

CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an anti-BCMA binding domain (e.g., human anti-BCMA binding domain), a transmembrane domain, and an intracellular signaling domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain ~~complementary-complementarity~~ determining region 1 (HC CDR1), a heavy chain ~~complementary-complementarity~~ determining region 2 (HC CDR2), and a heavy chain ~~complementarity-complementary~~ determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain ~~complementarity-complementary~~ determining region 1 (LC CDR1), a light chain ~~complementarity-complementary~~ determining region 2 (LC CDR2), and a light chain ~~complementarity-complementary~~ determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:

- (i) SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively;
- (ii) ~~SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively; or~~
- (iii) ~~SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively.~~

2. An isolated CAR comprising an anti-BCMA binding domain (e.g., human anti-BCMA binding domain), a transmembrane domain, and an intracellular signaling domain, wherein the anti-BCMA binding domain comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:

- (i) SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively;
- (ii) ~~SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively; or~~
- (iii) ~~SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively.~~

~~3. The isolated nucleic acid molecule or CAR of claim 1 or 2, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively.~~

~~43.~~ The isolated nucleic acid molecule of claim 1 or CAR of claim ~~32~~, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:

- (i) SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively;
- (ii) SEQ ID NOs: 86, 109, 88, 95, 114, and 115, respectively; or

(iii) SEQ ID NOs: 86, 109, 88, 95, 114, and 97, respectively.

~~54~~. The isolated nucleic acid molecule of claim 1 or 3 or CAR of claim 2 or 3-~~or 4~~, wherein the VH comprises the amino acid sequence of SEQ ID NO: 93 or 112, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~65~~. The isolated nucleic acid molecule of any one of claims 3-~~51~~, 3, or 4, comprising a nucleic acid sequence encoding the VH, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 260, 94 or 113, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~76~~. The isolated nucleic acid molecule of any one of claims 1 or 3-5 or CAR of any one of claims 3-~~62~~-4, wherein the VL comprises the amino acid sequence of SEQ ID NO: 102, 118, or 124, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~87~~. The isolated nucleic acid molecule of any one of claims 3-~~71~~ or 3-6, comprising a nucleic acid sequence encoding the VL, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 261, 103, 119, or 125, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~98~~. The isolated nucleic acid molecule of any one of claims 1 or 3-7 or CAR of any one of claims 3-~~82~~-4, or 6, wherein the VH and VL comprise the amino acid sequences of:

- (i) SEQ ID NOs: 93 and 102, respectively;
- (ii) SEQ ID NOs: 112 and 118, respectively; or
- (iii) SEQ ID NOs: 112 and 124, respectively.

~~109~~. The isolated nucleic acid molecule of any one of claims 1 or 3-8 or CAR of any one of claims 3-~~92~~-4, 6, or 8, wherein the anti-BCMA binding domain comprises a single-chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 105, 120, or 126, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~110~~. The isolated nucleic acid molecule of any one of claims 1-~~101~~ or 3-9, wherein the anti-BCMA binding domain comprises a scFv, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding the scFv, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 253, 106, 121, or 127, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~1211.~~ The isolated nucleic acid molecule of any one of claims 1 or 3-10 or CAR of any one of claims ~~3-112-4, 6, 8, or 9~~, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 107, 122, or 128, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~1312.~~ The isolated nucleic acid molecule of any one of claims ~~3-121~~ or ~~3-11~~, wherein the nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 259, 258, 108, 123, or 129, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~14.~~ The isolated nucleic acid molecule or CAR of claim ~~1 or 2~~, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 ~~comprise the amino acid sequences of SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively.~~

~~15.~~ The isolated nucleic acid molecule or CAR of claim ~~14~~, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 ~~comprise the amino acid sequences of:~~

- ~~(i) SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively;~~
- ~~(ii) SEQ ID NOs: 44, 45, 46, 54, 55, and 56, respectively; or~~
- ~~(iii) SEQ ID NOs: 44, 45, 68, 54, 55, and 56, respectively.~~

~~16.~~ The isolated nucleic acid molecule or CAR of claim ~~14 or 15~~, wherein the VH comprises the amino acid sequence of SEQ ID NO: 78, 52, or 70, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~17.~~ The isolated nucleic acid molecule of any one of claims ~~14-16~~, comprising a nucleic acid sequence encoding the VH, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 79, 53, or 71, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~18.~~ The isolated nucleic acid molecule or CAR of any one of claims ~~14-17~~, wherein the VL comprises the amino acid sequence of SEQ ID NO: 61, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~19.~~ The isolated nucleic acid molecule of any one of claims ~~14-18~~, comprising a nucleic acid sequence encoding the VL, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 62, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

20. The isolated nucleic acid molecule or CAR of any one of claims 14-19, wherein the VH and VL comprise the amino acid sequences of:

- (i) SEQ ID NOs: 78 and 61, respectively;
- (ii) SEQ ID NOs: 52 and 61, respectively; or
- (iii) SEQ ID NOs: 70 and 61, respectively.

21. The isolated nucleic acid molecule or CAR of any one of claims 14-20, wherein the anti-BCMA binding domain comprises a single chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 80, 64, or 72, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

22. The isolated nucleic acid molecule of any one of claims 14-21, wherein the anti-BCMA binding domain comprises a scFv, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding the scFv, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 81, 65, or 73, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

23. The isolated nucleic acid molecule or CAR of any one of claims 14-22, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 82, 66, or 74, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

24. The isolated nucleic acid molecule of any one of claims 14-23, wherein the nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 83, 67, or 75, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

25. The isolated nucleic acid molecule or CAR of claim 1 or 2, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively.

26. The isolated nucleic acid molecule or CAR of claim 25, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:

- (i) SEQ ID NOs: 137, 138, 139, 147, 148, and 149, respectively; or
- (ii) SEQ ID NOs: 160, 161, 162, 147, 170, and 171, respectively.

27. The isolated nucleic acid molecule or CAR of claim 25 or 26, wherein the VH comprises the amino acid sequence of SEQ ID NO: 145 or 168, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

28. The isolated nucleic acid molecule of any one of claims 25-27, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding the VH, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 146 or 169, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

29. The isolated nucleic acid molecule or CAR of any one of claims 25-28, wherein the VL comprises the amino acid sequence of SEQ ID NO: 154 or 173, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

30. The isolated nucleic acid molecule of any one of claims 25-29, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding the VL, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 155 or 174, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

31. The isolated nucleic acid molecule or CAR of any one of claims 25-30, wherein the VH and VL comprise the amino acid sequences of:

- (i) SEQ ID NOs: 145 and 154, respectively, or
- (ii) SEQ ID NOs: 168 and 173, respectively.

32. The isolated nucleic acid molecule or CAR of any one of claims 25-31, wherein the anti-BCMA binding domain comprises a single chain fragment variable (scFv) comprising the amino acid sequence of SEQ ID NO: 156 or 175, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

33. The isolated nucleic acid molecule of any one of claims 25-32, wherein the anti-BCMA binding domain comprises a scFv, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding the scFv, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 157 or 176, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

34. The isolated nucleic acid molecule or CAR of any one of claims 25-33, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 158 or 177, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~35. The isolated nucleic acid molecule of any one of claims 25-34, wherein the nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 159 or 178, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.~~

~~36~~13. The isolated nucleic acid molecule of any one of claims 1 or 3-12 or CAR of any one of claims ~~1-35~~2-4, 6, 8, 9, or 11, wherein the VH and VL are connected by a linker, optionally wherein the linker comprises the amino acid sequence of SEQ ID NO: 63 or 104.

~~37~~14. The isolated nucleic acid molecule of any one of claims 1 or 3-13 or CAR of any one of claims ~~1-36~~2-4, 6, 8, 9, 11 or 13, wherein:

(i) the transmembrane domain comprises a transmembrane domain of a protein chosen from the alpha, beta or zeta chain of T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 or CD154;

(ii) the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(iii) the nucleic acid molecule comprises a nucleic acid sequence encoding the transmembrane domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 17, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~38~~15. The isolated nucleic acid molecule of any one of claims 1 or 3-14 or CAR of any one of claims ~~1-37~~2-4, 6, 8, 9, 11, 13, or 14, wherein the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region, optionally wherein:

(i) the hinge region comprises the amino acid sequence of SEQ ID NO: 2, 3, or 4, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(ii) the nucleic acid molecule comprises a nucleic acid sequence encoding the hinge region, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 13, 14, or 15, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~39~~16. The isolated nucleic acid molecule of any one of claims 1 or 3-15 or CAR of any one of claims ~~1-38~~2-4, 6, 8, 9, 11, or 13-15, wherein the intracellular signaling domain comprises a primary signaling domain, optionally wherein:

(i) the primary signaling domain comprises a functional signaling domain derived from CD3 zeta, TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (ICOS), FcεRI, DAP10, DAP12, or CD66d;

(ii) the primary signaling domain comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(iii) the nucleic acid molecule comprises a nucleic acid sequence encoding the primary signaling domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 256, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~4017~~. The isolated nucleic acid molecule of any one of claims 1 or 3-16 or CAR of any one of claims ~~1-392-4, 6, 8, 9, 11, or 13-16~~, wherein the intracellular signaling domain comprises a costimulatory signaling domain, optionally wherein:

(i) the costimulatory signaling domain comprises a functional signaling domain derived from a MHC class I molecule, a TNF receptor protein, an Immunoglobulin-like protein, a cytokine receptor, an integrin, a signalling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD28-OX40, CD28-4-1BB, or a ligand that specifically binds with CD83;

(ii) the costimulatory signaling domain comprises the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(iii) the nucleic acid molecule comprises a nucleic acid sequence encoding the costimulatory signaling domain, wherein the nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO: 18 or SEQ ID NO: 255, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

~~4118~~. The isolated nucleic acid molecule of any one of claims 1 or 3-17 or CAR of any one of claims ~~1-402-4, 6, 8, 9, 11, or 13-17~~, wherein the intracellular signaling domain comprises a functional signaling domain derived from 4-1BB and a functional signaling domain derived from CD3 zeta, optionally wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto) and the amino acid sequence of SEQ ID NO: 9 or 10 (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), optionally wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or 10.

~~42~~19. The isolated nucleic acid molecule of any one of claims 1 or 3-18 or CAR of any one of claims ~~1-41~~2-4, 6, 8, 9, 11, or 13-18, wherein the CAR further comprises a leader sequence comprising the amino acid sequence of SEQ ID NO: 1.

~~43~~20. The isolated nucleic acid molecule of any one of claims 1 or 3-19 or CAR of any one of claims ~~1-42~~2-4, 6, 8, 9, 11, or 13-19, wherein the CAR comprises one or more (e.g., 1, 2 or all) of the following properties:

(i) the CAR, when expressed in a cell (e.g., a T cell), activates NFAT signaling in the cell in the presence of BCMA-expressing cells, e.g., as measured by the JNL Screening Reporter Assay described in Example 1, e.g., as assessed using methods described in Example 1 with respect to FIG. 1A or 1C;

(ii) the CAR, when expressed in a cell (e.g., a T cell), induces cytotoxicity of BCMA-expressing cells, e.g., as assessed using methods described in Example 1 with respect to FIG. 3A; and

(iii) the CAR, when expressed in a cell (e.g., a T cell), induces expression of a cytokine (e.g., IFN- γ) in the cell in the presence of BCMA-expressing cells, e.g., as assessed using methods described in Example 1 with respect to FIG. 3C.

~~44. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1 or 3-43.~~

~~45. An anti-BCMA binding domain comprising a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:~~

- ~~(i) SEQ ID NOs: 86, 130, 88, 95, 131, and 132, respectively;~~
- ~~(ii) SEQ ID NOs: 44, 45, 84, 54, 55, and 56, respectively; or~~
- ~~(iii) SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively.~~

~~46. The anti-BCMA binding domain of claim 45, wherein the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequences of:~~

- ~~(i) SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively;~~
- ~~(ii) SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively;~~
- ~~(iii) SEQ ID NOs: 86, 109, 88, 95, 114, and 115, respectively;~~
- ~~(iv) SEQ ID NOs: 86, 109, 88, 95, 114, and 97, respectively;~~
- ~~(v) ID NOs: 44, 45, 46, 54, 55, and 56, respectively;~~
- ~~(vi) SEQ ID NOs: 44, 45, 68, 54, 55, and 56, respectively;~~
- ~~(vii) SEQ ID NOs: 137, 138, 139, 147, 148, and 149, respectively; or~~
- ~~(viii) SEQ ID NOs: 160, 161, 162, 147, 170, and 171, respectively.~~

47. The anti-BCMA binding domain of claim 45 or 46, wherein the VH and VL comprise the amino acid sequences of:

- (i) SEQ ID NOs: 93 and 102, respectively;
- (ii) SEQ ID NOs: 78 and 61, respectively;
- (iii) SEQ ID NOs: 112 and 118, respectively;
- (iv) SEQ ID NOs: 112 and 124, respectively;
- (v) SEQ ID NOs: 52 and 61, respectively;
- (vi) SEQ ID NOs: 70 and 61, respectively;
- (vii) SEQ ID NOs: 145 and 154, respectively, or
- (viii) SEQ ID NOs: 168 and 173, respectively.

4821. A vector comprising the nucleic acid molecule of any one of claims 1 or 3-~~43~~20, or a nucleic acid molecule encoding the CAR of any one of claims ~~2-5, 7, 9, 10, 12, 14-16, 18, 20, 21, 23, 25-27, 29, 31, 32, 34, or 36-43~~2-4, 6, 8, 9, 11, or 13-20, optionally wherein the vector is chosen from a DNA vector, a RNA vector, a plasmid, a lentivirus vector, an adenoviral vector, or a retrovirus vector.

4922. The vector of claim 4821, further comprising an EF-1 promoter comprising the nucleic acid sequence of SEQ ID NO: 11.

5023. An immune effector cell (e.g., a T cell or an NK cell) comprising the nucleic acid molecule of any one of claims 1 or 3-~~43~~20, the CAR of any one of claims 2-4, 6, 8, 9, 11, or 13-20~~2-5, 7, 9, 10, 12, 14-16, 18, 20, 21, 23, 25-27, 29, 31, 32, 34, or 36-43~~, the polypeptide molecule of claim 44, the anti-BCMA binding domain of any of claims ~~45-47~~, or the vector of claim 48 or 49.

5124. A method of making a cell comprising transducing an immune effector cell (e.g., a T cell or an NK cell) with the vector of claim ~~48 or 49~~22 or 23.

5225. A method of making an RNA-engineered cell comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell (e.g., a T cell or an NK cell), where the RNA comprises the nucleic acid molecule of any one of claims 1 or 3-~~43~~20, a nucleic acid molecule encoding the CAR of any one of claims ~~2-5, 7, 9, 10, 12, 14-16, 18, 20, 21, 23, 25-27, 29, 31, 32, 34, or 36-43~~2-4, 6, 8, 9, 11, or 13-20, or a nucleic acid molecule encoding the anti-BCMA binding domain of any of claims ~~45-47~~.

5326. Use of an effective amount of the immune effector cell of claim ~~50-25~~ in the manufacture of a medicament for providing anti-tumor immunity in a subject having a disease associated with expression of BCMA.

5427. Use of an effective amount of the immune effector cell of claim ~~50-25~~ in the manufacture of a medicament for treating a subject having a disease associated with expression of BCMA.

~~55~~28. The use of claim ~~53 or 54~~26 or 27, wherein the immune effector cell is an autologous T cell or an allogeneic T cell.

~~56~~29. The use of ~~claim 54 or 55~~any one of claims 26-28, wherein the disease associated with BCMA expression is:

- (i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or
- (ii) a non-cancer related indication associated with expression of BCMA.

~~57~~30. The use of any one of claims ~~54-56~~26-29, wherein the disease is a hematologic cancer or a solid cancer.

~~58~~31. The use of any one of claims ~~54-57~~26-30, wherein the disease is selected from the group consisting of: acute leukemia, B-cell acute lymphoblastic leukemia (“BALL”), T-cell acute lymphoblastic leukemia (“TALL”), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer, a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytoma (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, or POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof.

~~59~~32. The use of any one of claims ~~54-58~~26-31, wherein the disease is multiple myeloma.

~~60~~33. The use of any one of claims ~~53-59~~26-32, wherein the medicament is formulated for administration in combination with a second therapeutic agent, optionally wherein the second therapeutic agent is chosen from:

(i) a PD-1 inhibitor, optionally wherein the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224;

(ii) a PD-L1 inhibitor, optionally wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559;

- (iii) a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767;
- (iv) a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is selected from the group consisting of MBG453, TSR-022, and LY3321367;
- (v) a CTLA-4 inhibitor, optionally wherein the CTLA-4 inhibitor is Ipilimumab or Tremelimumab;
- (vi) an interleukin-15 (IL-15) polypeptide, an interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both an IL-15 polypeptide and an IL-15Ra polypeptide, e.g., hetIL-15;
- (vii) an interleukin-12 (IL-12) polypeptide; or
- (viii) an mTOR inhibitor, optionally wherein the mTOR inhibitor is RAD001 or rapamycin.

~~61~~6434. A chimeric antigen receptor (CAR) that binds to BCMA, comprising, from N-terminus to C-terminus:

- (i) leader sequence of SEQ ID NO: 1;
- (ii) a HC CDR1 of SEQ ID NO: 86;
- (iii) a HC CDR2 of SEQ ID NO: 87;
- (iv) a HC CDR3 of SEQ ID NO: 88;
- (v) a LC CDR1 of SEQ ID NO: 95;
- (vi) a LC CDR2 of SEQ ID NO: 96;
- (vii) a LC CDR3 of SEQ ID NO: 97;
- (viii) a CD8 transmembrane domain and hinge of SEQ ID NO: 202;
- (ix) a functional signaling domain of 4-1BB of SEQ ID NO: 7; and
- (x) a functional signaling domain of CD3 zeta of SEQ ID NO: 10.

~~62~~6335. The CAR of claim ~~61~~6434, which comprises a VH region of SEQ ID NO: 93 and a VL region of SEQ ID NO: 102 and/or a scFv of SEQ ID NO: 105.

~~63~~6336. The CAR of claim ~~61~~ or ~~62~~6434 or 35, which comprises an amino acid sequence of SEQ ID NO: 257 or SEQ ID NO: 107.

~~64~~6437. An isolated nucleic acid molecule encoding the CAR molecule of any one of claims ~~61~~–~~63~~6334–36.

~~65~~6538. A vector comprising a nucleic acid molecule encoding a chimeric antigen receptor (CAR) that binds to BCMA, wherein the CAR comprises, from N-terminus to C-terminus:

- (i) leader sequence of SEQ ID NO: 1;
- (ii) a HC CDR1 of SEQ ID NO: 86;
- (iii) a HC CDR2 of SEQ ID NO: 87;
- (iv) a HC CDR3 of SEQ ID NO: 88;

- (v) a LC CDR1 of SEQ ID NO: 95;
- (vi) a LC CDR2 of SEQ ID NO: 96;
- (vii) a LC CDR3 of SEQ ID NO: 97;
- (viii) a CD8 transmembrane domain and hinge of SEQ ID NO: 202;
- (ix) a functional signaling domain of 4-1BB of SEQ ID NO: 7; and
- (x) a functional signaling domain of CD3 zeta of SEQ ID NO: 10.

~~66~~39. An immune effector cell (e.g., a T cell or an NK cell) comprising a chimeric antigen receptor (CAR) that binds to BCMA, wherein the CAR comprises, from N-terminus to C-terminus:

- (i) leader sequence of SEQ ID NO: 1;
- (ii) a HC CDR1 of SEQ ID NO: 86;
- (iii) a HC CDR2 of SEQ ID NO: 87;
- (iv) a HC CDR3 of SEQ ID NO: 88;
- (v) a LC CDR1 of SEQ ID NO: 95;
- (vi) a LC CDR2 of SEQ ID NO: 96;
- (vii) a LC CDR3 of SEQ ID NO: 97;
- (viii) a CD8 transmembrane domain and hinge of SEQ ID NO: 202;
- (ix) a functional signaling domain of 4-1BB of SEQ ID NO: 7; and
- (x) a functional signaling domain of CD3 zeta of SEQ ID NO: 10.

~~67~~40. An immune effector cell (e.g., a T cell or an NK cell) comprising the CAR molecule of any one of claims ~~61-63~~34-36, the nucleic acid molecule of claim ~~64~~37, or the vector of claim ~~65~~38.

~~68~~41. Use of the CAR of any of claims ~~61-63~~34-36 or the immune effector cell of claim ~~66 or 67~~39 or 40 in the manufacture of a medicament for treating a disease associated with expression of BCMA.

~~69~~42. The use of claim ~~68~~41, wherein the disease associated with expression of BCMA is a multiple myeloma.