffuse~~
15 ~~large B-cell lymphoma associated with chronic inflammation, lymphomatoid granulomatosis,~~
~~plasmablastic lymphoma, primary effusion lymphoma, post-transplant lymphoproliferative~~
~~disorder, nasopharyngeal carcinoma, gastric adenocarcinoma, lymphoepithelioma-associated~~
~~carcinoma, immunodeficiency-related leiomyosarcoma, or Hodgkin's lymphoma.~~