

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: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:66; (2) a spacer of at least 125 amino acids comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region; (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 of SEQ ID NO: 27; 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 of SEQ ID NO: 66; (2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region; (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 of SEQ ID NO: 125; (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 126; and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 122; and (ii) a variable light chain (V_L) region comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 130; (b) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 131; and (c) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 132; (2) a spacer of at least 125 amino acids comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region; (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

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 (GPRC5D), 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.

[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 (GPRC5D), 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 (CD3ζ) 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 (GPRC5D), 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.

[0033a] 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 set forth in SEQ ID NO: 27; and (ii) a variable light chain (V_L) region comprising an amino acid sequence set forth in SEQ ID NO: 66; (2) a spacer comprising at least at or about 95% sequence identity to 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 ζ) chain and an intracellular signaling domain of 4-1BB.

[0033b] 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 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; (2) a spacer comprising at least at or about 95% sequence identity to 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 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

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.

[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

[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.

[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.

[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

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.

[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.

[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 T 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 T cell comprising the polynucleotide disclosed herein.

[0176b] In another aspect, the present disclosure refers to a T cell comprising the polynucleotide disclosed herein, which is the first polynucleotide, wherein the T 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.

[0180c] In yet another aspect, the present disclosure refers to a composition comprising: a plurality of first T 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 T 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 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 T 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 T 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 T 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 T cells comprising a second chimeric antigen receptor.

[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

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 of SEQ ID NO: 27; 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 of SEQ ID NO: 66;

(2) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region;

(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: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:66;

(2) a spacer of at least 125 amino acids comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region;

(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 (GPCR5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:125; (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:126; and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:122; and

(ii) a variable light chain (V_L) region comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 130; (b) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 131; and (c) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 132;

(2) a spacer of at least 125 amino acids comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge, an IgG2/4 chimeric CH2 region, and an IgG4 CH3 region;

(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: 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: 66.

5. The chimeric antigen receptor of any of claims 1-4, wherein the V_H region and the V_L region comprise the amino acid sequence set forth in SEQ ID NOs: 27 and 66, respectively.

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

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.

7. The chimeric antigen receptor of any of claims 1-6, wherein the extracellular antigen-binding domain is or comprises a single chain variable fragment (scFv).

8. The chimeric antigen receptor of any of claims 1-7, wherein the extracellular antigen-binding domain comprises the amino acid sequence of 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 of SEQ ID NO: 8.

9. The chimeric antigen receptor of any of claims 1-8, wherein the extracellular antigen-binding domain is encoded by the nucleotide sequence of SEQ ID No: 264 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 of SEQ ID No: 264.

10. The chimeric antigen receptor of any of claims 1-9, wherein the intracellular signaling region 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.

11. The chimeric antigen receptor of claim 10, wherein the cytoplasmic domain of the CD3 ζ chain is set forth in SEQ ID NO:20.

12. The chimeric antigen receptor of claim 10, wherein the intracellular signaling region further comprises a costimulatory signaling region.

13. The chimeric antigen receptor of claim 12, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof.

14. The chimeric antigen receptor of claim 13, wherein the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB.

15. The chimeric antigen receptor of claim 13 or 14, wherein the intracellular signaling domain of 4-1BB is set forth in SEQ ID NO:19.

16. The chimeric antigen receptor of any of claims 1-15, wherein the transmembrane domain is or comprises a transmembrane domain from CD4, CD28, or CD8.

17. The chimeric antigen receptor of claim 16, wherein the transmembrane domain is or comprises a transmembrane domain from CD28.

18. The chimeric antigen receptor of claim 16 or 17, wherein the intracellular signaling domain of CD28 is set forth in SEQ ID NO:18.

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 (GPRC5D), wherein the extracellular antigen-binding domain comprises:

(i) a variable heavy chain (V_H) region comprising an amino acid sequence set forth in SEQ ID NO: 27; and (ii) a variable light chain (V_L) region comprising an amino acid sequence set forth in SEQ ID NO: 66;

(2) a spacer comprising at least at or about 95% sequence identity to 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 4-1BB.

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 (GPRC5D), wherein the extracellular antigen-binding domain comprises:

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;

(2) a spacer comprising at least at or about 95% sequence identity to 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 ($CD3\zeta$) chain and an intracellular signaling domain of a human 4-1BB.

21. The chimeric antigen receptor of any of claims 1-20, wherein the spacer is or comprises the sequence set forth in SEQ ID NO:17.

22. The chimeric antigen receptor of any one of claims 1-21, wherein:

(a) the scFv is set forth in SEQ ID NO:8;

(b) the spacer is set forth in SEQ ID NO:17;

- (c) the transmembrane domain is set forth in SEQ ID NO:18;
- (d) the cytoplasmic domain of the CD3 ζ chain is set forth in SEQ ID NO:20; and
- (e) the intracellular signaling domain of 4-1BB is set forth in SEQ ID NO:19.

23. The chimeric antigen receptor of any of claims 1-22, wherein the spacer is or comprises the amino acid sequence encoded by the nucleotide sequence set forth in SEQ ID NO:74.

24. The chimeric antigen receptor of any of claims 1-23, 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.

25. The CAR of claim 24, wherein the CAR has the sequence set forth in SEQ ID NO: 290.

26. The chimeric antigen receptor of any of claims 1-25, wherein 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.

27. The CAR of claim 26, wherein the CAR is encoded by the nucleotide sequence set forth in SEQ ID NO: 289.

28. A polynucleotide comprising a nucleotide sequence encoding the chimeric antigen receptor of any of claims 1-27.

29. The polynucleotide of claim 28, 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, 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 cagtttctctgtatagtagactcaccgtggataaatcaa (SEQ ID NO:186) and/or cgcttctctctgtgtccgcctctctgttgccggacct (SEQ ID NO:188).

30. The polynucleotide of claim 28 or 29, 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 cagtttctctgtatagtagactcacgtggataaatcaa (SEQ ID NO:186).

31. The polynucleotide of any of claims 28-30, wherein the spacer is encoded by the nucleotide sequence set forth in SEQ ID NO:74.

32. The polynucleotide of any of claims 28-31, wherein the polynucleotide is codon-optimized for expression in a human cell.

33. The polynucleotide of any of claims 28-32, 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.

34. The polynucleotide of claim 33, wherein the second chimeric antigen receptor (CAR) comprises an extracellular antigen-binding domain that specifically binds a second antigen, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

35. A vector comprising the polynucleotide of any of claims 28-34.

36. The vector of claim 35, which is a viral vector.

37. A T cell comprising the chimeric antigen receptor of any of claims 1-27.

38. The T cell of claim 37, 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.

39. A T cell comprising the polynucleotide of any of claims 28-34.

40. A T cell comprising the polynucleotide of any of claims 28-32, which is the first polynucleotide, wherein the T cell further comprises a second polynucleotide comprising a nucleotide sequence encoding a second chimeric antigen receptor (CAR).

41. The T cell of claim 40, wherein the second chimeric antigen receptor (CAR) comprises an extracellular antigen-binding domain that specifically binds a second antigen, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

42. A composition comprising:
a plurality of first T cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-27 or encoded by the polynucleotide of any of claims 28-32; and
a plurality of second T cells comprising a second chimeric antigen receptor.

43. The composition of claim 42, wherein the second chimeric antigen receptor (CAR) comprises an extracellular antigen-binding domain that specifically binds a second antigen, wherein the second antigen is selected from B cell maturation antigen (BCMA), CD38, CD138, CS-1, BAFF-R, TACI, and FcRH5.

44. Use of a composition comprising the cells of any of claims 37-41 or the composition of claim 42 or 43 for the manufacture of a medicament for treatment of a disease or disorder, optionally wherein the disease or condition is a cancer.

45. A composition comprising a first dose of a plurality of first T cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-27 or encoded by the polynucleotide of any of claims 28-32 and a composition comprising a second dose of a plurality of second T 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.

46. 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 1-27 or encoded by the polynucleotide of any of claims 28-32 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.

47. The compositions of claim 45 or the use of claim 46, 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.

48. A combination comprising:
a plurality of first T cells comprising a first chimeric antigen receptor that is the chimeric antigen receptor of any of claims 1-27 and/or encoded by the polynucleotide of any of claims 28-32; and
a plurality of second T cells comprising a second chimeric antigen receptor.

49. The combination of claim 48, 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.