

What is claimed is:

1. An isolated cell comprising:

(a) a first antigen-binding domain which is an anti-BCMA binding 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), 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;
- (iii) SEQ ID NOs: 179, 180, 181, 147, 182, and 183, respectively;
- (iv) SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively;
- (v) SEQ ID NOs: 86, 109, 88, 95, 114, and 115, respectively;
- (vi) SEQ ID NOs: 86, 109, 88, 95, 114, and 97, respectively;
- (vii) SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively;
- (viii) SEQ ID NOs: 44, 45, 46, 54, 55, and 56, respectively;
- (ix) SEQ ID NOs: 44, 45, 68, 54, 55, and 56, respectively;
- (x) SEQ ID NOs: 137, 138, 139, 147, 148, and 149, respectively; or
- (xi) SEQ ID NOs: 160, 161, 162, 147, 170, and 171, respectively; and

(b) a second antigen-binding domain;

wherein (i) the first antigen-binding domain and the second antigen-binding domain are disposed in two chimeric antigen receptor (CARs), or (ii) the first antigen-binding domain and the second antigen-binding domain are disposed in one CAR.

2. The isolated cell of claim 1, wherein:

(a) the VH:

(i) 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;

(ii) is encoded by 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;

(iii) 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;

(iv) is encoded by 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;

(v) 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; or

(vi) is encoded by 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;

(b) the VL:

(i) 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; and/or

(ii) is encoded by 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;

(iii) 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;

(iv) is encoded by 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;

(v) 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; or

(vi) is encoded by 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; and/or

(c) 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;

(iii) SEQ ID NOs: 112 and 124, respectively;

- (iv) SEQ ID NOs: 78 and 61, 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.

3. The isolated cell of claim 1 or 2, wherein:

(i) the first antigen-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;

(ii) the first antigen-binding domain is encoded by 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;

(iii) the first antigen-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;

(iv) the first antigen-binding domain is encoded by 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;

(v) the first antigen-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; or

(vi) the first antigen-binding domain is encoded by 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.

4. The isolated cell of any one of claims 1-3, wherein the first antigen-binding domain is disposed in a first CAR, wherein:

(i) the first CAR comprises the amino acid sequence of SEQ ID NO: 107, 226, 122, or 128, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(ii) the first CAR is encoded by 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;

(iii) the first CAR comprises the amino acid sequence of SEQ ID NO: 224, 82, 66, or 74, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(iv) the first CAR is encoded by 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;

(v) the first 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; or

(vi) the first CAR is encoded by 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.

5. The isolated cell of any one of claims 1-4, wherein the second antigen-binding domain binds to :

(i) CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, or FLT3;

(ii) EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-

CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR α 4, or a peptide of any of these antigens presented on MHC; or

(iii) CD19, wherein:

(a) the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and/or LC CDR3 of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOs: 295 and 245-249, respectively;

(b) the second antigen-binding domain comprises a VH and/or VL of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a VH and VL comprising the amino acid sequences of SEQ ID NOs: 250 and 251, respectively, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(c) the second antigen-binding domain comprises a scFv of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a scFv comprising the amino acid sequence of SEQ ID NO: 211, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; and/or

(d) the second antigen-binding domain is disposed in a second CAR, wherein the CAR comprises a CAR of an anti-CD19 sequence listed in Table 19 or Table 22, for example, a CAR comprising the amino acid sequence of SEQ ID NO: 225 or 229, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

6. The isolated cell of any one of claims 1-5, wherein:

(i) the first antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR comprising the amino acid sequences of:

(a) SEQ ID NOs: 86, 87, 88, 95, 96, and 97, respectively;

(b) SEQ ID NOs: 44, 45, 76, 54, 55, and 56, respectively; or

(c) SEQ ID NOs: 44, 45, 46, 54, 55, and 56, respectively,

and the second antigen-binding domain comprises a HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprising the amino acid sequences of SEQ ID NOs: 295 and 245-249, respectively;

(ii) the first antigen-binding domain comprises a VH and VL comprising the amino acid sequences of:

- (a) SEQ ID NOs: 93 and 102, respectively;
- (b) SEQ ID NOs: 78 and 61, respectively; or
- (c) SEQ ID NOs: 52 and 61, respectively,

and the second antigen-binding domain comprises a VH and VL comprising the amino acid sequences of SEQ ID NOs: 250 and 251, respectively;

(iii) the first antigen-binding domain comprises a scFv comprising the amino acid sequence of SEQ ID NO: 105, 80, or 64, and the second antigen-binding domain comprises a scFv comprising the amino acid sequence of SEQ ID NO: 211; or

(iv) the first antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 253, 106, 81, or 65, and the second antigen-binding domain is encoded by the nucleic acid sequence of SEQ ID NO: 212.

7. The isolated cell of any one of claims 1-6, wherein;

(i) the first antigen-binding domain is disposed in a first CAR and the second antigen-binding domain is disposed in a second CAR, wherein the first CAR further comprises a first transmembrane domain and a first intracellular signaling domain, and/or the second CAR further comprises a second transmembrane domain and a second intracellular signaling domain;

(ii) the first CAR is encoded by a first nucleic acid sequence and the second CAR is encoded by a second nucleic acid sequence, wherein the first and second nucleic acid sequences are disposed on separate nucleic acid molecules; or

(iii) the first CAR is encoded by a first nucleic acid sequence and the second CAR is encoded by a second nucleic acid sequence, wherein the first and second nucleic acid sequences are disposed on a single nucleic acid molecule.

8. The isolated cell of claim 7, wherein;

(a) the single nucleic acid molecule comprises the following configuration in a 5' to 3' orientation:

(i) a nucleic acid sequence encoding the first antigen-binding domain – a nucleic acid sequence encoding a first transmembrane domain – a nucleic acid sequence encoding a first intracellular signaling domain – a nucleic acid sequence encoding a linker – a nucleic acid

sequence encoding the second antigen-binding domain – a nucleic acid sequence encoding a second transmembrane domain – a nucleic acid sequence encoding a second intracellular signaling domain; or

(ii) a nucleic acid sequence encoding the second antigen-binding domain – a nucleic acid sequence encoding a second transmembrane domain – a nucleic acid sequence encoding a second intracellular signaling domain – a nucleic acid sequence encoding a linker – a nucleic acid sequence encoding the first antigen-binding domain – a nucleic acid sequence encoding a first transmembrane domain – a nucleic acid sequence encoding a first intracellular signaling domain,

optionally wherein the linker comprises a self-cleavage site, optionally wherein the linker comprises a P2A site, a T2A site, an E2A site, or an F2A site, optionally wherein the linker comprises a P2A site, optionally wherein:

the linker is encoded by the nucleic acid sequence of SEQ ID NO: 209, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto, or

the linker comprises the amino acid sequence of SEQ ID NO: 208, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(b) the single nucleic acid molecule comprises the nucleic acid sequence of SEQ ID NO: 215, 217, 219, 221, or 223, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(c) the single nucleic acid molecule encodes the amino acid sequence of SEQ ID NO: 214, 216, 218, 220, or 222, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

9. The isolated cell of any one of claims 1-6, wherein the first antigen-binding domain and the second antigen-binding domain are disposed in one CAR, wherein the CAR further comprises a transmembrane domain and an intracellular signaling domain.

10. The isolated cell of claim 9, wherein the first antigen-binding domain comprises a first VH (VH1) and a first VL (VL1) and the second antigen-binding domain comprises a second VH (VH2) and a second VL (VL2), wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus:

- (i) VH2 – optionally linker 1 (“L1”) – VL1 – optionally linker 2 (“L2”) – VH1 – optionally linker 3 (“L3”) – VL2;
- (ii) VH1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VL1;
- (iii) VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2;
- (iv) VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2;
- (v) VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2;
- (vi) VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1;
- (vii) VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1; or
- (viii) VH1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VL1.

11. The isolated cell of claim 10, wherein:

(i) the VH1 and VL1 comprise the amino acid sequences of:

(a) SEQ ID NOs: 93 and 102, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(b) SEQ ID NOs: 333 and 334, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(c) SEQ ID NOs: 78 and 61, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or

(d) SEQ ID NOs: 335 and 336, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), and/or

(ii) the VH2 and VL2 comprise the amino acid sequences of:

(a) SEQ ID NOs: 250 and 251, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or

(b) SEQ ID NOs: 331 and 332, respectively (or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto).

12. The isolated cell of any one of claims 9-11, wherein the CAR:

(a) comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 321-330, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto; or

(b) comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 339-348, or an amino acid sequence having at least 80, 85, 90, 95, or 99% identity thereto;

(c) is encoded by a nucleic acid molecule comprising the following configuration in a 5' to 3' orientation:

(i) a nucleic acid sequence encoding the first antigen-binding domain – optionally a nucleic acid sequence encoding a linker – a nucleic acid sequence encoding the second antigen-binding domain – a nucleic acid sequence encoding a transmembrane domain – a nucleic acid sequence encoding an intracellular signaling domain; or

(ii) a nucleic acid sequence encoding the second antigen-binding domain – optionally a nucleic acid sequence encoding a linker – a nucleic acid sequence encoding the first antigen-binding domain – a nucleic acid sequence encoding a transmembrane domain – a nucleic acid sequence encoding an intracellular signaling domain; or

(d) comprises the following configuration in an N- to C- orientation:

(i) the first antigen-binding domain – optionally a linker – the second antigen-binding domain – a transmembrane domain – an intracellular signaling domain; or

(ii) the second antigen-binding domain – optionally a linker – the first antigen-binding domain – a transmembrane domain – an intracellular signaling domain.

13. The isolated cell of any one of claims 1-12, wherein the first antigen-binding domain or second antigen-binding domain comprises a VH and a VL, wherein the VH and VL are connected by a linker, optionally wherein the linker comprises the amino acid sequence of SEQ ID NO: 5, 63, 104, or 243, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

14. The isolated cell of any one of claims 7-13, wherein:

(i) the transmembrane domain, first transmembrane domain, or second 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, first transmembrane domain, or second 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;

(iii) the transmembrane domain, first transmembrane domain, or second transmembrane domain is encoded by 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;

(iv) the first antigen-binding domain or second antigen-binding domain is connected to the transmembrane domain, first transmembrane domain, or second transmembrane domain by a hinge region (e.g., a first or second hinge region), optionally wherein:

(a) 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;

(b) the hinge region is encoded by 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;

(c) the hinge region and the transmembrane domain comprise the amino acid sequence of SEQ ID NO: 202, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(d) the hinge region and the transmembrane domain are encoded by the nucleic acid sequence of SEQ ID NO: 203 or 213, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(v) the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises a primary signaling domain (e.g., a first or second primary signaling domain), optionally wherein:

(a) 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;

(b) 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

(c) the primary signaling domain is encoded by the nucleic acid sequence of SEQ ID NO: 20, 21, or 205, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(vi) the intracellular signaling domain, first intracellular signaling domain, or second intracellular signaling domain comprises a costimulatory signaling domain (e.g., a first or second costimulatory signaling domain), optionally wherein:

(a) 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, BAFTR, 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;

(b) 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

(c) the costimulatory signaling domain is encoded by the nucleic acid sequence of SEQ ID NO: 18 or 204, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(vii) the intracellular signaling domain, first intracellular signaling domain, or second 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, first intracellular signaling domain, or second intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 (or an amino acid

quence 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, first intracellular signaling domain, or second 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; or

(viii) the CAR, first CAR, or second CAR further comprises a leader sequence (e.g., a first or second leader sequence), wherein:

(a) the leader sequence comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; or

(b) the leader sequence is encoded by the nucleic acid sequence of SEQ ID NO: 199 or 210, or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

15. The isolated cell of any one of claims 7, 8, 13 or 14, wherein:

(a)

(i) the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%);

(ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%);

(iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%); and/or

(iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), and/or the first costimulatory signaling domain and the

second costimulatory signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%); (b):

(i) the first leader sequence and the second leader sequence comprise the same amino acid sequence (e.g., the first leader sequence and the second leader sequence comprise the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or comprise different amino acid sequences;

(ii) the first hinge region and the second hinge region comprise the same amino acid sequence (e.g., the first hinge region and the second hinge region comprise the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or comprise different amino acid sequences;

(iii) the first transmembrane domain and the second transmembrane domain comprise the same amino acid sequence (e.g., the first transmembrane domain and the second transmembrane domain comprise 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 comprise different amino acid sequences; and/or

(iv) the first intracellular signaling domain and the second intracellular signaling domain comprise the same amino acid sequence, or comprise different amino acid sequences,

optionally wherein the first primary signaling domain and the second primary signaling domain comprise the same amino acid sequence (e.g., the first primary signaling domain and the second primary signaling domain comprise the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or comprise different amino acid sequences, and/or

the first costimulatory signaling domain and the second costimulatory signaling domain comprise the same amino acid sequence (e.g., the first costimulatory signaling domain and the second costimulatory signaling domain comprise 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 comprise different amino acid sequences

(e.g., the first and second costimulatory signaling domains comprise a 4-1BB costimulatory domain sequence and a CD28 costimulatory domain sequence, respectively; or comprise a CD28 costimulatory domain sequence and a 4-1BB costimulatory domain sequence, respectively);

(c):

(i) the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOs: 199 and 210, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or SEQ ID NOs: 210 and 199, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(ii) the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOs: 337 and 13, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 13 and 337, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(iii) the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 338 and 17, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 17 and 338, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(iv) the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 204 and 18, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 18 and 204, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); and/or

(v) the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 205 and 21, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 21 and 205, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or

(d) the CAR, first CAR, or second CAR is encoded by a nucleic acid molecule comprising a woodchuck hepatitis post-transcriptional regulatory element (WPRE).

16. An isolated nucleic acid molecule comprising:

(a) a first nucleic acid sequence encoding a first antigen-binding domain which is an anti-BCMA binding 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), 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; and

(b) a second nucleic acid sequence encoding a second antigen-binding domain; wherein the nucleic acid molecule comprises a first nucleic acid molecule and a second nucleic acid molecule, which are separate nucleic acid molecules, and wherein the first nucleic acid sequence is disposed on the first nucleic acid molecule and the second nucleic acid sequence is disposed on the second nucleic acid molecule.

17. An isolated CAR, wherein the CAR comprises:

(a) a first antigen-binding domain which is an anti-BCMA binding 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), 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; and
- (b) a second antigen-binding domain.

18. An isolated CAR, wherein the CAR comprises:

(a) a first antigen-binding domain which is an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises:

(i) a VH comprising a HC CDR1, HC CDR2, and HC CDR3 of an anti-BCMA sequence listed in Table 20 or 26 and a VL comprising a LC CDR1, LC CDR2, and LC CDR3 of an anti-BCMA sequence listed in Table 20 or 26, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243;

(ii) a VH and VL comprising the amino acid sequences of SEQ ID NOs: 239 and 242, respectively, wherein the VH and VL are connected by a linker comprising the amino acid sequence of SEQ ID NO: 243; or

(iii) an scFv comprising the amino acid sequence of SEQ ID NO: 200; and

(b) a second antigen-binding domain.

19. A vector comprising the nucleic acid molecule of claim 16, or a nucleic acid molecule encoding the CAR of claim 17 or 18, 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.

20. An isolated cell comprising the nucleic acid molecule of claim 16.

21. A method of making a cell comprising transducing a cell with the vector of claim 20, optionally wherein the cell is a T cell or NK cell.

22. A method of making an RNA-engineered cell comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, wherein the RNA comprises the nucleic acid molecule of claim 16, or a nucleic acid molecule encoding the CAR of claim 17 or 18, optionally wherein the cell is a T cell or NK cell.

23. A pharmaceutical composition comprising the cell of any one of claims 1-15 or 20, and a pharmaceutically acceptable carrier.

24. A method of providing an anti-tumor immunity in a subject, wherein an effective amount of the cell of any one of claims 1-15 or 20, or the pharmaceutical composition of claim 23 is to be administered to the subject.

25. Use of the cell of any one of claims 1-15 or 20 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for the treatment of a disease associated with expression of BCMA, wherein an effective amount of the medicament is to be administered to the subject.

26. The use of claim 25, 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,
- (ii) a non-cancer related indication associated with expression of BCMA;
- (iii) a hematologic cancer or a solid cancer;
- (iv) chosen from: acute leukemia, B-cell acute lymphoid leukemia (“BALL”), T-cell acute lymphoid leukemia (“TALL”), acute lymphoid 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; or

(v) multiple myeloma.

27. The use of claim 25 or 26, wherein a second therapeutic agent is to be further administered to the subject, 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, Pidilizumab, 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.

28. An isolated cell comprising:

(a) a first CAR comprising a first antigen-binding domain that binds to a first antigen, a first transmembrane domain, and a first intracellular signaling domain (e.g., a first primary signaling domain and/or a first costimulatory signaling domain), optionally wherein the first CAR further comprises a first leader sequence and/or a first hinge region; and

(b) a second CAR comprising a second antigen-binding domain that binds to a second antigen, a second transmembrane domain, and a second intracellular signaling domain (e.g., a second primary signaling domain and/or a second costimulatory signaling domain), optionally

wherein the second CAR further comprises a second leader sequence and/or a second hinge region, wherein:

(i) the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second leader sequences comprise the same amino acid sequence;

(ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second hinge regions comprise the same amino acid sequence;

(iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second transmembrane domains comprise the same amino acid sequence; and/or

(iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%),

optionally wherein the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), and/or

the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%).

29. An isolated nucleic acid molecule comprising:

(a) a first nucleic acid sequence encoding a first CAR, wherein the first CAR comprises a first antigen-binding domain that binds to a first antigen, a first transmembrane domain, and a first intracellular signaling domain (e.g., a first primary signaling domain and/or a first costimulatory signaling domain), optionally wherein the first CAR further comprises a first leader sequence and/or a first hinge region; and

(b) a second nucleic acid sequence encoding a second CAR, wherein the second CAR comprises a second antigen-binding domain that binds to a second antigen, a second

transmembrane domain, and a second intracellular signaling domain (e.g., a second primary signaling domain and/or a second costimulatory signaling domain), optionally wherein the second CAR further comprises a second leader sequence and/or a second hinge region, wherein:

(i) the first leader sequence and the second leader sequence are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second leader sequences comprise the same amino acid sequence;

(ii) the first hinge region and the second hinge region are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second hinge regions comprise the same amino acid sequence;

(iii) the first transmembrane domain and the second transmembrane domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), optionally wherein the first and second transmembrane domains comprise the same amino acid sequence; and/or

(iv) the first intracellular signaling domain and the second intracellular signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%),

optionally wherein the first primary signaling domain and the second primary signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%), and/or

the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by different nucleic acid sequences (e.g., differ by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100%).

30. The isolated cell of claim 28 or isolated nucleic acid molecule of claim 29, wherein the

(a) first primary signaling domain and the second primary signaling domain comprise the same amino acid sequence or comprise different amino acid sequences, and/or the first costimulatory signaling domain and the second costimulatory signaling domain comprise the same amino acid sequence or comprise different amino acid sequences (e.g., the first and second costimulatory signaling domains comprise a 4-1BB costimulatory domain sequence and

a CD28 costimulatory domain sequence, respectively; or comprise a CD28 costimulatory domain sequence and a 4-1BB costimulatory domain sequence, respectively);

(b) the first leader sequence and the second leader sequence comprise the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(c) the first hinge region and the second hinge region comprise the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(d) the first transmembrane domain and the second transmembrane domain comprise 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;

(e) the first costimulatory signaling domain and the second costimulatory signaling domain comprise 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;

(f) the first primary signaling domain and the second primary signaling domain comprise the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto;

(g) the first leader sequence and the second leader sequence are encoded by nucleic acid sequences comprising SEQ ID NOs: 199 and 210, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto), or SEQ ID NOs: 210 and 199, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(h) the first hinge region and the second hinge region are encoded by nucleic acid sequences comprising SEQ ID NOs: 337 and 13, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 13 and 337, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(i) the first transmembrane domain and the second transmembrane domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 338 and 17, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 17 and 338, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto);

(j) the first costimulatory signaling domain and the second costimulatory signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 204 and 18, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 18 and 204, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); and/or

(k) the first primary signaling domain and the second primary signaling domain are encoded by nucleic acid sequences comprising SEQ ID NOs: 205 and 21, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); or SEQ ID NOs: 21 and 205, respectively (or a nucleic acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto); and/or

(l) the first or second antigen is chosen from: BCMA, CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR α 4, or a peptide of any of these antigens presented on MHC.

31. An isolated CAR, wherein the CAR comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second

antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus:

- (i) VH1 – optionally linker 1 (“L1”) – VH2 – optionally linker 2 (“L2”) – VL2 – optionally linker 3 (“L3”) – VL1;
- (ii) VH1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VL1;
- (iii) VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1;
- (iv) VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1;
- (v) VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2;
- (vi) VH2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VL2;
- (vii) VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2; or
- (viii) VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2.

32. The isolated CAR of claim 31, wherein;

(a) the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus:

- (i) VH1 – linker 1 (“L1”) – VH2 – linker 2 (“L2”) – VL2 – linker 3 (“L3”) – VL1;
- (ii) VH1 – L1 – VL2 – L2 – VH2 – L3 – VL1;
- (iii) VL1 – L1 – VH2 – L2 – VL2 – L3 – VH1;
- (iv) VL1 – L1 – VL2 – L2 – VH2 – L3 – VH1;
- (v) VH2 – L1 – VH1 – L2 – VL1 – L3 – VL2;
- (vi) VH2 – L1 – VL1 – L2 – VH1 – L3 – VL2;
- (vii) VL2 – L1 – VH1 – L2 – VL1 – L3 – VH2; or
- (viii) VL2 – L1 – VL1 – L2 – VH1 – L3 – VH2;

(b) L1 or L3 comprises the amino acid sequence of SEQ ID NO: 5, and/or L2 comprises the amino acid sequence of SEQ ID NO: 63;

(c) the CAR comprises the following configuration from the N-terminus to the C-terminus:

- (i) VH1 – optionally linker 1 (“L1”) – VH2 – optionally linker 2 (“L2”) – VL2 – optionally linker 3 (“L3”) – VL1 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
- (ii) VH1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VL1 – optionally a hinge region – transmembrane domain – intracellular signaling domain;

- (iii) VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
 - (iv) VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
 - (v) VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
 - (vi) VH2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VL2 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
 - (vii) VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2 – optionally a hinge region – transmembrane domain – intracellular signaling domain; or
 - (viii) VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2 – optionally a hinge region – transmembrane domain – intracellular signaling domain;
- (d) the first and second antigens are different and the first or second antigen is chosen from: BCMA, CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, or IL4R, optionally wherein the B cell antigen is chosen from CD19, CD20, CD22, FcRn5, FcRn2, CS-1, CD138, CD123, CD33, CD34, CLL-1, folate receptor beta, FLT3, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFR α 4, or a peptide of any of these antigens presented on MHC;

(e) the VH1, VL1, VH2, or VL2 comprises a CDR, VH, or VL sequence disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto; and/or

(f) the hinge region, transmembrane domain, or intracellular signaling domain (e.g., a primary signaling domain and/or a costimulatory signaling domain) comprises a hinge region sequence, transmembrane domain sequence, or intracellular signaling domain sequence (e.g., a primary signaling domain sequence and/or a costimulatory signaling domain sequence) disclosed herein, or an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity thereto.

33. An isolated nucleic acid molecule encoding the CAR of claim 31 or 32.

34. An isolated vector comprising the nucleic acid molecule of claim 33.

35. An isolated cell comprising the CAR of claim 31 or 32, the nucleic acid molecule of claim 33, or the vector of claim 34.

36. A method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising:

(i) contacting (for example, binding) a population of cells (for example, T cells, for example, T cells isolated from a frozen or fresh leukapheresis product) with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells;

(ii) contacting the population of cells (for example, T cells) with a nucleic acid molecule (for example, a DNA or RNA molecule) encoding the CAR, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and

(iii) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein:

(a) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and

step (iii) is performed no later than 30 (for example, 26) hours after the beginning of step (i), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (i), for example, no later than 24 hours after the beginning of step (i),

(b) step (ii) is performed together with step (i) or no later than 20 hours after the beginning of step (i), for example, no later than 12, 13, 14, 15, 16, 17, or 18 hours after the beginning of step (i), for example, no later than 18 hours after the beginning of step (i), and

step (iii) is performed no later than 30 hours after the beginning of step (ii), for example, no later than 22, 23, 24, 25, 26, 27, 28, 29, or 30 hours after the beginning of step (ii), or

(c) the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (i),

optionally wherein the nucleic acid molecule in step (ii) is on a viral vector, optionally wherein the nucleic acid molecule in step (ii) is an RNA molecule on a viral vector, optionally wherein step (ii) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR,

wherein:

(I) the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein:

the first and second nucleic acid sequences are disposed on a single nucleic acid molecule, e.g., wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence encoding a self-cleavage site (e.g., a P2A site, a T2A site, an E2A site, or an F2A site), or

the first and second nucleic acid sequences are disposed on separate nucleic acid molecules; or

(II) the nucleic acid molecule comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1 – optionally linker 1 (“L1”) – VH2 – optionally linker 2 (“L2”) – VL2 – optionally linker 3 (“L3”) – VL1, VH1 – optionally L1 – VL2 – optionally L2 – VH2 –

optionally L3 – VL1, VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1, VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1, VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2, VH2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VL2, VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2; or VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2.

37. The method of claim 36, wherein the first and second nucleic acid molecules are on separate viral vectors, and wherein step (ii) comprises transducing the population of cells (for example, T cells) with a first viral vector comprising the nucleic acid molecule encoding the first CAR and a second viral vector comprising the second nucleic acid molecule encoding the second CAR, optionally wherein the first CAR comprises an anti-BCMA binding domain (e.g., an anti-BCMA CAR) and the second CAR comprises an anti-CD19 binding domain (e.g., an anti-CD19 CAR).

38. The method of claim 37, wherein in step (ii);

(a) the population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than, equal to, or less than an MOI at which the population of cells is contacted with the second viral vector,

optionally wherein in step (ii), the population of cells is contacted with the first viral vector at a multiplicity of infection (MOI) that is higher than an MOI at which the population of cells is contacted with the second viral vector;

(b) the population of cells is contacted with the first viral vector at a first MOI and with the second viral vector at a second MOI, such that a resultant population of cells comprises a first population of cells that comprise the anti-BCMA CAR but not the anti-CD19 CAR, a second population of cells that comprise the anti-CD19 CAR but not the anti-BCMA CAR, and a third population of cells that comprise both the anti-BCMA CAR and the anti-CD19 CAR, wherein:

(i) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;

(ii) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined; and/or

(iii) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the resultant population,

e.g., as determined by a method described in Example 10;

(c) the population of cells is contacted with:

(i) the first viral vector at an MOI of about 1 to about 10 (e.g., about 2 to about 9, about 3 to about 8, about 4 to about 7, about 5 to about 6, about 1 to about 8, about 1 to about 6, about 1 to about 4, about 8 to about 10, about 6 to about 10, about 4 to about 10, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 4 to about 6, about 5 to about 7, about 6 to about 8, about 7 to about 9, about 8 to about 10, about 2.5 to about 5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10),

optionally wherein the population of cells is contacted with the first viral vector at an MOI of about 2.5 to about 5;

(ii) the second viral vector at an MOI of about 0.1 to about 5 (e.g., about 0.2 to about 4, about 0.3 to about 3, about 0.4 to about 2, about 0.5 to about 1, about 0.6 to about 0.9, about 0.7 to about 0.8, about 0.1 to about 4, about 0.1 to about 3, about 0.1 to about 2, about 0.1 to about 1, about 0.1 to about 0.5, about 4 to about 5, about 3 to about 5, about 2 to about 5, about 1 to about 5, about 0.5 to about 5, about 0.2 to about 5, about 0.1 to about 0.5, about 0.2 to about 1, about 0.5 to about 2, about 1 to about 3, about 2 to about 4, about 3 to about 5, about 0.5 to about 1, about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1, about 2, about 3, about 4, or about 5),

optionally wherein the population of cells is contacted with the second viral vector at an MOI of about 0.5 to about 1.0;

(iii) the first viral vector at an MOI that is at least about 10% (e.g., at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) or at least about 1 fold (e.g., at least

about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, or 100 fold, e.g., about 2 to about 50 fold, about 3 to 20 fold, about 5 to about 15 fold, or about 8 to about 10 fold) higher than an MOI at which the population of cells is contacted with the second viral vector,

optionally wherein the first viral vector at an MOI that is about 8 to about 10 fold higher than an MOI at which the population of cells is contacted with the second viral vector; and/or

(iv) the second viral vector at an MOI that is no more than $1/X$, wherein X is 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100, of an MOI at which the population of cells is contacted with the first viral vector,

optionally the second viral vector at an MOI that is no more than $1/X$, wherein X is 6, 8, 10, or 12, of an MOI at which the population of cells is contacted with the first viral vector;

(d) the population of cells is contacted with:

(i) the first viral vector at an MOI of between about 4 and about 5 (e.g., about 4.75);

and/or

(ii) the second viral vector at an MOI between about 0.2 and about 1 (e.g., about 0.5);

and/or

(e) the population of cells comprises about 1×10^8 to about 5×10^9 (e.g., about 2×10^8 to about 2×10^9 or about 4×10^8 to about 1×10^9 total viable cells, optionally wherein the cells are suspended in a culture at a concentration of about 1×10^6 to about 1×10^7 (e.g., about 2×10^6 to about 5×10^6 or about 3×10^6 to about 4×10^6) viable cells/mL).

39. The method of any one of claims 36-38, wherein the agent that stimulates a CD3/TCR complex is an agent that stimulates CD3 (for example, an anti-CD3 antibody) and wherein the agent that stimulates a costimulatory molecule is an agent that stimulates CD28, ICOS, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, CD2, CD226, or any combination thereof, optionally wherein the agent that stimulates a CD3/TCR complex or the agent that stimulates a costimulatory molecule is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand), optionally wherein the agent that stimulates a CD3/TCR

complex or the agent that stimulates a costimulatory molecule does not comprise a bead, optionally wherein the agent that stimulates a CD3/TCR complex comprises an anti-CD3 antibody and the agent that stimulates a costimulatory molecule comprises an anti-CD28 antibody, optionally wherein the agent that stimulates a CD3/TCR complex comprises an anti-CD3 antibody covalently attached to a colloidal polymeric nanomatrix and the agent that stimulates a costimulatory molecule comprises an anti-CD28 antibody covalently attached to a colloidal polymeric nanomatrix, optionally wherein the agent that stimulates a CD3/TCR complex and the agent that stimulates a costimulatory molecule comprise T Cell TransAct™.

40. The method of any one of claims 36-39, wherein;

(a) steps (i) and/or (ii) are performed in cell media (for example, serum-free media) comprising IL-2, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-7, IL-21, IL-6 (for example, IL-6/sIL-6Ra), a LSD1 inhibitor, a MALT1 inhibitor, or a combination thereof;

(b) steps (i) and/or (ii) are performed in serum-free cell media comprising a serum replacement, optionally wherein the serum replacement is CTS™ Immune Cell Serum Replacement (ICSR);

(c) the method further comprises, prior to step (i):

(iv) (optionally) receiving a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider, and

(v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a fresh leukapheresis product (or an alternative source of hematopoietic tissue such as a fresh whole blood product, a fresh bone marrow product, or a fresh tumor or organ biopsy or removal (for example, a fresh product from thymectomy)), optionally wherein:

step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v), or

the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as

assessed by the number of living cells, compared to the population of cells at the end of step (v);

(d) the method further comprises, prior to step (i): receiving cryopreserved T cells isolated from a leukapheresis product (or an alternative source of hematopoietic tissue such as cryopreserved T cells isolated from whole blood, bone marrow, or tumor or organ biopsy or removal (for example, thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider;

(e) the method further comprises, prior to step (i):

(iv) (optionally) receiving a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider, and

(v) isolating the population of cells (for example, T cells, for example, CD8+ and/or CD4+ T cells) contacted in step (i) from a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)), optionally wherein:

step (iii) is performed no later than 35 hours after the beginning of step (v), for example, no later than 27, 28, 29, 30, 31, 32, 33, 34, or 35 hours after the beginning of step (v), for example, no later than 30 hours after the beginning of step (v), or

the population of cells from step (iii) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the end of step (v);

(f) the method further comprises step (vi): culturing a portion of the population of cells from step (iii) for at least 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, or 7 days, for example, at least 2 days and no more than 7 days, and measuring CAR expression level in the portion (for example, measuring the percentage of viable, CAR-expressing cells in the portion), optionally wherein: step (iii) comprises harvesting and freezing the population of cells (for example, T cells) and step (vi) comprises thawing a portion of the population of cells from step (iii),

culturing the portion for at least 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, or 7 days, for example, at least 2 days and no more than 7 days, and measuring CAR expression level in the portion (for example, measuring the percentage of viable, CAR-expressing cells in the portion, for example, measuring the percentage of viable, anti-BCMA CAR-expressing cells in the portion);

(g) (i) the population of cells at the beginning of step (i) or step (1) has been enriched for IL6R-expressing cells (for example, cells that are positive for IL6R α and/or IL6R β); or (ii) the population of cells at the beginning of step (i) or step (1) comprises no less than 50, 60, or 70% of IL6R-expressing cells (for example, cells that are positive for IL6R α and/or IL6R β); and/or

(h) steps (i) and (ii) or steps (1) and (2) are performed in cell media comprising IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)).

41. The method of claim 40, wherein the cells from step (iii) are cultured for about two to about four days, e.g., about three days (e.g., about 72 hours following harvesting) prior to measuring CAR expression level in the portion (for example, measuring the percentage of viable, CAR-expressing cells in the portion, for example, measuring the percentage of viable, anti-BCMA CAR-expressing cells in the portion).

42. A method of making a population of cells (for example, T cells) that express a chimeric antigen receptor (CAR), the method comprising:

(1) contacting a population of cells (for example, T cells, for example, T cells isolated from a frozen leukapheresis product) with a cytokine chosen from IL-2, IL-7, IL-15 (for example, hetIL-15 (IL15/sIL-15Ra)), IL-21, IL-6 (for example, IL-6/sIL-6Ra), or a combination thereof,

(2) contacting the population of cells (for example, T cells) with a nucleic acid molecule (for example, a DNA or RNA molecule) encoding the CAR, thereby providing a population of cells (for example, T cells) comprising the nucleic acid molecule, and

(3) harvesting the population of cells (for example, T cells) for storage (for example, reformulating the population of cells in cryopreservation media) or administration, wherein:

(a) step (2) is performed together with step (1) or no later than 5 hours after the beginning of step (1), for example, no later than 1, 2, 3, 4, or 5 hours after the beginning of step (1), and

step (3) is performed no later than 26 hours after the beginning of step (1), for example, no later than 22, 23, or 24 hours after the beginning of step (1), for example, no later than 24 hours after the beginning of step (1), or

(b) the population of cells from step (3) are not expanded, or expanded by no more than 5, 10, 15, 20, 25, 30, 35, or 40%, for example, no more than 10%, for example, as assessed by the number of living cells, compared to the population of cells at the beginning of step (1),

optionally wherein the nucleic acid molecule in step (2) is on a viral vector, optionally wherein the nucleic acid molecule in step (ii) is an RNA molecule on a viral vector, optionally wherein step (ii) comprises transducing the population of cells (for example, T cells) with a viral vector comprising a nucleic acid molecule encoding the CAR,

wherein:

(I) the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein:

the first and second nucleic acid sequences are disposed on a single nucleic acid molecule, e.g., wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence encoding a self-cleavage site (e.g., a P2A site, a T2A site, an E2A site, or an F2A site), or

the first and second nucleic acid sequences are disposed on separate nucleic acid molecules; or

(II) the nucleic acid molecule comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1 – optionally linker 1 (“L1”) – VH2 – optionally linker 2 (“L2”) – VL2 – optionally linker 3 (“L3”) – VL1, VH1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VL1, VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1, VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1, VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2, VH2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VL2, VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2; or VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2.

43. The method of claim 42, wherein the population of cells is not contacted in vitro with an agent that stimulates a CD3/TCR complex and/or an agent that stimulates a costimulatory molecule on the surface of the cells, or if contacted, the contacting step is less than 2 hours, for example, no more than 1 or 1.5 hours, optionally wherein the agent that stimulates a CD3/TCR complex is an agent that stimulates CD3 (for example, an anti-CD3 antibody) and wherein the agent that stimulates a costimulatory molecule is an agent that stimulates CD28, ICOS, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, CD2, CD226, or any combination thereof, optionally wherein the agent that stimulates a CD3/TCR complex or the agent that stimulates a costimulatory molecule is chosen from an antibody (for example, a single-domain antibody (for example, a heavy chain variable domain antibody), a peptibody, a Fab fragment, or a scFv), a small molecule, or a ligand (for example, a naturally-existing, recombinant, or chimeric ligand).

44. The method of claim 42 or 43, wherein;

(a) steps (1) and/or (2) are performed in cell media comprising:

no more than 5, 4, 3, 2, 1, or 0% serum, optionally wherein steps (1) and/or (2) are performed in cell media comprising about 2% serum, or

a LSD1 inhibitor or a MALT1 inhibitor; and/or

(b) the method further comprises receiving a cryopreserved leukapheresis product (or an alternative source of hematopoietic tissue such as a cryopreserved whole blood product, a cryopreserved bone marrow product, or a cryopreserved tumor or organ biopsy or removal (for example, a cryopreserved product from thymectomy)) from an entity, for example, a laboratory, hospital, or healthcare provider.

45. A population of cells made by the method of claim 37 or 38, wherein the population comprises:

a first population of cells comprising an anti-BCMA CAR but not an anti-CD19 CAR;

a second population of cells comprising an anti-CD19 CAR but not an anti-BCMA CAR;

and

a third population of cells comprising both an anti-BCMA CAR and an anti-CD19 CAR.

46. The population of cells of claim 45, wherein:

(i) the total number of viable cells in the second and third populations combined is less than or equal to about 110% (e.g., less than or equal to about 105%, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 1%, or less) of the total number of viable cells in the first and third populations combined;

(ii) the total number of viable cells in the first and third populations combined is greater than or equal to about 90% (e.g., greater than or equal to about 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400%, 500%, 750%, 1000%, 2000%, 5000, 10000% or more) of the total number of viable cells in the second and third populations combined; and/or

(iii) the total number of viable cells in the first and third populations combined is greater than or equal to about 5% (e.g., greater than or equal to about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the total number of viable cells in the population; optionally, wherein the population further comprises a fourth population of cells that do not comprise a CAR.

47. A population of cells engineered to express a CAR (“a population of CAR-expressing cells”), said population comprising:

(a) about the same percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR;

(b) a change within about 5% to about 10% of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, for example, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR;

(c) an increased percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ T cells, for example, increased by at least 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, or 3-fold, as compared to the percentage of naïve cells, for example, naïve T cells, for example, CD45RO- CCR7+ cells, in the same population of cells prior to being engineered to express the CAR;

(d) about the same percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of central memory

cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR;

(e) a change within about 5% to about 10% of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR;

(f) a decreased percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, for example, decreased by at least 20, 25, 30, 35, 40, 45, or 50%, as compared to the percentage of central memory cells, for example, central memory T cells, for example, CCR7+CD45RO+ T cells, in the same population of cells prior to being engineered to express the CAR;

(g) about the same percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR;

(h) a change within about 5% to about 10% of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR; or

(i) an increased percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, as compared to the percentage of stem memory T cells, for example, CD45RA+CD95+IL-2 receptor β +CCR7+CD62L+ T cells, in the same population of cells prior to being engineered to express the CAR,

wherein the population comprises a cell comprising a nucleic acid molecule (for example, a DNA or RNA molecule) encoding the CAR, wherein:

(I) the nucleic acid molecule comprises a first nucleic acid sequence encoding a first CAR and a second nucleic acid sequence encoding a second CAR, wherein:

the first and second nucleic acid sequences are disposed on a single nucleic acid molecule, e.g., wherein the first nucleic acid sequence and the second nucleic acid sequence are separated by a third nucleic acid sequence encoding a self-cleavage site (e.g., a P2A site, a T2A site, an E2A site, or an F2A site), or

the first and second nucleic acid sequences are disposed on separate nucleic acid molecules; or

(II) the nucleic acid molecule comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises a first VH (VH1), a first VL (VL1), a second VH (VH2), a second VL (VL2), a transmembrane domain, and an intracellular signaling domain, wherein the VH1 and VL1 bind to a first antigen and the VH2 and VL2 bind to a second antigen, wherein the VH1, VL1, VH2, and VL2 are arranged in the following configuration from the N-terminus to the C-terminus: VH1 – optionally linker 1 (“L1”) – VH2 – optionally linker 2 (“L2”) – VL2 – optionally linker 3 (“L3”) – VL1, VH1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VL1, VL1 – optionally L1 – VH2 – optionally L2 – VL2 – optionally L3 – VH1, VL1 – optionally L1 – VL2 – optionally L2 – VH2 – optionally L3 – VH1, VH2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VL2, VH2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VL2, VL2 – optionally L1 – VH1 – optionally L2 – VL1 – optionally L3 – VH2; or VL2 – optionally L1 – VL1 – optionally L2 – VH1 – optionally L3 – VH2.

48. The cell of any one of claims 1-15 or 20 pharmaceutical composition of claim 23 for use in the treatment of a disease associated with expression of BCMA, wherein an effective amount is to be administered to the subject.