

binding chimeric antigen receptors (CARs), and cells expressing such CARs, are available. However, there remains a need for improved GPRC5D-binding CARs and engineered GPRC5D-CAR expressing targeting cells, such as for use in adoptive cell therapy. Provided herein are embodiments that meet such needs.

Summary

[0005] Provided herein are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NO:21, 23, 25, 27, 29, 31 or 33; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO:22, 24, 26, 28, 30, 32 or 34; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0005a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises: (i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:21, 23, 25, 27, 29, 31 or 33; and (ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:22, 24, 26, 28, 30, 32, 34, 63, 64, 65, 66, 67, 68 or 69; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0006] Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence selected from any one of SEQ ID NOs: 21, 23, 25, 27, 29, 31 or 33; and (ii) a variable light chain (V_L) region containing a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence selected from any one of SEQ ID NOs: 22, 24, 26, 28, 30, 32 or 34; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0006a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises: (i) a variable heavy chain (V_H) region comprising a heavy chain complementarity determining region 1 (CDR-H1), heavy chain complementarity determining region 2 (CDR-H2) and heavy chain complementarity determining region 3 (CDR-H3) contained within the V_H region amino acid sequence selected from SEQ ID NOs: 21, 23, 25, 27, 29, 31, and 33; and (ii) a variable light chain (V_L) region comprising a light chain complementarity determining region 1 (CDR-L1), light chain complementarity determining region 2 (CDR-L2) and light chain complementarity determining region 3 (CDR-L3) contained within the V_L region amino acid sequence selected from SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34, 63, 64, 65, 66, 67, 68, and 69; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0007] Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D) wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a heavy chain complementarity determining region 1 (CDR-H1) containing the amino acid sequence selected from any one of SEQ ID NOs: 75, 78, 80, 82, 90, 93, 95, 97, 105, 108, 110, 112, 120, 123, 125, 127, 135, 138, 140, 142, 135, 152, 162, 165, 167 or 169; (b) a heavy chain complementarity determining region 2 (CDR-H2) containing the amino acid sequence selected from any one of SEQ ID NOs: 76, 79, 81, 83, 91, 94, 96, 98, 106, 109, 111, 113, 121, 124, 126, 128, 136, 139, 141, 143, 150, 153, 154, 155, 163, 166, 169 or 170; and (c) a heavy chain complementarity determining region 3 (CDR-H3) containing the amino acid sequence selected from any one of SEQ ID NOs: 77, 84, 92, 99, 107, 114, 133, 129, 137, 144, 151, 156, 164 or 171; and (ii) a variable light chain (V_L) region containing a light chain complementarity determining region 1 (CDR-L1) containing the amino acid sequence selected from any one of SEQ ID NOs: 85, 88, 100, 103, 115, 118, 130, 133, 145, 148, 157, 160, 172 or 174; (b) a light

chain complementarity determining region 2 (CDR-L2) containing the amino acid sequence selected from any one of SEQ ID NOs: 86, 89, 101, 104, 116, 119, 131, 134, 146, 149, 158 or 161; and (c) a light chain complementarity determining region 3 (CDR-L3) containing the amino acid sequence selected from any one of SEQ ID NOs: 87, 102, 117, 132, 147, 159, 173, 175, or 297; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0007a] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises: (i) a variable heavy chain (V_H) region comprising a CDR-H1 comprising the amino acid sequence selected from SEQ ID NOs: 75, 78, 80, 90, 93, 95, 105, 108, 110, 120, 123, 125, 135, 138, 140, 152, 162, 165, and 167; (b) a CDR-H2 comprising the amino acid sequence selected from SEQ ID NOs: 76, 79, 81, 91, 94, 96, 106, 109, 111, 121, 124, 126, 136, 139, 141, 150, 153, 154, 163, 166, and 168; and (c) a CDR-H3 comprising the amino acid sequence selected from SEQ ID NOs: 77, 92, 107, 122, 137, 151, and 164; and (ii) a variable light chain (V_L) region comprising a CDR-L1 comprising the amino acid sequence selected from SEQ ID NOs: 85, 100, 115, 130, 145, 157, and 172; (b) a CDR-L2 comprising the amino acid sequence selected from SEQ ID NOs: 86, 101, 116, 131, 146, and 158; and (c) a CDR-L3 comprising the amino acid sequence selected from SEQ ID NOs: 87, 102, 117, 132, 147, 159, 173, and 297; (2) a spacer of at least 125 amino acids in length; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0008] In some of any of the provided examples, the extracellular antigen-binding domain of the chimeric antigen receptor contains: (i) a variable heavy chain (V_H) containing: an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NO: 21, 23, 25, 27, 29, 31 or 33; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 22, 24, 26, 28, 30, 32 or 34.

[0009] In some of any of the provided examples, the spacer has a length from or from about 125 to 300 amino acids in length, 125 to 250 amino acids in length, 125 to 230 amino acids in length, 125 to 200 amino acids in length, 125 to 180 amino acids in length, 125 to 150 amino acids in length, 150 to 300 amino acids in length, 150 to 250 amino acids in length, 150 to 230 amino acids in length, 150 to 200 amino acids in length, 150 to 180 amino acids in length, 180 to 300 amino acids in length, 180 to 250 amino acids in length, 180 to 230 amino acids in length, 180 to 200 amino acids in length, 200 to 300 amino acids in length, 200 to 250 amino acids in length, 200 to 230 amino acids in length, 230 to 300 amino acids in length, 230 to 250 amino acids in length or 250 to 300 amino acids in length. In some of any of the provided examples, the spacer is at least or at least about or is or is about 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 221, 222, 223, 224, 225, 226, 227, 228 or 229 amino acids in length, or has a length between any of the foregoing.

[0010] In some of any of the provided examples, the spacer is derived from an immunoglobulin. In some of any of the provided examples, the spacer contains a sequence of a hinge region, a CH2 and CH3 region. In some of any of the provided examples, one of more of the hinge, CH2 and CH3 is derived all or in part from IgG4 or IgG2, optionally human IgG4 or human IgG2. In some of any of the provided examples, the hinge, CH2 and CH3 is derived from IgG4. In some of any of the provided examples, one or more of the hinge, CH2 and CH3 is chimeric and contains a sequence derived from IgG4 and IgG2. In some of any of the provided examples, the spacer contains an IgG4/2 chimeric hinge or a modified IgG4 containing at least one amino acid replacement compared to human IgG4, an IgG2/4 chimeric CH2, and an IgG4 CH3 region.

[0011] In some of any of the provided examples, the spacer is or contains (i) the sequence set forth in SEQ ID NO: 17; (ii) a functional variant of SEQ ID NO: 17 that has at least 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 17; or (iii) a contiguous portion of (i) or (ii) that is at least 125 amino acids in length. In some of any of the provided examples, the spacer is or contains the

sequence set forth in SEQ ID NO:17. In some of any of the provided examples, the spacer is or contains a sequence encoded by the sequence of nucleotides set forth in SEQ ID NO:48 (also set forth in SEQ ID NO:74).

[0012] In some of any of the provided examples, the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:21 and 22, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:21 and 22, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:23 and 24, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:23 and 24, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:25 and 26, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:25 and 26, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:27 and 28, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:27 and 28, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:29 and 30, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:29 and 30, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:31 and 32, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:31 and 32, respectively; or the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:33 and 34, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:33 and 34, respectively.

[0013] In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:80, 81 and 77, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:85, 86 and 87, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:82, 83 and 84, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:88, 89 and 87, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:95, 96, 92, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:100, 101 and 102, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:97, 98 and 99, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:103, 104 and 102, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:110,

111 and 107, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:115, 116 and 117, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:112, 113 and 114, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:118, 119 and 117, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:127, 128 and 129, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:133, 134 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:140, 141 and 137, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:145, 146 and 147, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:142, 143 and 144, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:148, 149 and 147, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:140, 154 and 151, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:157, 158 and 159, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:142, 155 and 156, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:160, 161 and 159, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:167, 168 and 164, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:172, 86, 173, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:169, 170 and 171, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:174, 89 and 175, respectively; or the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:169, 170 and 171, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:174, 89 and 297, respectively.

[0014] In some of any of the provided examples, the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:21 and 22, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:23 and 24, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:25 and 26, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:27 and 28,

respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:29 and 30, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:31 and 32, respectively; or the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:33 and 34, respectively.

[0015] In some of any of the provided examples, the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:21 and 22, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:21 and 22, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:23 and 24, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:23 and 24, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:27 and 28, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:27 and 28, respectively; or the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:31 and 32, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:31 and 32, respectively.

[0016] In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:80, 81 and 77, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:85, 86 and 87, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:82, 83 and 84, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:88, 89 and 87, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:95, 96, 92, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:100, 101 and 102, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:97, 98 and 99, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:103, 104 and 102, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:127, 128 and 129, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:133, 134 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:140, 154 and 151, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID

NOS:157, 158 and 159, respectively; or the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:142, 155 and 156, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:160, 161 and 159, respectively.

[0017] In some of any of the provided examples, the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:21 and 22, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:23 and 24, respectively; the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:27 and 28, respectively; or the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOS:31 and 32, respectively.

[0018] In some of any of the provided examples, the extracellular antigen-binding domain is cross-reactive or binds mouse GPRC5D and/or is cross-reactive or binds cynomolgus GPRC5D. In some of any of the provided examples, the extracellular antigen-binding domain is not cross-reactive to or does not bind mouse GPRC5D or cynomolgus GPRC5D.

[0019] In some of any of the provided examples, the V_H region and the V_L region contain the amino acid sequences set forth in SEQ ID NOS:27 and 28, respectively, or a sequence of amino acids having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOS:27 and 28, respectively.

[0020] In some of any of the provided examples, the chimeric antigen receptor contains a variable heavy chain (V_H) containing a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light chain (V_L) region containing a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28. In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively. In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:127, 128 and 129, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:133, 134 and 132, respectively. In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:120, 121 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively. In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:123, 124 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130,

131 and 132, respectively. In some of any of the provided examples, the V_H region and the V_L regions contain the amino acid sequence set forth in SEQ ID NOs:27 and 28, respectively.

[0021] In some of any of the provided examples, the extracellular antigen-binding domain is a single chain antibody fragment. In some of any of the provided examples, the fragment is or contains a single chain variable fragment (scFv).

[0022] In some of any of the provided examples, the V_H region and the V_L region are joined by a flexible linker. In some of any of the provided examples, the V_H region and the V_L region are joined by a linker containing the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:52). In some of any of the provided examples, the V_H region and the V_L region are joined by a flexible linker. In some of any of the provided examples, the V_H region and the V_L region are joined by a linker containing the amino acid sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:320).

[0023] In some of any of the provided examples, the V_H region is amino-terminal to the V_L region. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11 or 13 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11 or 13. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11 or 13. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 7 or 11 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 7 or 11. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 1, 3, 7 or 11. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence set forth in SEQ ID NO: 7 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence set forth in SEQ ID NO: 7.

[0024] In some of any of the provided examples, the V_H region is carboxy-terminal to the V_L region. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12 or 14 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12 or 14. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12 or 14. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 8 or 12 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or

99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 8 or 12. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence selected from any one of SEQ ID NOs: 2, 4, 8 or 12. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence set forth in SEQ ID NO: 8 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8. In some of any of the provided examples, the antigen-binding domain contains the amino acid sequence set forth in SEQ ID NO: 8. In some of any of the provided examples, the antigen-binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:264.

[0025] In some of any of the provided examples, the intracellular signaling region contains an intracellular cytoplasmic signaling domain. In some of any of the provided examples, the intracellular signaling domain is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples, the intracellular signaling domain is or contains a cytoplasmic signaling domain of a zeta chain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof.

[0026] In some of any of the provided examples, the intracellular signaling domain is human or is derived from a human protein. In some of any of the provided examples, the intracellular signaling domain is or contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20.

[0027] In some of any of the provided examples, the intracellular signaling region further contains a costimulatory signaling region. In some of any of the provided examples, the costimulatory signaling region contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region contains an intracellular signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region contains an intracellular signaling domain of a 4-1BB or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region is human or is derived from a human protein. In some of any of the provided examples, the costimulatory signaling region contains an intracellular signaling domain of CD28, such as an intracellular signaling domain of human CD28.

[0028] In some of any of the provided examples, the costimulatory signaling region is or contains the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46. In some of any of the provided examples, the costimulatory signaling region contains an intracellular signaling domain of 4-1BB. In some of any of the provided examples, the costimulatory signaling region is or contains the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that

exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19.

[0029] In some of any of the provided examples, the costimulatory signaling region is between the transmembrane domain and the intracellular signaling region. In some of any of the provided examples, the transmembrane domain is or contains a transmembrane domain derived from CD4, CD28, or CD8. In some of any of the provided examples, the transmembrane domain is or contains a transmembrane domain derived from a CD28. In some of any of the provided examples, the transmembrane domain is human or is derived from a human protein. In some of any of the provided examples, the transmembrane domain is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18.

[0030] Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor (GPCR5D), wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in SEQ ID NO: 27; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 28; (2) a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain derived from a human CD28; and (4) an intracellular signaling region containing a cytoplasmic signaling domain of a zeta chain of a CD3-zeta ($CD3\zeta$) chain and an intracellular signaling domain of a T cell costimulatory molecule.

[0030a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPCR5D), wherein the extracellular antigen-binding domain comprises: (i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 27; and (ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28 or 66; (2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length or a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain from human CD28; and (4) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and an intracellular signaling domain of a T cell costimulatory molecule.

[0031] In some of any of the provided examples, the V_H region contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28; or the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:127, 128 and 129, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:133, 134 and 132, respectively; the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:120, 121 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; or the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:123, 124 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively. In some of any of

the provided examples, the V_H region contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28; or the V_H region contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively.

[0032] Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor (GPCR5D), wherein the extracellular antigen-binding domain contains: a variable heavy (V_H) region containing a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light (V_L) region containing a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28; or a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:127, 128 and 129, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:133, 134 and 132, respectively; a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:120, 121 and 122, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; or a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:123, 124 and 122, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; (2) a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain derived from a human CD28; and (4) an intracellular signaling region containing a cytoplasmic signaling domain of a zeta chain of a human CD3-zeta (CD3 ζ) chain and an intracellular signaling domain of a human CD28 or a human 4-1BB.

[0032a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPCR5D), wherein the extracellular antigen-binding domain comprises: a V_H region comprising a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light (V_L) region comprising a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28 or 66; or a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:120, 121 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; or a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:123, 124 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; (2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length or a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain from human CD28; and (4) an intracellular signaling region comprising a cytoplasmic signaling domain of a human CD3-zeta (CD3 ζ) chain and an intracellular signaling domain of a human CD28 or a human 4-1BB.

[0033] Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor (GPCR5D), wherein the extracellular antigen-binding domain contains: a variable heavy (V_H) region containing a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light (V_L) region containing a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28; or a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; (2) a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain derived from a human CD28; and (4) an intracellular signaling region containing a cytoplasmic signaling domain

of a zeta chain of a human CD3-zeta (CD3 ζ) chain and an intracellular signaling domain of a human CD28. Also provided are chimeric antigen receptors containing: (1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor (GPCR5D), wherein the extracellular antigen-binding domain contains: a variable heavy (V_H) region containing a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light (V_L) region containing a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28; or a V_H region containing a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and a V_L region containing a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; (2) a spacer set forth in SEQ ID NO:17; (3) a transmembrane domain derived from a human CD28; and (4) an intracellular signaling region containing a cytoplasmic signaling domain of a zeta chain of a human CD3-zeta (CD3 ζ) chain and an intracellular signaling domain of a human 4-1BB.

[0034] In some of any of the provided examples, the extracellular antigen-binding domain contains the V_H region amino acid sequence set forth in SEQ ID NO:27 and the V_L region amino acid sequence set forth in SEQ ID NO:28; and/or in some of any of the provided examples, the extracellular antigen-binding domain contains an scFv set forth in SEQ ID NO:7 or SEQ ID NO:8. In some of any of the provided examples, the extracellular antigen-binding domain contains the V_H region amino acid sequence set forth in SEQ ID NO:27 and the V_L region amino acid sequence set forth in SEQ ID NO:28; and the extracellular antigen-binding domain contains an scFv set forth in SEQ ID NO:7. In some of any of the provided examples, the extracellular antigen-binding domain contains the V_H region amino acid sequence set forth in SEQ ID NO:27 and the V_L region amino acid sequence set forth in SEQ ID NO:28; and the extracellular antigen-binding domain contains an scFv set forth in SEQ ID NO:8.

[0035] In some of any of the provided examples, the transmembrane domain is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18. In some of any of the provided examples, the transmembrane domain is or contains the sequence set forth in SEQ ID NO:18.

[0036] In some of any of the provided examples, the intracellular signaling region contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20 and the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46. In some of any of the provided examples, the intracellular signaling region is or contains the sequences set forth in SEQ ID NO:20 and SEQ ID NO:46. In some of any of the provided examples, the intracellular

signaling region contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20 and the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19. In some of any of the provided examples, the intracellular signaling region is or contains the sequences set forth in SEQ ID NO:20 and SEQ ID NO:19.

[0037] In some of any of the provided examples, the chimeric antigen receptor contains from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0038] Also provided are polynucleotides containing a sequence of nucleotides encoding any of the chimeric antigen receptors provided herein.

[0038a] In one aspect, the present disclosure refers to a polynucleotide comprising a nucleotide sequence encoding the chimeric antigen receptor disclosed herein.

[0039] In some of any of the provided examples, the nucleic acid encoding the spacer contains at least one modified splice donor and/or splice acceptor site, said modified splice donor and/or acceptor site containing one or more nucleotide modifications corresponding to a reference splice donor site and/or reference splice acceptor site contained in the sequence set forth in SEQ ID NO:73. In some of any of the provided examples, the one or more nucleotide modifications contain an amino acid substitution. In some of any of the provided examples, the reference splice donor and/or reference splice acceptor sites are canonical, non-canonical, or cryptic splice sites. In some of any of the provided examples, the reference splice donor and/or reference splice acceptor site(s) has a splice site prediction score of at least or about 0.4, 0.5, 0.6, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 0.99, or 1.0; and/or the reference splice donor and/or reference splice acceptor site(s) is/are predicted to be involved in a splice event with a probability of at least 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%.

[0040] In some of any of the provided examples, the reference splice donor site contains the sequence aatctaagtacggac (SEQ ID NO: 176), tcaactggtacgtgg (SEQ ID NO:177), acaattagtaaggca (SEQ ID NO:178) and/or accacaggtgtatac (SEQ ID NO:179); and/or the reference splice acceptor site contains the sequence aagtttctttctgtattccaggctgaccgtggataaatctc (SEQ ID NO:180) and/or gggcaacgtgttctcttcagtgatgcacgaagccctgc (SEQ ID NO:181).

[0041] In some of any of the provided examples, the reference splice donor and/or reference splice acceptor site(s) has a splice site prediction score of at least or about 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 0.99, or 1.0; and/or In some of any of the provided examples, the reference splice donor and/or reference splice acceptor site(s) is/are predicted to be involved in a splice event with a probability of at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100%.

[0042] In some of any of the provided examples, the reference splice donor site contains the sequence tcaactggtacgtgg (SEQ ID NO:177); and/or the reference splice acceptor site contains the sequence aagtttctttctgtattccaggctgaccgtggataaatctc (SEQ ID NO:180).

[0043] In some of any of the provided examples, at least one of the one or more nucleotide modifications are within 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues of the splice site junction of the reference splice acceptor and/or reference splice donor site.

[0044] In some of any of the provided examples, the one or more nucleotide modifications is silent and/or results in a degenerate codon compared to SEQ ID NO:73 and/or does not change the amino acid sequence of the encoded spacer.

[0045] In some of any of the provided examples, the modified splice donor site is set forth in agtctaataacggac (SEQ ID NO:182), tcaactggtatgtgg (SEQ ID NO:183), accatctccaaggcc (SEQ ID NO:184) and/or gccccaggtttacac (SEQ ID NO:185); and/or the modified splice acceptor site is set forth in cagtttctctgtatagtagactaccgtggataaatcaa (SEQ ID NO:186), gggcaacgtgttcagctgcagcgtgatgcagaggccctgc (SEQ ID NO: 187) and/or cgcttctctctctgtcccgctcctctgttgccggacct (SEQ ID NO:188). In some of any of the provided examples, the modified splice donor site is set forth in tcaactggtatgtgg (SEQ ID NO:183) and/or the modified acceptor site is set forth in cagtttctctgtatagtagactaccgtggataaatcaa (SEQ ID NO:186) and/or cgcttctctctctgtcccgctcctctgttgccggacct (SEQ ID NO:188).

[0046] In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:74 (also set forth in SEQ ID NO:48) or a portion thereof. In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:73 or a portion thereof. In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:74 or a portion thereof. In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:283 or a portion thereof. In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:284 or a portion thereof. In some of any of the provided examples, the spacer is encoded by a sequence of nucleotide set forth in SEQ ID NO:305 or a portion thereof.

[0047] In some of any of the provided examples, upon expression of the polynucleotide in a cell, the transcribed RNA, optionally messenger RNA (mRNA), from the polynucleotide, exhibits at least 70%, 75%, 80%, 85%, 90%, or 95% RNA homogeneity.

[0048] In some of any of the provided examples, upon expression in a cell, the transcribed RNA, optionally messenger RNA (mRNA), from the polynucleotide exhibits reduced heterogeneity compared to the heterogeneity of the mRNA transcribed from a reference polynucleotide, said reference polynucleotide encoding the same amino acid sequence as the polynucleotide, wherein the reference polynucleotide differs by the presence of one or more splice donor site and/or one or more splice acceptor site in the nucleic acid encoding the spacer and/or contains one or more nucleotide modifications compared to the polynucleotide and/or contains the spacer set forth in SEQ ID NO:73. In some of any of the provided examples, the RNA heterogeneity is reduced by greater than or greater than about 10%, 15%, 20%, 25%, 30%, 40%, 50% or more. In some of any of the provided

examples, the transcribed RNA, optionally messenger RNA (mRNA), from the reference polynucleotide exhibits greater than or greater than about 10%, 15%, 20%, 25%, 30%, 40%, 50% or more RNA heterogeneity. In some of any of the provided examples, the RNA homogeneity and/or heterogeneity is determined by agarose gel electrophoresis, chip-based capillary electrophoresis, analytical ultracentrifugation, field flow fractionation, or liquid chromatography.

[0049] In some of any of the provided examples, the polynucleotide is codon-optimized for expression in a human cell.

[0050] In some of any of the provided examples, the chimeric receptor is a first chimeric receptor and the polynucleotide further contains a sequence of nucleotides encoding a second chimeric antigen receptor. Thus, also provided herein are polynucleotides that encode a first chimeric receptor that is directed against GPRC5D, including any as provided herein, and a second chimeric receptor. In some of any of the provided examples, the first and second chimeric receptors are separated by one or more multicistronic element(s). In some of any of the provided examples, the one or more multicistronic element is or contains a ribosome skip sequence. In some examples, the ribosome skip sequence is a T2A, a P2A, an E2A, or an F2A element. In some of any of the provided examples, the one or more multicistronic element contains the amino acid sequence set forth in SEQ ID NO:37. In some of any of the provided examples, the one or more multicistronic element is encoded by a nucleotide sequence selected from among SEQ ID NOS: 44, 45, and 319. In some of any of the provided examples, the nucleotide sequence encoding the one or more multicistronic element is codon diverged. In some of any of the provided examples, nucleotide sequence encoding the multicistronic element is or comprises the sequence set forth in SEQ ID NO:319.

[0051] In some of any of the provided examples, the second chimeric receptor contains an extracellular antigen binding domain that specifically binds a second antigen, such as other than GPRC5D, expressed on or associated with multiple myeloma. In some of any of the provided examples, the second CAR contains an extracellular antigen binding domain that binds the second antigen, a spacer, a transmembrane domain, and an intracellular signaling region. In some of any of the provided examples, the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI or FcRH5. In some of any of the provided examples, the second antigen is BCMA.

[0052] In some of any of the provided examples, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NOS: 189, 191, 193, 195 or 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 190, 192,

194, 196 or 198; (2) a spacer; (3) a transmembrane; and (4) an intracellular signaling region. In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in any of SEQ ID NOs: 190, 192, 194, 196 or 198.

[0053] In some of any of the provided examples, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in SEQ ID NO: 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO:198; (2) a spacer; (3) a transmembrane domain; and (4) an intracellular signaling region. In some of any of the provided examples, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in SEQ ID NO: 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO:198; (2) a spacer set forth in SEQ ID NO: 17; (3) a transmembrane domain derived from a human CD28; and (4) an intracellular signaling region containing a cytoplasmic signaling domain of a zeta chain of a human CD3-zeta (CD3ζ) chain and an intracellular signaling domain of a human 4-1BB. In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in any of SEQ ID NOs: 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in any of SEQ ID NOs:198. In some of any of the provided examples, the second CAR is or comprises the amino acid sequence set forth in SEQ ID NO:251. In some of any of the provided examples, the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:246.

[0054] In some of any of the provided examples, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a heavy chain complementarity determining region 1 (CDR-H1) containing the amino acid sequence selected from any one of SEQ ID NOs: 199, 202, 206, 209, 212 or 215; (b) a heavy chain complementarity determining region 2 (CDR-H2) containing the amino acid sequence selected from any one of SEQ ID NOs: 200, 203, 207, 210, 213 or 216; and (c) a heavy chain complementarity determining region 3 (CDR-H3) containing

the amino acid sequence selected from any one of SEQ ID NOs: 201, 204, 205, 208, 211, 214 or 217; and (ii) a variable light chain (V_L) region containing a light chain complementarity determining region 1 (CDR-L1) containing the amino acid sequence selected from any one of SEQ ID NOs: 218, 221, 224, 227, 230, 233 or 235; (b) a light chain complementarity determining region 2 (CDR-L2) containing the amino acid sequence selected from any one of SEQ ID NOs: 219, 222, 225, 228, 231, 234 or 236; and (c) a light chain complementarity determining region 3 (CDR-L3) containing the amino acid sequence selected from any one of SEQ ID NOs: 220, 223, 226, 229 or 232; (2) a spacer; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0055] In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:212, 213 and 214, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:233, 234 and 229, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0056] In some of any of the provided examples, the V_H region of the encoded second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region

of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively. In some of any of the provided examples, the V_H region of the encoded second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively. In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0057] In some of any of the provided examples, the V_H region and V_L region of the encoded second CAR contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:189 and SEQ ID NO:190; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

[0058] In some of any of the provided examples, the V_H region and V_L region of the encoded second CAR contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively. In some of any of the provided examples, the V_H region

and V_L region of the encoded second CAR contain the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively.

[0059] In some of any of the provided examples, the extracellular antigen-binding domain of the encoded second CAR is a single chain antibody fragment. In some of any of the provided examples, the encoded fragment is or contains a single chain variable fragment (scFv). In some of any of the provided examples, the V_H region and the V_L region of the encoded second CAR are joined by a flexible linker. In some of any of the provided examples, the scFv of the encoded second CAR contains a linker containing the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:52). In some of any of the provided examples, the scFv of the encoded second CAR contains a linker containing the amino acid sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:320). In some of any of the provided examples, the V_H region is amino-terminal to the V_L region in the encoded second CAR. In some of any of the provided examples, the V_H region is carboxy-terminal to the V_L region in the encoded second CAR.

[0060] In some of any of the provided examples, the antigen-binding domain of the encoded second CAR contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples, the antigen-binding domain of the encoded second CAR contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples, the antigen-binding domain of the encoded second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 241. In some of any of the provided examples, the antigen-binding domain of the encoded second CAR contains the amino acid sequence set forth in SEQ ID NO: 241.

[0061] In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively; and/or the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in

SEQ ID NO:241. In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; and/or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241. In some of any of the provided examples, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively; and/or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241.

[0062] In some of any of the provided examples, the transmembrane domain of the encoded second CAR is or contains a transmembrane domain derived from CD4, CD28, or CD8, optionally from a human CD4, a human CD28 or a human CD8.

[0063] In some of any of the provided examples, the transmembrane domain of the encoded second CAR is or contains a transmembrane domain derived from a human CD28 and/or is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18. In some of any of the provided examples, the transmembrane domain of the encoded second CAR is or contains the sequence set forth in SEQ ID NO:18.

[0064] In some of any of the provided examples, the intracellular signaling region of the encoded second CAR contains an intracellular signaling domain. In some of any of the provided examples, the intracellular signaling domain of the encoded second CAR is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples, the intracellular signaling domain of the encoded second CAR is or contains a cytoplasmic signaling domain of a zeta chain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain. In some of any of the provided examples, the intracellular signaling region of the encoded second CAR contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20.

[0065] In some of any of the provided examples, the intracellular signaling region of the encoded second CAR further contains a costimulatory signaling region. In some of any of the provided examples, the costimulatory signaling region of the encoded second CAR contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region of the encoded second CAR contains an intracellular signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof, optionally a human CD28, a human 4-1BB, or a human ICOS. In some of any of the provided examples, the costimulatory signaling region of the encoded second CAR contains an intracellular signaling domain of a 4-1BB or a signaling portion thereof. In some of any of the provided examples, at least one of the first chimeric antigen receptor and the second chimeric antigen receptor contains an intracellular signaling region containing an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB.

[0066] In some of any of the provided examples, the costimulatory signaling region of the encoded second CAR contains: an intracellular signaling domain of a human CD28; and/or the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46.

[0067] In some of any of the provided examples, the costimulatory signaling region of the encoded second CAR contains: an intracellular signaling domain of a human 4-1BB; and/or the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19.

[0068] In some of any of the provided examples, the encoded second chimeric antigen receptor contains from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0069] In some of any of the provided examples, at least one of the polynucleotide sequence encoding the first chimeric antigen receptor and the polynucleotide sequence encoding the second chimeric antigen receptor is codon diverged. In some of any of the provided examples, the polynucleotide sequence encoding the first chimeric antigen receptor and the polynucleotide sequence encoding the second chimeric antigen receptor have no more than about 30, no more than about 20, or no more than about 10 consecutive base pairs of sequence homology.

[0070] In some of any of the provided examples, the sequence of nucleotides encoding the CAR is operably linked to a promoter to control expression of the encoded CAR when expressed from a cell introduced with the polynucleotide, optionally wherein the promoter is a heterologous promoter, optionally wherein the heterologous promoter is or contains a human elongation factor 1 alpha (EF1 α) promoter or an MND promoter or a variant thereof.

[0071] In some of any of the provided examples, wherein the polynucleotide encodes two CARs, the sequence of nucleotides encoding the first CAR is operably linked to a first promoter to

control expression of the first CAR when expressed from a cell introduced with the polynucleotide and the sequence of nucleotides encoding the second CAR is operably linked to a second promoter to control expression of the second CAR when expressed from a cell introduced with the polynucleotide. In some examples, the first and second promoter independently is a heterologous promoter, such as wherein the heterologous promoter is or contains a human elongation factor 1 alpha (EF1 α) promoter or an MND promoter or a variant thereof. In some of such examples, the first and second promoters are the same. In some of such examples, the first and second promoter are different.

[0072] Also provided are vectors containing any of the provided polynucleotides. In some of any of the provided examples, the vector is a viral vector. In some of any of the provided examples, the viral vector is a lentiviral vector or a retroviral vector.

[0073] Also provided are engineered cells containing any of the chimeric antigen receptors provided herein. In some of any of the provided examples, the engineered cell contains a chimeric antigen receptor provided herein and further contains a polynucleotide containing a sequence of nucleotides encoding a second chimeric antigen receptor.

[0074] Also provided are engineered cells containing any of the polynucleotides provided herein.

[0075] In some of any of the provided examples, the second chimeric receptor of the provided cell contains an extracellular antigen binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma. In some of any of the provided examples, the second CAR contains the extracellular antigen binding domain that binds the second antigen, a spacer, a transmembrane domain, and an intracellular signaling region. In some of any of such examples, the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI or FcRH5. In some of any of the provided examples, the second antigen is BCMA.

[0076] In some of any of the provided examples of engineered cells, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 190, 192, 194, 196 or 198; (2) a spacer; (3) a transmembrane; and (4) an intracellular signaling region. In some of such examples, the V_H region contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in any of SEQ ID NOs: 190, 192, 194, 196 or 198.

[0077] In some of any of the provided examples of engineered cells, the second CAR contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular

antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a heavy chain complementarity determining region 1 (CDR-H1) containing the amino acid sequence selected from any one of SEQ ID NOs: 199, 202, 206, 209, 212 or 215; (b) a heavy chain complementarity determining region 2 (CDR-H2) containing the amino acid sequence selected from any one of SEQ ID NOs: 200, 203, 207, 210, 213 or 216; and (c) a heavy chain complementarity determining region 3 (CDR-H3) containing the amino acid sequence selected from any one of SEQ ID NOs: 201, 204, 205, 208, 211, 214 or 217; and (ii) a variable light chain (V_L) region containing a light chain complementarity determining region 1 (CDR-L1) containing the amino acid sequence selected from any one of SEQ ID NOs: 218, 221, 224, 227, 230, 233 or 235; (b) a light chain complementarity determining region 2 (CDR-L2) containing the amino acid sequence selected from any one of SEQ ID NOs: 219, 222, 225, 228, 231, 234 or 236; and (c) a light chain complementarity determining region 3 (CDR-L3) containing the amino acid sequence selected from any one of SEQ ID NOs: 220, 223, 226, 229 or 232; (2) a spacer; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0078] In some of any of the provided examples of engineered cells, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:212, 213 and 214, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:233, 234 and 229, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains

a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0079] In some of any of the provided examples of engineered cells, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0080] In some of any of the provided examples of engineered cells, the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:189 and SEQ ID NO:190; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

[0081] In some of any of the provided examples of engineered cells, the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively.

[0082] In some of any of the provided examples of engineered cells, the extracellular antigen-binding domain of the second CAR is a single chain antibody fragment. In some of any of such examples, the fragment is or contains a single chain variable fragment (scFv).

[0083] In some of any of the provided examples of engineered cells, the V_H region and the V_L region of the second CAR are joined by a flexible linker. In some of such examples, the linker contains the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:52). In some of such examples, the linker contains the amino acid sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:320).

[0084] In some of any of the provided examples of engineered cells, the V_H region is amino-terminal to the V_L region in the second CAR. In some of any of the provided examples of engineered cells, the V_H region is carboxy-terminal to the V_L region in the second CAR. In some of any of the provided examples of engineered cells, the antigen-binding domain of the second CAR contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241.

[0085] In some of any of the provided examples of engineered cells, the antigen-binding domain of the second CAR contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples of engineered cells, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively; and/or the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241.

[0086] In some of any of the provided examples of engineered cells, the antigen-binding domain of the second CAR contains the amino acid set forth in SEQ ID NO: 241. In some of any of the provided examples of engineered cells, the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; and/or the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198,

respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241.

[0087] In some of any of the provided examples of engineered cells, the transmembrane domain of the second CAR is or contains a transmembrane domain derived from CD4, CD28, or CD8, optionally from a human CD4, a human CD28 or a human CD8. In some of any of the provided examples of engineered cells, the transmembrane domain of the second CAR is or contains a transmembrane domain derived from a human CD28; and/or the transmembrane domain is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18. In some of any of the provided examples of engineered cells, the transmembrane domain of the second CAR is or contains the sequence set forth in SEQ ID NO:18.

[0088] In some of any of the provided examples of engineered cells, the intracellular signaling region of the second CAR contains an intracellular signaling domain.

[0089] In some of any of the provided examples of engineered cells, the intracellular signaling domain of the second CAR is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples of engineered cells, the intracellular signaling domain of the second CAR is or contains a cytoplasmic signaling domain of a zeta chain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain. In some of any of the provided examples of engineered cells, the intracellular signaling region of the second CAR contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20.

[0090] In some of any of the provided examples of engineered cells, the intracellular signaling region of the second CAR further contains a costimulatory signaling region. In some of any of the provided examples of engineered cells, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples of engineered cells, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof, optionally a human CD28, a human 4-1BB, or a human ICOS. In some of any of the provided examples of engineered cells, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of 4-1BB or a signaling portion thereof. In some of any of the provided examples, at least one of the first chimeric antigen receptor and the second chimeric antigen receptor contains an intracellular signaling region containing an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB.

[0091] In some of any of the provided examples of engineered cells, the costimulatory signaling region of the second CAR contains: an intracellular signaling domain of a human CD28; and/or the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46.

[0092] In some of any of the provided examples of engineered cells, the costimulatory signaling region of the second CAR contains: an intracellular signaling domain of a human 4-1BB; and/or the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19.

[0093] In some of any of the provided examples of engineered cells, the encoded second chimeric antigen receptor contains from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0094] In some of any of the provided examples, the engineered cell is a lymphocyte. In some of any of the provided examples, the engineered cell is an NK cell or a T cell. In some of any of the provided examples, the engineered cell is a T cell and the T cell is a CD4+ or a CD8+ T cell.

[0095] In some of any of the provided examples, the engineered cell was engineered from a primary cell obtained from a subject.

[0096] In some of any of the provided examples, the engineered cell is among a plurality of the engineered cells, where less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen-independent activity or signaling.

[0097] Also provided are compositions containing any of the chimeric receptors provided herein. Also provided are compositions containing any of the engineered cells provided herein. In some of any of the provided examples, the composition contains CD4+ and CD8+ T cells and the ratio of CD4+ to CD8+ T cells is from or from about 1:3 to 3:1, optionally 1:2 to 2:1. In some of any of the provided examples, the composition contains CD4+ and CD8+ T cells and the ratio of CD4+ to CD8+ T cells is about 1:1.

[0098] Also provided are compositions containing: a plurality of first engineered cells containing a first chimeric antigen receptor that is any of the chimeric antigen receptors provided herein or encoded by any of the polynucleotides provided herein; and a plurality of second engineered cells containing a second chimeric antigen receptor. In some of any of the provided examples, among a plurality of the first engineered cells, less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen independent activity or signaling. In some of any of the provided examples, among a plurality of the second engineered cells, less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen independent activity or signaling.

[0099] In some of any of the provided examples, the second chimeric receptor in the plurality of second engineered cells in the composition contains an extracellular antigen binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma. In some of any of the provided examples, the second CAR in the plurality of second engineered cells in the composition contains the extracellular antigen binding domain that binds the second antigen, a spacer, a transmembrane domain, and an intracellular signaling region. In some of any of the provided examples, the second antigen in the plurality of second engineered cells in the composition is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI or FcRH5. In some of any of the provided examples, the second antigen in the plurality of second engineered cells in the composition is BCMA.

[0100] In some of any of the provided examples, the second CAR in the plurality of second engineered cells in the composition contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 190, 192, 194, 196 or 198; (2) a spacer; (3) a transmembrane; and (4) an intracellular signaling region. In some of such examples, the V_H region contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in any of SEQ ID NOs: 190, 192, 194, 196 or 198.

[0101] In some of any of the provided examples, the second CAR in the plurality of second engineered cells in the composition contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a heavy chain complementarity determining region 1 (CDR-H1) containing the amino acid sequence selected from any one of SEQ ID NOs: 199, 202, 206, 209, 212 or 215; (b) a heavy chain complementarity determining region 2 (CDR-H2) containing the amino acid sequence selected from any one of SEQ ID NOs: 200, 203, 207, 210, 213 or 216; and (c) a heavy chain complementarity determining region 3 (CDR-H3) containing the amino acid sequence selected from any one of SEQ ID NOs: 201, 204, 205, 208, 211, 214 or 217; and (ii) a variable light chain (V_L) region containing a light chain complementarity determining region 1 (CDR-L1) containing the amino acid sequence selected from any one of SEQ ID NOs: 218, 221, 224, 227, 230, 233 or 235; (b) a light chain complementarity determining region 2 (CDR-L2) containing the amino acid sequence selected from any one of SEQ ID NOs: 219, 222, 225, 228, 231, 234 or 236; and (c) a light chain complementarity determining region 3 (CDR-L3)

containing the amino acid sequence selected from any one of SEQ ID NOS: 220, 223, 226, 229 or 232; (2) a spacer; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0102] In some of any of the provided examples, the V_H region of the second CAR of the composition contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:212, 213 and 214, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:233, 234 and 229, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0103] In some of any of the provided examples, the V_H region of the second CAR in the composition contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0104] In some of any of the provided examples, the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID

NO:190, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:189 and SEQ ID NO:190; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

[0105] In some of any of the provided examples, the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively; the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192; the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194; the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and V_L region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively.

[0106] In some of any of the provided examples, the extracellular antigen-binding domain of the second CAR in the composition is a single chain antibody fragment. In some of such examples, the fragment is or contains a single chain variable fragment (scFv). In some of any of the provided examples, the V_H region and the V_L region in the second CAR in the composition are joined by a flexible linker. In some of any of the provided examples, the linker in the second CAR in the composition contains the amino acid sequence GGGSGGGSGGGGS (SEQ ID NO:52). In some of any of the provided examples, the linker in the second CAR in the composition contains the amino acid sequence GGGSGGGSGGGSGGGGS (SEQ ID NO:320).

[0107] In some of any of the provided examples, the V_H region is amino-terminal to the V_L region in the second CAR in the composition. In some of any of the provided examples, the V_H region is carboxy-terminal to the V_L region in the second CAR in the composition. In some of any of the provided examples, the antigen-binding domain in the second CAR in the composition contains the

amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples, the antigen-binding domain in the second CAR in the composition contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241.

[0108] In some of any of the provided examples, the V_H region of the second CAR in the composition contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively; and/or the V_H region and VL region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR in the composition contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241. In some of any of the provided examples, the V_H region of the second CAR in the composition contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; and/or the V_H region and VL region of the second CAR in the composition contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR in the composition contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241.

[0109] In some of any of the provided examples, the transmembrane domain of the second CAR in the composition is or contains a transmembrane domain derived from CD4, CD28, or CD8, optionally from a human CD4, a human CD28 or a human CD8. In some of any of the provided examples, the transmembrane domain of the second CAR in the composition is or contains a transmembrane domain derived from a human CD28; and/or the transmembrane domain of the second CAR in the composition is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18. In some of any of the provided examples, the transmembrane domain of the second CAR in the composition is or contains the sequence set forth in SEQ ID NO:18.

[0110] In some of any of the provided examples, the intracellular signaling region of the second CAR in the composition contains an intracellular signaling domain. In some of any of the provided examples, the intracellular signaling domain of the second CAR in the composition is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples, the intracellular signaling domain of the second CAR in the composition is or contains a cytoplasmic signaling domain of a zeta chain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain. In some of any of the provided examples, the intracellular signaling region of the second CAR in the composition contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20.

[0111] In some of any of the provided examples, the intracellular signaling region of the second CAR in the composition further contains a costimulatory signaling region. In some of any of the provided examples, the costimulatory signaling region of the second CAR in the composition contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region of the second CAR in the composition contains an intracellular signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof, optionally a human CD28, a human 4-1BB, or a human ICOS. In some of any of the provided examples, the costimulatory signaling region of the second CAR in the composition contains an intracellular signaling domain of a 4-1BB or a signaling portion thereof, optionally a human 4-1BB. In some of any of the provided examples, at least one of the first chimeric antigen receptor and the second chimeric antigen receptor contains an intracellular signaling region containing an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB. In some of any of the provided examples, the costimulatory signaling region of the second CAR in the composition contains: an intracellular signaling domain of a human CD28; and/or the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46. In some of any of the provided examples, the costimulatory signaling region of the second CAR in the composition contains: an intracellular signaling domain of a human 4-1BB; and/or the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19.

[0112] In some of any of the provided examples, the encoded second chimeric antigen receptor of the composition contains from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0113] In some of any of the provided examples, the plurality of first engineered cells in the composition contains T cells, optionally wherein the T cells include CD4⁺ and CD8⁺ T cells, optionally

wherein the ratio of CD4+ to CD8+ T cells is from or from about 1:3 to 3:1, optionally 1:2 to 2:1. In some of any of the provided examples, the plurality of first engineered cells in the composition contains T cells, optionally wherein the T cells include CD4+ and CD8+ T cells, optionally wherein the ratio of CD4+ to CD8+ T cells is about 1:1.

[0114] In some of any of the provided examples, the plurality of second engineered cells in the composition contains T cells, optionally wherein the T cells include CD4+ and CD8+ T cells, optionally wherein the ratio of CD4+ to CD8+ T cells is from or from about 1:3 to 3:1, optionally 1:2 to 2:1. In some of any of the provided examples, the plurality of second engineered cells in the composition contains T cells, optionally wherein the T cells include CD4+ and CD8+ T cells, optionally wherein the ratio of CD4+ to CD8+ T cells is about 1:1.

[0115] In some of any of the provided examples, the composition contains a ratio of the first plurality of engineered cells and the second plurality of engineered cells that is from or from about 1:3 to 3:1, optionally 1:2 to 2:1, optionally is or is about 1:1. In some of any of the provided examples, the composition contains the first plurality of cells expressing the first chimeric antigen receptor and the second plurality of cells expressing the second chimeric antigen receptor at a ratio that is from about 1:3 to 3:1, optionally about 1:2 to 2:1. In particular examples, the ratio of the first plurality of engineered cells and the second plurality of engineered cells in the composition is or is about 1:1. In some of any of the provided examples, the composition further contains a pharmaceutically acceptable excipient. In some of any of the provided examples, the composition is sterile.

[0116] Also provided herein are uses of any of the compositions provided herein. In some of any of the provided examples, the composition is for use in treating a subject with a disease or condition. In some of any of the provided examples, the disease or condition is a cancer. In some of any of the provided examples, the disease or condition is multiple myeloma, optionally relapsed/refractory multiple myeloma. The provided uses and compositions for use provided herein can be for treating a subject in accord with examples of any of the provided methods.

[0116a] In one aspect, the present disclosure refers to the cells disclosed herein or the composition disclosed herein for use in the treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

[0117] Also provided herein are methods of treatment, containing administering any of the compositions provided herein containing any of the engineered cells provided herein or any of the compositions provided herein containing any of the chimeric antigen receptors provided herein to a subject having a disease or disorder. In some of any of the provided examples, the dose of cells contains between at or about 1.0×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between about 1.25×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between about 1.5×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between about 5.0×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between about 1.5×10^8 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells. In some of any of the provided examples, the dose of cells contains between at or about 2.5×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T

cells, between at or about 5.0×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between at or about 1.5×10^8 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells.

[0118] In some of any examples, the dose of cells contains between at or about 1×10^7 CAR-expressing T cells and at or about 2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains between at or about 2.5×10^7 CAR-expressing T cells and at or about 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and at or about 4.5×10^8 CAR-expressing T cells, or between at or about 1.5×10^8 CAR-expressing T cells and at or about 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 1.0×10^7 , at or about 1.5×10^7 , at or about 2.5×10^7 , at or about 5.0×10^7 , at or about 7.5×10^7 , at or about 1.5×10^8 , at or about 2.25×10^8 , at or about 3.0×10^8 , at or about 4.5×10^8 , at or about 6.0×10^8 , at or about 8.0×10^8 , or at or about 1.2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 CAR-expressing T cells.

[0119] Also provided herein are uses of a first composition containing a plurality of first engineered cells containing a first chimeric antigen receptor that is any chimeric antigen receptor provided herein or encoded by any of the polynucleotides provided herein and a second composition containing a plurality of second engineered cells containing a second chimeric antigen receptor. In some of any of the provided examples, the compositions are used together for use in treating a subject with a disease or condition. In some of any of the provided examples, the disease or condition is a cancer. In some of any of the provided examples, the disease or condition is multiple myeloma, optionally relapsed/refractory multiple myeloma. The provided uses and compositions for use provided herein can be for treating a subject in accord with examples of any of the provided methods.

[0120] Also provided here in are methods of treatment, that include: administering a composition containing a plurality of first engineered cells containing a first chimeric antigen receptor that is any chimeric antigen receptor provided herein or encoded by any of the polynucleotides provided herein to a subject having a disease or disorder; and administering to the subject a composition containing a plurality of second engineered cells containing a second chimeric antigen receptor. In some of any of the provided examples, the dose of the plurality of first engineered cells and the dose of the plurality of second engineered cells independently contain between at or about 1.0×10^7 CAR-expressing T cells and 1.5×10^9 CAR-expressing T cells, between at or about 1.25×10^7 CAR-expressing T cells and 0.6×10^8 CAR-expressing T cells, between at or about 2.5×10^7 CAR-expressing T cells and 2.25×10^8 CAR-expressing T cells, between at or about 7.5×10^7 CAR-expressing T cells and 1.5×10^8 CAR-expressing T cells, between at or about 2.5×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between at or about 1.5

1.0×10^8 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of the plurality of first engineered cells and the dose of the plurality of second engineered cells independently contain between at or about 1×10^7 CAR-expressing T cells and at or about 2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains between at or about 2.5×10^7 CAR-expressing T cells and at or about 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and at or about 4.5×10^8 CAR-expressing T cells, or between at or about 1.5×10^8 CAR-expressing T cells and at or about 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 1.5×10^7 , at or about 2.5×10^7 , at or about 5.0×10^7 , at or about 7.5×10^7 , at or about 1.5×10^8 , at or about 2.25×10^8 , at or about 3.0×10^8 , at or about 4.5×10^8 , at or about 6.0×10^8 , at or about 8.0×10^8 , or at or about 1.2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 CAR-expressing T cells.

[0121] In some of any of the provided examples, the composition containing the plurality of first engineered cells and the composition containing the plurality of second engineered cells are administered simultaneously, sequentially or intermittently. In some of any of the provided examples, the composition containing the plurality of first engineered cells and the composition containing the plurality of second engineered cells are administered sequentially in any order.

[0122] In some of any of the provided examples, among a plurality of the first engineered cells of compositions in the provided methods of treatment or for uses in treating, less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen independent activity or signaling.

[0123] In some of any of the provided examples, among a plurality of the second engineered cells of compositions in the provided methods of treatment or for uses in treating, less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen independent activity or signaling.

[0124] In some of any of the provided examples, the second chimeric receptor in engineered cells of compositions in the methods of treatment or for uses in treating contains an extracellular antigen binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma.

[0125] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains the extracellular antigen binding domain that binds the second antigen, a spacer, a transmembrane domain, and an intracellular signaling region.

[0126] In some of any of the provided examples, the second antigen targeted by the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI or FcRH5. In some of any of the provided examples, the second antigen in the provided methods contains is BCMA.

[0127] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in any of SEQ ID NO: 190, 192, 194, 196 or 198; (2) a spacer; (3) a transmembrane; and (4) an intracellular signaling region. In some of any of the provided examples, the V_H region of the second CAR in the provided methods contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in any of SEQ ID NOs: 189, 191, 193, 195 or 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in any of SEQ ID NOs: 190, 192, 194, 196 or 198.

[0128] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_H region amino acid sequence set forth in SEQ ID NO: 197; and (ii) a variable light chain (V_L) region containing an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the V_L region amino acid sequence set forth in SEQ ID NO: 198; (2) a spacer; (3) a transmembrane; and (4) an intracellular signaling region. In some of any of the provided examples, the V_H region of the second CAR in the provided methods contains a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 197; and the V_L region contains a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 198.

[0129] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains: (1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain contains: (i) a variable heavy chain (V_H) containing a heavy chain complementarity determining region 1 (CDR-H1) containing the amino acid sequence selected from any one of SEQ ID NOs: 199, 202, 206,

209, 212 or 215; (b) a heavy chain complementarity determining region 2 (CDR-H2) containing the amino acid sequence selected from any one of SEQ ID NOs: 200, 203, 207, 210, 213 or 216; and (c) a heavy chain complementarity determining region 3 (CDR-H3) containing the amino acid sequence selected from any one of SEQ ID NOs: 201, 204, 205, 208, 211, 214 or 217; and (ii) a variable light chain (V_L) region containing a light chain complementarity determining region 1 (CDR-L1) containing the amino acid sequence selected from any one of SEQ ID NOs: 218, 221, 224, 227, 230, 233 or 235; (b) a light chain complementarity determining region 2 (CDR-L2) containing the amino acid sequence selected from any one of SEQ ID NOs: 219, 222, 225, 228, 231, 234 or 236; and (c) a light chain complementarity determining region 3 (CDR-L3) containing the amino acid sequence selected from any one of SEQ ID NOs: 220, 223, 226, 229 or 232; (2) a spacer; (3) a transmembrane domain; and (4) an intracellular signaling region.

[0130] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:212, 213 and 214, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:233, 234 and 229, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively.

[0131] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR in the provided methods contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively. In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively.

[0132] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region and VL region contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:189 and SEQ ID NO:190; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:191 and SEQ ID NO:192; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:193 and SEQ ID NO:194; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

[0133] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region and VL region contains the amino acid sequences set forth in SEQ ID

NO:197 and SEQ ID NO:198, respectively, or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

[0134] In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region and VL region contains the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194; the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196; or the V_H region and VL region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively. In some of any of the provided examples, the second CAR in engineered cells of compositions in the provided methods or for uses in treating contains an extracellular antigen-binding domain in which the V_H region and VL region contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively.

[0135] In some of any of the provided examples, the extracellular antigen-binding domain of the second CAR in engineered cells in compositions in the provided methods or for uses in treating is a single chain antibody fragment. In some of any of the provided examples, the fragment is or contains a single chain variable fragment (scFv).

[0136] In some of any of the provided examples of the provided methods or for uses in treating, the V_H region and the V_L region of the extracellular antigen-binding domain of the second CAR in engineered cells in compositions are joined by a flexible linker. In some of any of the provided examples, the linker of the second CAR in engineered cells in compositions contains the amino acid sequence GGGGSGGGSGGGGS (SEQ ID NO:52). In some of any of the provided examples, the linker of the second CAR in engineered cells in compositions contains the amino acid sequence GGGGSGGGSGGGSGGGGS (SEQ ID NO:320).

[0137] In some of any of the provided examples of the provided methods or for uses in treating, the V_H region is amino-terminal to the V_L region in the extracellular antigen-binding domain of the second CAR. In some of any of the provided examples of the provided methods, the V_H region is carboxy-terminal to the V_L region in the second CAR.

[0138] In some of any of the provided examples of the provided methods or for uses in treating, the extracellular antigen-binding domain of the second CAR contains the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples of the provided methods, the antigen-binding domain of the second CAR contains the

amino acid sequence selected from any one of SEQ ID NOs: 227, 238, 239, 240 or 241. In some of any of the provided examples of the provided methods or for uses in treating, the extracellular antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:241. In some of any of the provided examples of the provided methods, the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241.

[0139] In some of any of the provided examples of the provided methods or for uses in treating, the extracellular antigen-binding domain of the second CAR has a V_H region and a V_L region in which the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; or the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:215, 216 and 217, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:235, 236 and 232, respectively; and/or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241. In some of any of the provided examples of the provided methods or for uses in treating, the extracellular antigen-binding domain of the second CAR has a V_H region and a V_L region in which the V_H region of the second CAR contains a CDR-H1, CDR-H2, and CDR-H3 containing the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR contains a CDR-L1, CDR-L2, and CDR-L3 containing the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively; and/or the V_H region and V_L region of the second CAR contains the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively; and/or the antigen-binding domain of the second CAR contains the amino acid sequence set forth in SEQ ID NO: 241 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO:241.

[0140] In some of any of the provided examples of the provided methods or for uses in treating, the transmembrane domain of the second CAR is or contains a transmembrane domain derived from CD4, CD28, or CD8, optionally from a human CD4, a human CD28 or a human CD8. In some of any of the provided examples of the provided methods, the transmembrane domain of the second CAR is or contains a transmembrane domain derived from a human CD28; and/or the transmembrane domain is or contains the sequence set forth in SEQ ID NO:18 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:18. In some of

any of the provided examples of the provided methods, the transmembrane domain of the second CAR is or contains the sequence set forth in SEQ ID NO:18.

[0141] In some of any of the provided examples of the provided methods or for uses in treating, the intracellular signaling region of the second CAR contains an intracellular signaling domain. In some of any of the provided examples of the provided methods, the intracellular signaling domain of the second CAR is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples of the provided methods, the intracellular signaling domain of the second CAR is or contains a cytoplasmic signaling domain of a zeta chain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain. In some of any of the provided examples of the provided methods, the intracellular signaling region of the second CAR contains the sequence set forth in SEQ ID NO:20 or a sequence of amino acids that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:20.

[0142] In some of any of the provided examples of the provided methods or for uses in treating, the intracellular signaling region of the second CAR further contains a costimulatory signaling region. In some of any of the provided examples of the provided methods, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples of the provided methods, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of a CD28, a 4-1BB or an ICOS or a signaling portion thereof, optionally a human CD28, a human 4-1BB, or a human ICOS. In some of any of the provided examples of the provided methods, the costimulatory signaling region of the second CAR contains an intracellular signaling domain of a 4-1BB or a signaling portion thereof, optionally a human 4-1BB. In some of any of the provided examples, at least one of the first chimeric antigen receptor and the second chimeric antigen receptor contains an intracellular signaling region containing an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB.

[0143] In some of any of the provided examples of the provided methods or for uses in treating, the costimulatory signaling region of the second CAR contains: an intracellular signaling domain of a human CD28; and/or the sequence set forth in SEQ ID NO:46 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 46.

[0144] In some of any of the provided examples of the provided methods or for uses in treating, the costimulatory signaling region of the second CAR contains: an intracellular signaling domain of a human 4-1BB; and/or the sequence set forth in SEQ ID NO:19 or a sequence of amino acids that exhibits at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequence set forth in SEQ ID NO: 19.

[0145] In some of any of the provided examples of the provided methods or for uses in treating, the encoded second chimeric antigen receptor contains from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0146] Among polynucleotides provided herein are polynucleotides containing (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) containing a first antigen binding domain; and (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) containing a second antigen binding domain; wherein the first CAR and second CAR each contain the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region; wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR contains the identical amino acid sequence; and wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

[0146a] In one aspect, the present disclosure refers to a polynucleotide comprising: (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) comprising a first antigen binding domain; and (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) comprising a second antigen binding domain; wherein the first CAR and second CAR each comprise the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region; wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR comprises the identical amino acid sequence; and wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

[0147] Also provided here are polynucleotides containing (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) containing a first antigen binding domain capable of binding to one of GPRC5D or BCMA and (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) containing a second antigen binding domain capable of binding to the other of GPRC5D or BCMA; wherein the first CAR and second CAR each contain the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region; wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR contains the identical amino acid sequence; and wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

[0147a] In one aspect, the present disclosure refers to a polynucleotide comprising: (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) comprising a first antigen binding domain capable of binding to one of GPRC5D or BCMA; and (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) comprising a second antigen binding domain capable of binding to the other of GPRC5D or BCMA; wherein the first CAR and second CAR each comprise the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region; wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR comprises the identical amino acid sequence; and wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

[0148] In some of any of the provided examples, the first and second antigen binding domains bind to the same antigen. In some of any of the provided examples, the first and second antigen binding domains bind different epitopes of the same antigen. In some of any of the provided examples, the first and second antigen binding domains bind to different antigens. In some of any of the provided examples, the first antigen binding domain binds a first antigen expressed by or associated with cells of a disease or condition and the second antigen binding domains binds a second antigen expressed by or associated with cells of the same disease or condition.

[0149] In some of any of the provided examples, the disease or condition is a cancer. In some of any of the provided examples, the disease or condition is a GPRC5D-expressing cancer. In some of any of the provided examples, the disease or condition is a BCMA-expressing cancer. In some of any of the provided examples, the disease or condition is a BCMA-expressing and GPRC5D-expressing

cancer. In some of any of the provided examples, the cancer is a plasma cell malignancy and the plasma cell malignancy is multiple myeloma (MM) or plasmacytoma. In some of any of the provided examples, the cancer is multiple myeloma. In some of any of the provided examples, the cancer is relapsed/refractory multiple myeloma.

[0150] In some of any of the provided examples, the first and second antigen binding domain independently bind to an antigen selected from the group consisting of GPRC5D, BCMA, CD38, CD138, CS-1, BAFF-R, TACI and FcRH5. In some of any of the provided examples, the first antigen binding domain binds to B cell maturation antigen (BCMA). In some of any of the provided examples, the first antigen binding domain bind to G protein-coupled receptor class C group 5 member D (GPRC5D). In some of any of the provided examples, the second antigen binding domain binds to BCMA. In some of any of the provided examples, the second antigen binding domain binds to GPRC5D.

[0151] In some of any of the provided examples, (a) is or contains the first antigen binding domain or the second antigen binding domain, (b) is or contains a spacer, (c) is or contains a transmembrane domain, and (d) is or contains an intracellular signaling region containing an intracellular signaling domain and a costimulatory signaling region. In some of any of the provided examples, the one or more of (b) through (d) is one of (b) through (d). In some of any of the provided examples, the one or more of (b) through (d) is two of (b) through (d). In some of any of the provided examples, the one or more of (b) through (d) is each of (b) through (d).

[0152] In some of any of the provided examples, (a) is or contains the first antigen binding domain or the second antigen binding domain, (b) is or contains a spacer, (c) is or contains a transmembrane domain, and (d) is or contains an intracellular signaling region containing an intracellular signaling domain and a costimulatory signaling region. In some of any of the provided examples, the nucleotide sequence(s) encoding the one or more of (a) through (d) in the first CAR and the nucleotide sequence(s) encoding the same one or more of (a) through (d) in the second CAR comprises no more than about 20 consecutive base pairs of sequence homology; and/or the first nucleic acid sequence encoding the first CAR and the second nucleic acid sequence encoding the second CAR contain no more than about 20 consecutive base pairs of sequence homology. In some of any of the provided examples, the nucleotide sequence(s) encoding the one or more of (a) through (d) in the first CAR and the nucleotide sequence(s) encoding the same one or more of (a) through (d) in the second CAR contains no more than between about 5 and about 15 consecutive base pairs of sequence homology; and/or the first nucleic acid sequence encoding the first CAR and the second nucleic acid sequence encoding the second CAR contain no more than about 5 and about 15 consecutive base pairs of sequence homology. In some of any of the provided examples, the nucleotide sequence(s) encoding the one or more of (a) through (d) in the first CAR and the nucleotide sequence(s) encoding the psame one or more of (a) through (d) in the second CAR contain no more than about 10 consecutive base pairs of homology;

and/or the first nucleic acid sequence encoding the first CAR and the second nucleic acid sequence encoding the second CAR contain no more than about 10 consecutive base pairs of sequence homology.

[0153] In some of any of the provided examples, the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by a nucleotide sequence encoding a multicistronic element, optionally wherein the multicistronic element is a bicistronic element. In some of any of the provided examples, the multicistronic element is an IRES or is a ribosome skip sequence or self-cleaving peptide. In some of any of the provided examples, the multicistronic element is a ribosome skip sequence or self-cleaving peptide and the ribosome skip sequence or self-cleaving peptide is a T2A, a P2A, an E2A, or an F2A element. In some of any of the provided examples, the nucleotide sequence encoding the one or more multicistronic element is codon diverged. In some of any of the provided examples, the nucleotide sequence encoding the T2A is codon diverged. In some of any of the provided examples, nucleotide sequence encoding the T2A is or contains the sequence set forth in SEQ ID NO:319.

[0154] In some of any of the provided examples, the first nucleic acid sequence encoding the first CAR is codon optimized for expression in a human cell. In some of any of the provided examples, the second nucleic acid sequence encoding the second CAR is codon optimized for expression in a human cell. In some of any of the provided examples, the polynucleotide is codon optimized for expression in a human cell. In some of any of the provided examples, following transcription of the polynucleotide in a human cell, optionally a human T cell, the transcribed mRNA, optionally messenger RNA, from the polynucleotide, exhibits at least about 70%, 75%, 80%, 85%, 90%, or 95% RNA homogeneity. In some of any of the provided examples, following transcription of the first nucleic acid encoding the first CAR of the polynucleotide in a human cell, optionally a human T cell, the transcribed mRNA, optionally messenger RNA, from the first nucleic acid exhibits at least about 70%, 75%, 80%, 85%, 90%, or 95% RNA homogeneity. In some of any of the provided examples, following transcription of the second nucleic acid encoding the second CAR of the polynucleotide in a human cell, optionally a human T cell, the transcribed mRNA, optionally messenger RNA, from the second nucleic acid exhibits at least about 70%, 75%, 80%, 85%, 90%, or 95% RNA homogeneity.

[0155] In some of any of the provided examples, any potential splice donor and/or splice acceptor site present in the first nucleic acid encoding the first CAR exhibits a splice prediction score of about or at least about less than 0.70, 0.65, 0.60, 0.55, 0.50, 0.45, 0.40, 0.35, 0.30, 0.25, 0.20 and/or is predicted to be involved in a splice event with a probability of less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, or less than 20%. In some of any of the provided examples, any potential splice donor or acceptor site in the second nucleic acid encoding the second CAR exhibits a splice prediction score of about or at least about less than 0.70, 0.65, 0.60, 0.55, 0.50, 0.45, 0.40, 0.35, 0.30, 0.25, 0.20 and/or is predicted to be involved in a splice event with a probability of less than 70%, less than 65%, less than

60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, or less than 20%. In some of any of the provided examples, any potential splice donor or acceptor sites in the polynucleotide exhibits a splice prediction score of about or at least about less than 0.70, 0.65, 0.60, 0.55, 0.50, 0.45, 0.40, 0.35, 0.30, 0.25, 0.20 and/or is predicted to be involved in a splice event with a probability of less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, or less than 20%.

[0156] In some of any of the provided examples, the first and/or second antigen binding domain of (a) is a single chain antibody fragment. In some of any of the provided examples, the first and/or second antigen binding domain of (a) is or contains a single chain variable fragment (scFv). In some of any of the provided examples, the first and/or second antigen binding domain of (a) contains a variable heavy chain (VH) region and a variable light chain (VL) region.

[0157] In some of any of the provided examples, the first antigen binding domain or the second antigen binding domain contains a VH region that contains a CDR-H1 as set forth in SEQ ID NO:209, a CDR-H2 as set forth in SEQ ID NO:210, and a CDR-H3 as set forth in SEQ ID NO:211 and a VL region that contains a CDR-L1 as set forth in SEQ ID NO:230, a CDR-L2 as set forth in SEQ ID NO:231, and a CDR-L3 as set forth in SEQ ID NO:232. In some of any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contain a VH region and a VL region that contain the amino acid sequences set forth in SEQ ID NOS:197 and 198, respectively. In any of the provided examples, the first antigen binding domain or the second antigen binding domain contains the amino acid sequence set forth in SEQ ID NO:241 or a sequence of amino acids that exhibits at least at or about 90%, at least at or about 91%, at least at or about 92%, at least at or about 93%, at least at or about 94%, at least at or about 95%, at least at or about 96%, at least at or about 97%, at least at or about 98%, at least at or about 99% sequence identity to SEQ ID NO:241.

[0158] In any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contains a VH region contains a CDR-H1 as set forth in SEQ ID NO:125, a CDR-H2 as set forth in SEQ ID NO:126, and a CDR-H3 as set forth in SEQ ID NO:127 and a VL region that contains a CDR-L1 as set forth in SEQ ID NO:130, a CDR-L2 as set forth in SEQ ID NO:131, and a CDR-L3 as set forth in SEQ ID NO:132. In any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contain a VH region and VL region that contain the amino acid sequences set forth in SEQ ID NOS:27 and 28, respectively. In any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contain the amino acid sequence set forth in SEQ ID NO:8 or a sequence of amino acids that exhibits at least at or about 90%, at least at or about 91%, at least at or about 92%, at least at or about 93%, at least at or about 94%, at least at or about 95%, at least at or about 96%, at least at or about 97%, at least at or about 98%, at least at or about 99% sequence identity to SEQ ID NO:8.

[0159] In any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contains a VH region that contains a CDR-H1 as set forth in SEQ ID NO:209, a CDR-H2 as set forth in SEQ ID NO:210, and a CDR-H3 as set forth in SEQ ID NO:211 and a VL region that contains a CDR-L1 as set forth in SEQ ID NO:230, a CDR-L2 as set forth in SEQ ID NO:231, and a CDR-L3 as set forth in SEQ ID NO:232; and the other of the first antigen binding domain or the second antigen binding domain contains a CDR-H1 as set forth in SEQ ID NO:125, a CDR-H2 as set forth in SEQ ID NO:126, and a CDR-H3 as set forth in SEQ ID NO:127 and a VL region that contains a CDR-L1 as set forth in SEQ ID NO:130, a CDR-L2 as set forth in SEQ ID NO:131, and a CDR-L3 as set forth in SEQ ID NO:132. In some of any of the provided examples, one of the first antigen binding domain or the second antigen binding domain contain a VH region and a VL region that contain the amino acid sequences set forth in SEQ ID NOS:197 and 198, respectively; and the other of the first antigen binding domain or the second antigen binding domain contains a VH region and VL region that contain the amino acid sequences set forth in SEQ ID NOS:27 and 28, respectively. In some of any of the provided examples, one of the first or second antigen binding domain contains the amino acid sequence set forth in SEQ ID NO:241 and the other of the first or second antigen binding domain contains the amino acid sequence set forth in SEQ ID NO:8.

[0160] In some of any of the provided examples, one of the first or second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310. In some of any of the provided examples, one of the first or second antigen binding domain is encoded by a nucleotide sequence set forth in SEQ ID NO:264 or SEQ ID NO: 311. In some of any of the provided examples, the first or second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310, and the other of the first or second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311

[0161] In some of any of the provided examples, (b) is or contains a spacer. In some of any of the provided examples, (b) contains a portion of an immunoglobulin. In some of any of the provided examples, (b) contains a sequence of a hinge region, a CH2 and CH3 region. In some of any of the provided examples, the hinge region contains all or a portion of an IgG4 hinge region and/or an IgG2 hinge region, wherein the IgG4 hinge region is optionally a human IgG4 hinge region and the IgG2 hinge region is optionally a human IgG2 hinge region; the CH2 region contains all or a portion of an IgG4 CH2 and/or an IgG2 CH2, wherein the IgG4 CH2 is optionally a human IgG4 CH2 and the IgG2 CH2 is optionally a human IgG2 CH2; and/or the CH3 region contains all or a portion of an IgG4 CH3 and/or an IgG2 CH3, wherein the IgG4 CH3 is optionally a human IgG4 CH3 and the IgG2 CH3 is optionally a human IgG2 CH3. In some of any of the provided examples, the hinge region, CH2 and CH3 contains all or a portion of a hinge, all or a portion of a CH2 and all or a portion of a CH3 from human IgG4. In some of any of the provided examples, one or more of the hinge region, the CH2 and the CH3 is chimeric and contains a hinge, CH2 and CH3 from human IgG4 and human IgG2. In some of any of the

provided examples, (b) contains an IgG4/2 chimeric hinge region or a modified IgG4 hinge region containing at least one amino acid replacement compared to a human IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region.

[0162] In some of any of the provided examples, (b) is or contains a spacer. In some of any of the provided examples (b) has a length from or from about 125 to 300 amino acids in length, 125 to 250 amino acids in length, 125 to 230 amino acids in length, 125 to 200 amino acids in length, 125 to 180 amino acids in length, 125 to 150 amino acids in length, 150 to 300 amino acids in length, 150 to 250 amino acids in length, 150 to 230 amino acids in length, 150 to 200 amino acids in length, 150 to 180 amino acids in length, 180 to 300 amino acids in length, 180 to 250 amino acids in length, 180 to 230 amino acids in length, 180 to 200 amino acids in length, 200 to 300 amino acids in length, 200 to 250 amino acids in length, 200 to 230 amino acids in length, 230 to 300 amino acids in length, 230 to 250 amino acids in length or 250 to 300 amino acids in length, optionally wherein the spacer is at or about 224, at or about 225, at or about 226, at or about 227, at or about 228 or at or about 229 amino acids in length. In some of any of the provided examples, (b) is or contains the amino acid sequence set forth in SEQ ID NO:17. In some of any of the provided examples, (b) in one of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:48 and (b) in the other of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:305.

[0163] In some of any of the provided examples, (c) is or contains a transmembrane domain. In some of any of the provided examples, (c) is or contains a transmembrane domain of CD4, CD28, or CD8, optionally a transmembrane domain from human CD4, human CD28 or human CD8. In some of any of the provided examples, (c) is or contains a human CD28 transmembrane domain. In some of any of the provided examples, (c) is or contains the amino acid sequence set forth in SEQ ID NO:18. In some of any of the provided examples, (c) in one of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NOS:56 and (c) in the other of the first CAR or second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO: 307.

[0164] In some of any of the provided examples, (d) is or contains an intracellular signaling region containing an intracellular signaling domain and a costimulatory signaling region. In some of any of the provided examples, the intracellular signaling domain of (d) is capable of inducing a primary activation signal in a T cell, is a T cell receptor (TCR) component and/or contains an immunoreceptor tyrosine-based activation motif (ITAM). In some of any of the provided examples, the intracellular signaling domain of (d) is or contains a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain.). In some of any of the provided examples, the intracellular signaling domain of (d) is or contains the amino acid sequence set forth in SEQ ID NO:20. In some of any of the provided examples, the intracellular signaling domain of (d) in one of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:58 and the intracellular signaling domain of (d) in the other of the first CAR or

the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:309. In some of any of the provided examples, (d) is or contains an intracellular signaling region containing an intracellular signaling domain and a costimulatory signaling region. In some of any of the provided examples, the costimulatory signaling region of (d) contains an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some of any of the provided examples, the costimulatory signaling region of (d) contains an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof, optionally of human CD28, human 4-1BB, or human ICOS. In some of any of the provided examples, the costimulatory signaling region of (d) contains an intracellular signaling domain of 4-1BB. In some of any of the provided examples, the costimulatory signaling region of (d) is or contains the amino acid sequence set forth in SEQ ID NO:19. In some of any of the provided examples, the costimulatory signaling region of (d) in one of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NOS:60 and the costimulatory signaling region of (d) in the other of the first CAR or the second CAR is encoded by the nucleotide sequence set forth in SEQ ID NO:308.

[0165] In some of any of the provided examples, (a) is or contains the first antigen binding domain or the second antigen binding domain, (b) is or contains a spacer, (c) is or contains a transmembrane domain, and (d) is or contains an intracellular signaling region containing an intracellular signaling domain and a costimulatory signaling region. In some of any of the provided examples, one of the first CAR or the second CAR contains (a) a first antigen binding domain that binds to GPRC5D, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311, (b) a spacer encoded by the nucleotide set forth in SEQ ID NO:305, (c) a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307, and (d) an intracellular signaling region containing an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308; the other of the first CAR or the second CAR contains (a) an antigen binding domain that binds to BCMA, optionally wherein the antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310, (b) a spacer encoded by the nucleotide set forth in SEQ ID NO:48, (c) a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56, and (d) an intracellular signaling region containing an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60.

[0166] In some of any of the provided examples, the first nucleic acid sequence encoding the first CAR is located toward the 5' end of the polynucleotide, relative to the second nucleic acid sequence encoding the first CAR. In some of any of the provided examples, the first CAR contains an antigen binding domain that binds to GPRC5D and the second CAR contains an antigen binding domain that binds to BCMA. In some of any of the provided examples, the first CAR contains an antigen binding

domain that binds to BCMA and the second CAR contains an antigen binding domain that binds to GPRC5D.

[0167] Also provided herein are polynucleotides containing (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element; wherein the first CAR contains a first antigen binding domain that binds to GPRC5D, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311; a spacer encoded by the nucleotide set forth in SEQ ID NO:305; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307; and an intracellular signaling region containing an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308; wherein the second CAR contains a second antigen binding domain that binds to BCMA optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310; a spacer encoded by the nucleotide set forth in SEQ ID NO:48; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56; and an intracellular signaling region containing an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60; and wherein the first nucleic acid sequence encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

[0167a] In one aspect, the present disclosure refers to a polynucleotide comprising (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element; wherein the first CAR comprises a first antigen binding domain that binds to GPRC5D, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311; a spacer encoded by the nucleotide set forth in SEQ ID NO:305; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307; and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308; wherein the second CAR comprises a second antigen binding domain that binds to BCMA optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310; a spacer encoded by the nucleotide set forth in SEQ ID NO:74; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56; and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60; and wherein the first nucleic acid sequence encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

[0168] Also provided herein are polynucleotides containing (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR), and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element; wherein the first CAR contains a first antigen binding domain that binds to BCMA, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310, a spacer encoded by the nucleotide set forth in SEQ ID NO:48, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56, and an intracellular signaling region containing an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60 wherein the second CAR contains a second antigen binding domain that binds to GPRC5D, optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311, a spacer encoded by the nucleotide set forth in SEQ ID NO:305, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307, and an intracellular signaling region containing an intracellular signaling domain encoded by

the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308; wherein the first nucleic acid encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

[0168a] In one aspect, the present disclosure refers to a polynucleotide comprising (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR), and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element; wherein the first CAR comprises a first antigen binding domain that binds to BCMA, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310, a spacer encoded by the nucleotide set forth in SEQ ID NO:74, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56, and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60 wherein the second CAR comprises a second antigen binding domain that binds to GPRC5D, optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311, a spacer encoded by the nucleotide set forth in SEQ ID NO:305, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307, and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308; wherein the first nucleic acid encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

[0169] In some of any of the provided examples, the multicistronic element contains the amino acid sequence set forth in SEQ ID NO:37. In some of any of the provided examples, the multicistronic element is encoded by a nucleotide sequence set forth in SEQ ID NOS:44 or SEQ ID NO: 45. In some of any of the provided examples, the multicistronic element is encoded by a nucleotide sequence set forth in SEQ ID NO:44. In some of any of the provided examples, the multicistronic element is encoded by a nucleotide sequence set forth in SEQ ID NO:45. In some of any of the provided examples, the multicistronic element is encoded by a nucleotide sequence set forth in SEQ ID NO:319.

[0170] In some of any of the provided examples, the polynucleotide contains the nucleotide sequence set forth in SEQ ID NO:299. In some of any of the provided examples, the polynucleotide encodes sequence set forth in SEQ ID NO:298.

[0171] In some of any of the provided examples, the polynucleotide contains the nucleotide sequence set forth in SEQ ID NO:302. In some of any of the provided examples, the polynucleotide encodes the sequence set forth in SEQ ID NO:301.

[0172] In some of any of the provided examples, the polynucleotide contains the nucleotide sequence set forth in SEQ ID NO:315. In some of any of the provided examples, the polynucleotide contains the nucleotide sequence set forth in SEQ ID NO:316.

[0173] Also provided herein are polynucleotides, wherein a polynucleotide encodes a GPRC5D-binding domain, a BCMA-binding domain, and an intracellular signaling region containing an intracellular signaling domain of a 4-1BB. In some of any of the provided examples, the polynucleotide contains the nucleotide sequence set forth in SEQ ID NO:317.

[0174] Also provided are vectors containing any of the provided polynucleotides. In some of any of the provided examples, the vector is a viral vector. In some of any of the provided examples, the viral vector is a lentiviral vector or a retroviral vector.

[0174a] In one aspect, the present disclosure refers to a vector comprising the polynucleotide disclosed herein.

[0175] Also provided are engineered cells containing any of the chimeric antigen receptors provided herein. In some of any of the provided examples, the engineered cell contains a chimeric antigen receptor provided herein and further contains a polynucleotide containing a sequence of nucleotides encoding a second chimeric antigen receptor.

[0175a] In one aspect, the present disclosure refers to a cell comprising the chimeric antigen receptor disclosed herein.

[0176] Also provided are engineered cells containing any of the polynucleotides provided herein.

[0176a] In one aspect, the present disclosure refers to a cell comprising the polynucleotide disclosed herein.

[0176b] In another aspect, the present disclosure refers to a cell comprising the polynucleotide disclosed herein, which is the first polynucleotide, wherein the cell further comprises a second polynucleotide comprising a nucleotide sequence encoding a second chimeric antigen receptor (CAR).

[0177] In some of any of the provided examples, the engineered cell is a lymphocyte. In some of any of the provided examples, the engineered cell is an NK cell or a T cell. In some of any of the provided examples, the engineered cell is a T cell and the T cell is a CD4⁺ or a CD8⁺ T cell.

[0178] In some of any of the provided examples, the engineered cell was engineered from a primary cell obtained from a subject.

[0179] In some of any of the provided examples, the engineered cell is among a plurality of the engineered cells, where less than or less than about 10%, 9%, 8%, 7%, 5%, 4%, 3%, 2% or 1% of the cells in the plurality contain a chimeric antigen receptor that exhibits tonic signaling and/or antigen-independent activity or signaling.

[0180] Also provided are compositions containing any of the chimeric receptors provided herein. In some of any of the provided examples, the composition contains CD4⁺ and CD8⁺ T cells and the ratio of CD4⁺ to CD8⁺ T cells is from or from about 1:3 to 3:1. In some examples, the ratio of CD4⁺ and CD8⁺ T cells in the composition is 1:2 to 2:1. In some examples, the ratio of CD4⁺ and CD8⁺ T cells in the composition is 1:1. In some of any of the provided examples, the composition further contains a pharmaceutically acceptable excipient. In some of any of the provided examples, the composition is sterile.

[0180a] In one aspect, the present disclosure refers to a composition comprising the chimeric antigen receptor disclosed herein.

[0180b] In another aspect, the present disclosure refers to a composition comprising the cell disclosed herein or a plurality of the cells disclosed herein.

[0180c] In yet another aspect, the present disclosure refers to a composition comprising: a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor disclosed herein or encoded by the polynucleotide disclosed herein; and a plurality of second cells comprising a second chimeric antigen receptor.

[0180d] In one aspect, the present disclosure refers to the use of a composition comprising the cells disclosed herein or the composition disclosed herein for the manufacture of a medicament for treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

[0181] Also provided herein are methods of treatment, including administering any of the compositions provided herein containing any of the engineered cells provided herein or any of the compositions provided herein containing any of the chimeric antigen receptors provided herein to a subject having a disease or disorder. In some of any of the provided examples, the dose of cells contains between at or about 2.5×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between at or about 1.5×10^8 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains between at or about 1×10^7 CAR-expressing T cells and at or about 2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains between at or about 2.5×10^7 CAR-expressing T cells and at or about 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and at or about 4.5×10^8 CAR-expressing T cells, or between at or about 1.5×10^8 CAR-expressing T cells and at or about 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 1.5×10^7 , at or about 2.5×10^7 , at or about 5.0×10^7 , at or about 7.5×10^7 , at or about 1.5×10^8 , at or about 2.25×10^8 , at or about 3.0×10^8 , at or about 4.5×10^8 , at or about 6.0×10^8 , at or about 8.0×10^8 or at or about 1.2×10^9 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of cells contains at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of the cells contains at or about 5.0×10^7 CAR-expressing T cells.

[0182] Also provided herein are methods of treatment, including administering any of the compositions provided herein containing any of the engineered cells provided herein or any of the compositions provided herein containing any of the chimeric antigen receptors provided herein to a

subject having a disease or disorder. In some of any of the provided examples, the dose of cells contains contain between at or about 1.0×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between at or about 1.5×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between at or about 2.0×10^7 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells.

[0183] Also provided here in are methods of treatment, that include: administering a composition containing a plurality of engineered cells containing a first chimeric antigen receptor and a second chimeric antigen receptor, wherein each is any chimeric antigen receptor provided herein or encoded by any of the polynucleotides provided herein, to a subject having a disease or disorder; and administering to the subject a composition containing a plurality of second engineered cells containing a second chimeric antigen receptor. In some of any of the provided examples, the dose of the plurality of first engineered cells and the dose of the plurality of second engineered cells independently contain between at or about 1.0×10^7 CAR-expressing T cells and 1.5×10^9 CAR-expressing T cells, between at or about 1.25×10^7 CAR-expressing T cells and 0.6×10^8 CAR-expressing T cells, between at or about 2.5×10^7 CAR-expressing T cells and 2.25×10^8 CAR-expressing T cells, between at or about 7.5×10^7 CAR-expressing T cells and 1.5×10^8 CAR-expressing T cells, between at or about 2.5×10^7 CAR-expressing T cells and 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and 4.5×10^8 CAR-expressing T cells, between at or about 1.5×10^8 CAR-expressing T cells and 3.0×10^8 CAR-expressing T cells.

[0183a] In one aspect, the present disclosure refers to a composition comprising a first dose of a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor disclosed herein or encoded by the polynucleotide disclosed herein and a composition comprising a second dose of a plurality of second cells comprising a second chimeric antigen receptor for use in the treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

[0183b] In another aspect, the present disclosure refers to the use of a composition comprising a first dose of a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor disclosed herein or encoded by the polynucleotide disclosed herein and a composition comprising a second dose of a plurality of second cells comprising a second chimeric antigen receptor for the manufacture of a medicament for treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

[0183c] In yet another aspect, the present disclosure refers to a combination comprising: a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor disclosed herein and/or encoded by the polynucleotide disclosed herein; and a plurality of second cells comprising a second chimeric antigen receptor.

[0183d] In one aspect, the present disclosure refers to the combination disclosed herein for use in the treatment of a disease or disorder, optionally wherein the disease or disorder is a cancer.

[0184] In some of any of the provided examples of the provided methods, the disease or disorder is associated with expression of G protein-coupled receptor class C group 5 member D (GPRC5D).

[0185] In some of any of the provided examples of the provided methods, the disease or disorder is further associated with expression of B cell maturation antigen (BCMA).

[0186] In some of any of the provided examples of the provided methods, the disease or disorder is a B cell-related disorder. In some of any of the provided examples of the provided methods, the disease or disorder associated with BCMA is an autoimmune disease or disorder. In some of any of the provided examples of the provided methods, the autoimmune disease or disorder is systemic lupus erythematosus (SLE), lupus nephritis, inflammatory bowel disease, rheumatoid arthritis, ANCA associated vasculitis, idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenia purpura (TTP), autoimmune thrombocytopenia, Chagas' disease, Grave's disease, Wegener's granulomatosis, poly-arteritis nodosa, Sjogren's syndrome, pemphigus vulgaris, scleroderma, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, vasculitis, diabetes mellitus, Reynaud's syndrome, anti-phospholipid syndrome, Goodpasture's disease, Kawasaki disease, autoimmune hemolytic anemia, myasthenia gravis, or progressive glomerulonephritis.

[0187] In some of any of the provided examples of the provided methods, the disease or disorder is a cancer. In some of any of the provided examples of the provided methods, the cancer is

a GPRC5D-expressing cancer. In some of any of the provided examples of the provided methods, the cancer is a plasma cell malignancy and the plasma cell malignancy is multiple myeloma (MM) or plasmacytoma. In some of any of the provided examples of the provided methods, the cancer is multiple myeloma (MM). In some of any of the provided examples of the provided methods, the cancer is a relapsed/refractory multiple myeloma.

[0188] In some of any of the provided examples of the provided methods, the subject is refractory to or has relapsed following administration of a BCMA-targeted therapy, optionally following administration of T cells comprising a CAR that specifically binds BCMA. In some of any of the provided examples of the provided methods, a subject is selected for treatment that is refractory to or has relapsed following administration of a BCMA-targeted therapy, optionally following administration T cells comprising a CAR that specifically binds BCMA. In some of any of the provided examples of the provided methods, prior to the administration of the dose of cells, the subject has previously received administration of a BCMA-targeted therapy for treating the disease or disorder. In some of any of the provided examples of the provided methods, prior to the administration of the first dose of cells and the second dose of cells, the subject has previously received administration of a BCMA-targeted therapy for treating the disease or disorder.

[0189] In some of any of the provided examples of the provided methods, the BCMA-targeted therapy comprises a composition comprising T cells comprising a CAR that specifically binds BCMA. In some of any of the provided examples of the provided methods, the subject is refractory to or has relapsed following administration of the BCMA-targeted therapy, optionally following administration of T cells comprising a CAR that specifically binds BCMA. In some of any of the provided examples of the provided methods, the subject comprises multiple myeloma cells exhibiting BCMA antigen or epitope loss, BCMA downregulation and/or BCMA-negative tumor cells following a previous administration.

Brief Description of the Drawings

[0190] **FIG. 1A** shows Cancer Cell Line Encyclopedia CD138 mRNA expression data (log₂scale). Type of cancer, from left to right: upper aerodigestive (32); esophagus (25); prostate (7); multiple myeloma (30); bile duct (8); lung (131); pancreas (44); kidney (34); breast (58); colorectal (61); stomach (38); meningioma (3); liver (28); glioma (62); osteosarcoma (10); thyroid (12); endometrium (27); soft tissue (21); mesothelioma (11); ovary (51); chondrosarcoma (4); small cell lung (53); melanoma (61); neuroblastoma (17); medulloblastoma (4); Ewing sarcoma (12); Hodgkin lymphoma (12); DLBCL (18); other lymphoma (28); B-cell (15); CML (15); Burkitt lymphoma (11); T-cell (16); AML (34); other leukemia (1).

Claims

1. A chimeric antigen receptor comprising:

(1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising a heavy chain complementarity determining region 1 (CDR-H1), heavy chain complementarity determining region 2 (CDR-H2) and heavy chain complementarity determining region 3 (CDR-H3) contained within the V_H region amino acid sequence selected from SEQ ID NOs: 21, 23, 25, 27, 29, 31, and 33; and

(ii) a variable light chain (V_L) region comprising a light chain complementarity determining region 1 (CDR-L1), light chain complementarity determining region 2 (CDR-L2) and light chain complementarity determining region 3 (CDR-L3) contained within the V_L region amino acid sequence selected from SEQ ID NOs: 22, 24, 26, 28, 30, 32, 34, 63, 64, 65, 66, 67, 68, and 69;

(2) a spacer of at least 125 amino acids in length;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

2. A chimeric antigen receptor comprising:

(1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:21, 23, 25, 27, 29, 31 or 33; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:22, 24, 26, 28, 30, 32, 34, 63, 64, 65, 66, 67, 68 or 69;

(2) a spacer of at least 125 amino acids in length;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

3. A chimeric antigen receptor comprising:

(1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPRC5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising a CDR-H1 comprising the amino acid sequence selected from SEQ ID NOs: 75, 78, 80, 90, 93, 95, 105, 108, 110, 120, 123, 125, 135, 138, 140, 152, 162, 165, and 167; (b) a CDR-H2 comprising the amino acid sequence selected from SEQ ID NOs: 76, 79, 81, 91, 94, 96, 106, 109, 111, 121, 124, 126, 136, 139, 141, 150, 153, 154, 163, 166, and 168; and (c) a CDR-H3 comprising the amino acid sequence selected from SEQ ID NOs: 77, 92, 107, 122, 137, 151, and 164; and

(ii) a variable light chain (V_L) region comprising a CDR-L1 comprising the amino acid sequence selected from SEQ ID NOs: 85, 100, 115, 130, 145, 157, and 172; (b) a CDR-L2 comprising the amino acid sequence selected from SEQ ID NOs: 86, 101, 116, 131, 146, and 158; and (c) a CDR-L3 comprising the amino acid sequence selected from SEQ ID NOs: 87, 102, 117, 132, 147, 159, 173, and 297;

(2) a spacer of at least 125 amino acids in length;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

4. The chimeric antigen receptor of claim 1 or claim 3, wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising: an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:21, 23, 25, 27, 29, 31 or 33; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:22, 24, 26, 28, 30, 32, 34, 63, 64, 65, 66, 67, 68 or 69.

5. The chimeric antigen receptor of any of claims 1-4, wherein:

(a) the spacer has a length of between 125 and 300;

(b) the spacer comprises a sequence of a hinge region, a CH2 and CH3 region;

(c) the spacer comprises an IgG4/2 chimeric hinge region or a modified IgG4 hinge region; an IgG2/4 chimeric CH2 region; and an IgG4 CH3 region;

(d) the spacer is or comprises (i) the sequence set forth in SEQ ID NO: 17; (ii) a functional variant of SEQ ID NO:17 that has at least at or about 95%, at or about 96%, at or about 97%, at or about

98% or at or about 99% sequence identity to SEQ ID NO:17; or (iii) a contiguous portion of (i) or (ii) that is at least 125 amino acids in length; and/or

(e) the spacer is or comprises the amino acid sequence encoded by the nucleotide sequence set forth in SEQ ID NO:74.

6. The chimeric antigen receptor of any of claims 1-5, wherein:

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:21 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:21; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:22 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:22;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:21 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:21; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:63 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:63;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:23 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:23; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:24 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:24;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:23 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:23; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:64 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:64;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:25 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or

identity to SEQ ID NO:29; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:67 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:67;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:31 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:31; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:32 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:32;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:31 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:31; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:68 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:68;

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:33 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:33; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:34 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:34; or

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:33 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:33; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:69 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:69.

7. The chimeric antigen receptor of any of claims 1-6, wherein:

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:80, 81 and 77, respectively, and the V_L region comprises the amino acid sequences of SEQ ID NOS:85, 86 and 87, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:95, 96, 92, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:100, 101 and 102, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:110, 111 and 107, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:115, 116 and 117, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:130, 131 and 132, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:140, 141 and 137, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:145, 146 and 147, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:140, 154 and 151, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:157, 158 and 159, respectively;

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:167, 168 and 164, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:172, 86, 173, respectively;
or

the V_H region comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:169, 170 and 171, respectively, and the V_L region comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:174, 89 and 297, respectively.

8. The chimeric antigen receptor of any of claims 1-7, wherein:

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:21 and 22, respectively or the amino acid sequence set forth in SEQ ID NOs: 21 and 63, respectively;

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:23 and 24, respectively or the amino acid sequence set forth in SEQ ID NOs:23 and 64, respectively;

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:25 and 26, respectively or the amino acid sequence set forth in SEQ ID NOs: 25 and 65, respectively;

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:27 and 28, respectively or the amino acid sequence set forth in SEQ ID NOs: 27 and 66, respectively;

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:29 and 30, respectively or the amino acid sequence set forth in SEQ ID NOs:29 and 67, respectively;

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:31 and 32, respectively or the amino acid sequence set forth in SEQ ID Nos: 31 and 68, respectively; or

the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:33 and 34 or the amino acid sequence set forth in SEQ ID Nos: 33 and 69, respectively, respectively.

9. The chimeric antigen receptor of any of claims 1-8, wherein:

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:27 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:27; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:28 or or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:28; or

the V_H region comprises the amino acid sequence set forth in SEQ ID NO:27 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:27; and the V_L region comprises the amino acid sequence set forth in SEQ ID NO:66 or or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% identity to SEQ ID NO:66.

10. The chimeric antigen receptor of any of claims 1-9, wherein:

(a) the V_H region comprises the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and the V_L region comprises the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; and/or

(b) the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs:27 and 28, respectively or the amino acid sequence set forth in SEQ ID Nos: 27 and 66, respectively.

11. The chimeric antigen receptor of any of claims 1-10, wherein the extracellular antigen-binding domain is or comprises a single chain variable fragment (scFv).

12. The chimeric antigen receptor of any of claims 1-11, wherein:
the extracellular antigen-binding domain comprises the amino acid sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, and 14 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence selected from SEQ ID NOs: 2, 4, 6, 8, 10, 12, and 14; and/or

the extracellular antigen-binding domain is encoded by the nucleotide sequence selected from SEQ ID Nos: 258, 260, 262, 264, 266, 268, and 270 or a nucleotide sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the nucleotide sequence selected from SEQ ID Nos: 258, 260, 262, 264, 266, 268, and 270.

13. The chimeric antigen receptor of any of claims 1-12, wherein the antigen-binding domain comprises the amino acid sequence set forth in SEQ ID NO: 8 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8.

14. The chimeric antigen receptor of any of claims 1-13, wherein the intracellular signaling region comprises an intracellular signaling domain that is or comprises a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain or a functional variant or signaling portion thereof.

15. The chimeric antigen receptor of claim 14, wherein the intracellular signaling region further comprises a costimulatory signaling region.

16. The chimeric antigen receptor of claim 15, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof.

17. The chimeric antigen receptor of any of claims 1-16, wherein the transmembrane domain is or comprises a transmembrane domain from CD4, CD28, or CD8.

18. The chimeric antigen receptor of any of claims 1-17, wherein:

the chimeric antigen receptor comprises the amino acid sequence set forth in SEQ ID NO:290, or an amino acid sequence that has at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98% or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO:290; and/or

the chimeric antigen receptor is encoded by the nucleotide sequence set forth in SEQ ID NO:289, or a nucleotide sequence that has at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98% or at or about 99% sequence identity to the nucleotide sequence set forth in SEQ ID NO:289.

19. A chimeric antigen receptor comprising:

(1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPCR5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 27; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 28 or 66;

(2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length or a spacer set forth in SEQ ID NO:17;

(3) a transmembrane domain from human CD28; and

(4) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and an intracellular signaling domain of a T cell costimulatory molecule.

20. A chimeric antigen receptor comprising:

(1) an extracellular antigen-binding domain that specifically binds human G-protein coupled receptor class C group 5 member D (GPCR5D), wherein the extracellular antigen-binding domain comprises:

a V_H region comprising a CDR-H1, CDR-H2 and CDR-H3 contained within the V_H region amino acid sequence set forth in SEQ ID NO: 27; and a variable light (V_L) region comprising a CDR-L1, CDR-L2 and CDR-L3 contained within the V_L region amino acid sequence set forth in SEQ ID NO: 28 or 66;
or

a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:125, 126 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively;

a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:120, 121 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively; or

a V_H region comprising a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:123, 124 and 122, respectively, and a V_L region comprising a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:130, 131 and 132, respectively;

(2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length or a spacer set forth in SEQ ID NO:17;

(3) a transmembrane domain from human CD28; and

(4) an intracellular signaling region comprising a cytoplasmic signaling domain of a human CD3-zeta (CD3ζ) chain and an intracellular signaling domain of a human CD28 or a human 4-1BB.

21. A polynucleotide comprising a nucleotide sequence encoding the chimeric antigen receptor of any of claims 1-20.

22. The polynucleotide of claim 21, wherein the nucleic acid encoding the spacer comprises at least one modified splice donor and/or splice acceptor site, said modified splice donor and/or acceptor site comprising one or more nucleotide modifications corresponding to a reference splice donor site and/or reference splice acceptor site contained in the sequence set forth in SEQ ID NO:73.

23. The polynucleotide of claim 22, wherein the one or more nucleotide modifications comprise an amino acid substitution.

24. The polynucleotide of any of claims 21-23, wherein:
the reference splice donor site comprises the sequence tcaactggtacgtgg (SEQ ID NO:177);
and/or
the reference splice acceptor site comprises the sequence
aagtttctttctgtattccagctgaccgtggataaatctc (SEQ ID NO:180).

25. The polynucleotide of any of claims 21-24, wherein the one or more nucleotide modifications is silent and/or results in a degenerate codon compared to SEQ ID NO:73 and/or does not change the amino acid sequence of the encoded spacer.

26. The polynucleotide of any of claims 21-25, wherein the modified splice donor site is set forth in tcaactggtatgtgg (SEQ ID NO:183) and/or the modified acceptor site is set forth in cagtttcttctgtatagtagactcacgtggataaatcaa (SEQ ID NO:186) and/or cgcttgcctccttgcctccgcctcctctgttgccggacct (SEQ ID NO:188).

27. The polynucleotide of any of claims 21-26, wherein the spacer is encoded by the nucleotide sequence set forth in SEQ ID NO:74.

28. The polynucleotide of any of claims 21-27, wherein the polynucleotide is codon-optimized for expression in a human cell.

29. The polynucleotide of any of claims 21-28, wherein the chimeric antigen receptor is a first chimeric antigen receptor and the polynucleotide further comprises a nucleotide sequence encoding a second chimeric antigen receptor.

30. The polynucleotide of claim 29, wherein the second chimeric antigen receptor (CAR) comprises:

- (a) an extracellular antigen-binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma; and
- (b) a spacer, a transmembrane domain, and an intracellular signaling region.

31. The polynucleotide of claim 30, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

32. The polynucleotide of any of claims 29-31, wherein the second CAR comprises:

(1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NOs: 189, 191, 193, 195 or 197; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 190, 192, 194, 196 or 198;

- (2) a spacer, optionally a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length, or a spacer set forth in SEQ ID NO:17;
- (3) a transmembrane domain; and
- (4) an intracellular signaling region.

33. The polynucleotide of claim 32, wherein:

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; or

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively.

34. The polynucleotide of claim 32 or claim 33, wherein:

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:189 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:190;

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:191 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:192;

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:193 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:194;

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:195 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:196; or

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:197 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:198.

35. The polynucleotide of any of claims 32-34, wherein the antigen-binding domain of the second CAR comprises an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241, or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241.

36. The polynucleotide of any of claims 30-35, wherein:

(a) the transmembrane domain of the second CAR is or comprises a transmembrane domain from CD4, CD28, or CD8, optionally from human CD4, human CD28 or human CD8;

(b) the intracellular signaling region of the second CAR comprises an intracellular signaling domain that is or comprises a cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain or a functional variant or signaling portion thereof, optionally a human CD3 zeta chain; and/or

(c) the intracellular signaling region of the second CAR further comprises a costimulatory signaling region.

37. The polynucleotide of any of claims 29-36, wherein at least one of the first chimeric antigen receptor and the second chimeric antigen receptor comprises an intracellular signaling region comprising an intracellular signaling domain of 4-1BB.

38. A polynucleotide comprising:

(i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) comprising a first antigen binding domain; and

(ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) comprising a second antigen binding domain;

wherein the first CAR and second CAR each comprise the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region;

wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR comprises the identical amino acid sequence; and

wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

39. A polynucleotide comprising:

(i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR) comprising a first antigen binding domain capable of binding to one of GPRC5D or BCMA; and

(ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) comprising a second antigen binding domain capable of binding to the other of GPRC5D or BCMA;

wherein the first CAR and second CAR each comprise the following: (a) the first antigen binding domain or the second antigen binding domain, (b) a spacer, (c) a transmembrane domain, and (d) an

intracellular signaling region comprising an intracellular signaling domain and a costimulatory signaling region;

wherein one or more of (b) through (d) in the first CAR and the same one or more of (b) through (d) in the second CAR comprises the identical amino acid sequence; and

wherein the nucleotide sequence(s) encoding the one or more of (b) through (d) in the first CAR differs in sequence from the nucleotide sequence(s) encoding the same one or more of (b) through (d) in the second CAR.

40. The polynucleotide of any of claims 29-39, wherein at least one of the nucleotide sequence encoding the first chimeric antigen receptor and the nucleotide sequence encoding the second chimeric antigen receptor is codon diverged.

41. A polynucleotide comprising (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor (CAR) and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element;

wherein the first CAR comprises a first antigen binding domain that binds to GPRC5D, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311; a spacer encoded by the nucleotide set forth in SEQ ID NO:305; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307; and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308;

wherein the second CAR comprises a second antigen binding domain that binds to BCMA optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310; a spacer encoded by the nucleotide set forth in SEQ ID NO:74; a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56; and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60;

and wherein the first nucleic acid sequence encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

42. A polynucleotide comprising (i) a first nucleic acid sequence encoding a first chimeric antigen receptor (CAR), (ii) a second nucleic acid sequence encoding a second chimeric antigen receptor

(CAR), and (iii) a nucleotide sequence encoding a multicistronic element, wherein the first nucleic acid encoding the first CAR and the second nucleic acid encoding the second CAR are separated by the multicistronic element;

wherein the first CAR comprises a first antigen binding domain that binds to BCMA, optionally wherein the first antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:310, a spacer encoded by the nucleotide set forth in SEQ ID NO:74, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:56, and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:58 and a co-stimulatory signaling domain region encoded by the nucleotide sequence set forth in SEQ ID NO:60

wherein the second CAR comprises a second antigen binding domain that binds to GPRC5D, optionally wherein the second antigen binding domain is encoded by the nucleotide sequence set forth in SEQ ID NO:311, a spacer encoded by the nucleotide set forth in SEQ ID NO:305, a transmembrane domain encoded by the nucleotide sequence set forth in SEQ ID NO:307, and an intracellular signaling region comprising an intracellular signaling domain encoded by the nucleotide sequence set forth in SEQ ID NO:309 and a co-stimulatory signaling region encoded by the nucleotide sequence set forth in SEQ ID NO:308;

wherein the first nucleic acid encoding the first CAR is located toward the 5' end of the polynucleotide relative to the second nucleic acid sequence encoding the second CAR.

43. The polynucleotide of any one of claims 29-42, wherein the nucleotide sequence encoding the first chimeric antigen receptor and the nucleotide sequence encoding the second chimeric antigen receptor have no more than about 30, no more than about 20, or no more than about 10 consecutive base pairs of sequence homology.

44. A vector comprising the polynucleotide of any of claims 21-43.

45. The vector of claim 44, which is a viral vector.

46. A cell comprising the chimeric antigen receptor of any of claims 1-20.

47. The cell of claim 46, wherein the chimeric antigen receptor is a first chimeric receptor and the cell further comprises a polynucleotide comprising a nucleotide encoding a second chimeric antigen receptor.

48. A cell comprising the polynucleotide of any of claims 21-43.

49. A cell comprising the polynucleotide of any of claims 21-28, which is the first polynucleotide, wherein the cell further comprises a second polynucleotide comprising a nucleotide sequence encoding a second chimeric antigen receptor (CAR).

50. The cell of claim 48 or claim 49, wherein the second chimeric antigen receptor (CAR) comprises:

(a) an extracellular antigen-binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma; and

(b) a spacer, a transmembrane domain, and an intracellular signaling region.

51. The cell of claim 50, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

52. The cell of any of claims 49-51, wherein the second CAR comprises:

(1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NOs: 189, 191, 193, 195 or 197; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 190, 192, 194, 196 or 198;

(2) a spacer, optionally a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is at or about 228 amino acids in length, or a spacer set forth in SEQ ID NO:17;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

53. The cell of claim 52, wherein:

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; or

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively.

54. The cell of claim 52 or claim 53, wherein:

the V_H region and VL region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:189 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:190;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:191 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:192;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:193

and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:194;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:195 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:196; or

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:197 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:198.

55. The cell of any of claims 50-54, wherein the antigen-binding domain of the second CAR comprises an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241.

56. A composition comprising the chimeric antigen receptor of any of claims 1-20.

57. A composition comprising the cell of any one of claims 46-55 or a plurality of the cells of any one of claims 46-55.

58. A composition comprising:
a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-20 or encoded by the polynucleotide of any of claims 21-28; and
a plurality of second cells comprising a second chimeric antigen receptor.

59. The composition of claim 58, wherein the second chimeric receptor comprises an extracellular antigen-binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma.

60. The composition of claim 59, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

61. The composition of any of claims 58-60, wherein the second CAR comprises:
(1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 189, 191, 193, 195 or 197; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 190, 192, 194, 196 or 198;

(2) a spacer, optionally a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_{H2} region; and an IgG4 C_{H3} region, optionally that is about 228 amino acids in length, or a spacer set forth in SEQ ID NO:17;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

62. The composition of claim 60 or claim 61, wherein:
the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:218, 219 and 220, respectively;

the V_H region of the second CAR comprise a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR

comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:224, 225, and 226, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:227, 228 and 229, respectively; or

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:230, 231 and 232, respectively.

63. The composition of any of claims 60-62, wherein:

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:189 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:190;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:191 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:192;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:193 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:194;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or

about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:195 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:196; or

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:197 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:198.

64. The composition of any of claims 60-63, wherein the antigen-binding domain of the second CAR comprises an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241, or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to an amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241.

65. The composition of any of claims 58-64, wherein at least one of the first chimeric antigen receptor and the second chimeric antigen receptor comprises an intracellular signaling region comprising an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB.

66. The cells of any of claims 46-55 or the composition of any of claims 56-65 for use in the treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

67. Use of a composition comprising the cells of any of claims 46-55 or the composition of any of claims 56-65 for the manufacture of a medicament for treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

68. A composition comprising a first dose of a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-20 or encoded by the polynucleotide of any of claims 21-28 and a composition comprising a second dose of a plurality of second cells comprising a second chimeric antigen receptor for use in the treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

69. Use of a composition comprising a first dose of a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-20 or encoded by the polynucleotide of any of claims 21-28 and a composition comprising a second dose of a plurality of second cells comprising a second chimeric antigen receptor for the manufacture of a medicament for treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

70. The compositions of claim 68 or the use of claim 69, wherein the second chimeric receptor comprises an extracellular antigen binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma, optionally

wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

71. The compositions of claim 68 or claim 70 or the use of claim 69 or claim 70, wherein the second CAR comprises:

(1) an extracellular antigen-binding domain that specifically binds BCMA, wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 189, 191, 193, 195 or 197; and

(ii) a variable light chain (V_L) region comprising an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 190, 192, 194, 196 or 198;

(2) a spacer, optionally a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, optionally that is about 228 amino acids in length, or a spacer set forth in SEQ ID NO:17;

(3) a transmembrane domain; and

(4) an intracellular signaling region.

72. The compositions or use of claim 71, wherein:

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:218, 219 and 220, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:221, 222 and 223, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:224, 225, and 226, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:227, 228 and 229, respectively; or

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:230, 231 and 232, respectively.

73. The compositions or use of claim 71 or claim 72, wherein:

the V_H region and VL region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:189 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:190;

the V_H region and VL region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:191 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:192;

the V_H region and VL region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:193

and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:194;

the V_H region and VL region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:195 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:196; or

the V_H region and VL region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:197 and SEQ ID NO:198.

74. The compositions or use of any of claims 71-73, wherein the antigen-binding domain of the second CAR comprises the amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence selected from SEQ ID NOs: 237, 238, 239, 240, and 241.

75. The compositions or use of any of claims 68-74, wherein at least one of the first chimeric antigen receptor and the second chimeric antigen receptor comprises an intracellular signaling region comprising an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of human 4-1BB.

76. The cells, compositions or use of any of claims 66-75, wherein the disease or disorder is associated with expression of GPRC5D, optionally

wherein the disease or disorder is further associated with expression of B cell maturation antigen (BCMA).

77. The cells, compositions or use of any one of claims 66-76, wherein the disease or disorder is a cancer, optionally

wherein the cancer is a GPRC5D-expressing cancer.

78. The cells, compositions or use of claim 77, wherein the cancer is a plasma cell malignancy and the plasma cell malignancy is multiple myeloma (MM) or plasmacytoma, optionally wherein the cancer is a relapsed/refractory multiple myeloma.

79. A combination comprising:
a plurality of first cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-20 and/or encoded by the polynucleotide of any of claims 21-28; and
a plurality of second cells comprising a second chimeric antigen receptor.

80. The combination of claim 79, wherein the second chimeric receptor comprises an extracellular antigen binding domain that specifically binds a second antigen expressed on or associated with multiple myeloma, optionally wherein the second antigen is selected from the group consisting of B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

81. The combination of claim 79 or claim 80, wherein:
the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:199, 200 and 201, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:218, 219 and 220, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequence of SEQ ID NOS:202, 203, 204, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequence of SEQ ID NOS:221, 222 and 223, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:199, 200, 205, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:224, 225, and 226, respectively;

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:206, 207, 208, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:227, 228 and 229, respectively; or

the V_H region of the second CAR comprises a CDR-H1, CDR-H2, and CDR-H3 comprising the amino acid sequences of SEQ ID NOS:209, 210 and 211, respectively, and the V_L region of the second CAR comprises a CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOS:230, 231 and 232, respectively.

82. The combination of any of claims 79-81, wherein:

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:189 and SEQ ID NO:190, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, at or about 99%, or at or about 100% sequence identity to SEQ ID NO:189 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:190;

the V_H region and V_L region of the second CAR comprise (a) the amino acid sequences set forth in SEQ ID NO:191 and SEQ ID NO:192, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:191 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:192;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:193 and SEQ ID NO:194, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:193 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:194;

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:195 and SEQ ID NO:196, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:195 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:196; or

the V_H region and V_L region of the second CAR comprises (a) the amino acid sequences set forth in SEQ ID NO:197 and SEQ ID NO:198, respectively, or (b) an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:197 and an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to SEQ ID NO:198.

83. The combination of any of claims 79-82, wherein the antigen-binding domain comprises the amino acid sequence set forth in SEQ ID NOs: 237, 238, 239, 240, or 241 or an amino acid sequence having at least at or about 90%, at or about 91%, at or about 92%, at or about 93%, at or about 94%, at or about 95%, at or about 96%, at or about 97%, at or about 98%, or at or about 99% sequence identity to the amino acid sequence set forth in SEQ ID NOs: 227, 238, 239, 240, or 241.

84. The combination of any of claims 79-83, wherein at least one of the first chimeric antigen receptor and the second chimeric antigen receptor comprises an intracellular signaling region comprising an intracellular signaling domain of 4-1BB or a signaling portion thereof, optionally of a human 4-1BB.

85. The combination of any of claims 79-84 for use in the treatment of a disease or disorder, optionally wherein the disease or disorder is a cancer.