

e.g. BCMA CAR-T cells), such CACCRs allow for increased immune cell activation, proliferation, persistence, and/or potency. The enhanced activities of BCMA CAR-T cells are dependent on the presence of the target BCMA. Also provided are methods of making and using the CACCRs described herein in BCMA CAR immune cells, such as BCMA CAR-T cells.

[0010] Accordingly, in one [aspectexample](#), provided herein is a BCMA CAR-I cell, e.g. a BCMA CAR-T cell that contains a CACCR composed of two monomers, each monomer comprising: (a) a transmembrane domain; (b) a Janus Kinase (JAK)-binding domain; and (c) a recruiting domain, wherein the monomers are constitutively dimerized.

[0011] In some [embodimentexamples](#), the CACCR's transmembrane domain and/or JAK-binding domain is derived from the TPOR/MPLR receptor. In some [embodimentexamples](#), the transmembrane domain and/or the JAK binding domain is derived from amino acids 478 – 582 of the naturally occurring TPOR/MPLR receptor of SEQ ID NO: 6. In some [embodimentexamples](#), the TPOR/MPLR receptor comprises one or more of the amino acid substitutions selected from H499L, S505N, W515K, and G509N. In some [embodimentexamples](#), the TPOR/MPLR receptor comprises the H499L, S505N and W515K substitutions, or the S505N and W515K substitutions.

[0012] In some [embodimentexamples](#), the recruiting domain is a STAT-recruiting domain. In some [embodimentexamples](#), the recruiting domain comprises the STAT-recruiting domain from IL7Ra, for example, IL7Ra(316-459). In some [embodimentexample](#), the recruiting domain comprises the STAT-recruiting domain from IL2Rb, for example, IL2Rb (333-551), IL2Rb(393-433, 518-551), IL2Rb(339-379, 393-433, 518-551), IL2Rb(333-551, Y381S, Y384S, Y387S), or IL2Rb(333-551, Y364S, Y381S, Y384S, Y387S). In some [embodimentexamples](#), the recruiting domain comprises the STAT-recruiting domain from IL12Rb1, for example, IL12Rb1(622-662). In some [embodimentexamples](#), the recruiting domain comprises the STAT-recruiting domain from IL12Rb2, for example, IL12Rb2(714-862) or IL12Rb2(775-825). In some [embodimentexamples](#), the recruiting domain comprises the STAT-recruiting domain from IL21R, for example, IL21R(322-538).

[0013] In a related [aspectexample](#) provided herein is a polynucleotide encoding any one of the CACCRs of the disclosure, and an expression vector comprising such polynucleotide. In some [embodimentexamples](#), the polynucleotide further encodes for a chimeric antigen receptor

(CAR), wherein the CAR binds to BCMA (a “BCMA CAR” or a “BCMA specific CAR”) (e.g., human BCMA, Uniprot accession number: Q02223-2).

[0013a] In one aspect, the present disclosure refers to at least one isolated polynucleotide encoding a BCMA CAR that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166 and encoding a CACCR that comprises a polypeptide that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

[0013b] In another aspect, the present disclosure refers to a vector that comprises the isolated polynucleotide as disclosed herein; optionally wherein the vector is a lentiviral vector.

[0014] In another aspectexample, provided herein is an engineered immune cell comprising at least one BCMA chimeric antigen receptor and at least one CACCR of the disclosure. In some embodimentexamples the immune cell is a T cell. In some embodimentexamples the immune cell is an allogeneic immune cell. In other embodimentexamples, the immune cell is an autologous immune cell. The immune cell may be selected from the group consisting of: T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell. In a related aspectexample, provided herein is a pharmaceutical composition comprising any of the engineered immune cells of the disclosure, and a kit comprising such a pharmaceutical composition. In a related aspectexample, the engineered immune cell comprises one or more polynucleotides that encode a BCMA CAR and a CACCR of the disclosure. In a related aspectexample, the engineered immune cell comprises a bicistronic or multicistronic polynucleotide that encodes a BCMA CAR and one or more than one CACCR of the disclosure.

[0014a] In another aspect, the present disclosure refers to an engineered immune cell comprising an anti-BCMA chimeric antigen receptor (CAR) and a constitutively active chimeric cytokine receptor (CACCR), wherein the CACCR comprises two monomers, each monomer comprising:
a transmembrane domain;
a Janus Kinase (JAK)-binding domain; and
a recruiting domain, wherein:

the transmembrane domain and JAK-binding domain are present in a polypeptide (“TM/JAK polypeptide”) that comprises an amino acid sequence that is at least about 90% identical to amino acids 478 – 582 of the naturally occurring TPOR/MPLR receptor (the amino acid sequence of SEQ ID NO: 7);

the anti-BCMA CAR comprises an extracellular ligand-binding domain, a transmembrane domain, and an intracellular signaling domain; wherein the extracellular ligand-binding domain specifically recognizes and binds to human BCMA and comprises a single chain variable fragment (scFv); wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region joined by a flexible linker; and

(i) the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 146, 147, or 148; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 149 or 150; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 151; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 152; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 153; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 154; or
ii) the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 157, 158 or 159; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 160 or 161; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 162; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 163; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 164; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 165.

[0014b] In another aspect, the present disclosure refers to an engineered immune cell that comprises one or more polynucleotides that encode an anti-BCMA CAR polypeptide that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166 and a CACCR polypeptide that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

[0015] In another aspectexample, provided herein is a method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of any of the engineered immune cells described herein.

[0015a] In another aspect, the present disclosure refers to an engineered immune cell as disclosed herein, for use in treating a patient suffering from a disease or condition.

[0015b] In another aspect, the present disclosure refers to use of the engineered immune cell as disclosed herein in the manufacture of a medicament for treating multiple myeloma in a patient in need thereof.

[0016] In another [aspectexample](#), a method of making an engineered immune cell is provided comprising providing a cell, for example, an immune cell, a T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell, macrophage, monocyte, B-cell and an immune cell derived from a stem cell, and introducing into the cell at least one polynucleotide that encodes a BCMA CAR and at least one polynucleotide that encodes a CACCR of the disclosure. In some [embodimentexamples](#), the cell is introduced with one or more polynucleotide molecules that encode a BCMA CAR and a CACCR. In some [embodimentexamples](#), a first vector comprises a BCMA CAR polynucleotide and a second vector comprises a CACCR polynucleotide. In some [embodimentexamples](#), one vector comprises both a BCMA CAR polynucleotide and a CACCR polynucleotide. In some [embodimentexamples](#), the vector is a viral vector such as a lentiviral vector. In some [embodimentexamples](#), the cell is an autologous cell, which can mean that it is derived from the same person who will be treated with the engineered immune cell prepared from that cell. In other [embodimentexamples](#), the cell is an allogeneic cell, which can mean that it is derived from a person other than the person who

will be treated with the engineered immune cell, e.g., from a healthy donor. In some [embodimentexamples](#), the allogeneic engineered immune cell further comprises one or more genetic modifications at the TCR alpha constant (TRAC) locus to reduce or negate the expression of the endogenous TCR alpha receptor. In some [embodimentexamples](#), the engineered immune cell further comprises one or more genetic modifications at the CD52 gene to reduce or negate the expression of CD52. In various [embodimentexamples](#), the BCMA CAR polynucleotide and/or the CACCR polynucleotide, and any vector that may comprise either or both polynucleotides is driven by the EF1alpha promoter. In some [embodimentexamples](#), at least one of the BCMA CAR polynucleotide, the CACCR polynucleotide, and the vector or vectors that comprise either or both polynucleotides, further encodes at least one selectable marker that facilitates and/or enables the identification of cells that contain the BCMA CAR polynucleotide and/or the CACCR polynucleotide. In various [embodimentexamples](#), the BCMA CAR polynucleotide and/or the CACCR polynucleotide, and any vector that may comprise either or both polynucleotides further comprises a wild type or mutant WPRE. In some [embodimentexamples](#), the vector further comprises a mutant WPRE. In various [embodimentexamples](#), the BCMA CAR polynucleotide and/or the CACCR polynucleotide, and any vector that may comprise either or both polynucleotides, may be introduced into the cell by methods known in the art, including but not limited to various methods of electroporation, transfection and viral transduction. In some [embodimentexamples](#), a patient in need of treatment with the engineered cell is a person who has a disease or condition that can be treated with the engineered cell or who might benefit from treatment with the engineered cell. In some [embodimentexamples](#), the condition is multiple myeloma. In some [embodimentexamples](#), the disease or condition is relapsed/refractory multiple myeloma. In some [embodimentexamples](#), the disease is relapsed multiple myeloma. In some [embodimentexamples](#), the disease is a plasma cell malignancy, for example, diffused large B-cell lymphoma (DLBCL). In certain [embodimentexamples](#), the patient who has received the engineered immune cells is administered an effective amount of rituximab or dasatinib to reduce or eliminate the engineered immune cells.

[0016a] [In another aspect, the present disclosure refers to a method of making an engineered immune cell as disclosed herein comprising introducing into a cell:](#)

- a) [at least one polynucleotide that encodes an anti-BCMA CAR and at least one polynucleotide that encodes a CACCR,](#)

- b) the at least one polynucleotide as disclosed herein, or
c) the vector as disclosed herein,

wherein the engineered immune cell expresses an anti-BCMA CAR and a CACCR;
optionally

5 wherein the immune cell is a T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell,
macrophage, monocyte, B-cell or an immune cell derived from a stem cell; and/or wherein
the cell is autologous or is allogeneic; and

optionally wherein the polynucleotide or vector further encodes at least one selectable
marker; or wherein the polynucleotide or vector is introduced into the cell by
10 electroporation, transfection and/or viral transduction.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** shows a schematic of an exemplary engineered CACCR of the disclosure.

[0018] **FIG. 2A** shows schematic representations of exemplary recruiting domains of the
CACCR of the disclosure that comprise one or more polypeptide subregions of the IL2Rb
15 intracellular domain. **FIGs. 2B-2D** show schematics of exemplary vectors that can be used

WHAT IS CLAIMED IS:

1. An engineered immune cell comprising an anti-BCMA chimeric antigen receptor (CAR) and a constitutively active chimeric cytokine receptor (CACCR), wherein the CACCR comprises two monomers, each monomer comprising:

a transmembrane domain;

a Janus Kinase (JAK)-binding domain; and

a recruiting domain, wherein:

the transmembrane domain and JAK-binding domain are present in a polypeptide (“TM/JAK polypeptide”) that comprises an amino acid sequence that is at least about 90% identical to amino acids 478 – 582 of the naturally occurring TPOR/MPLR receptor (the amino acid sequence of SEQ ID NO: 7);

the anti-BCMA CAR comprises an extracellular ligand-binding domain, a transmembrane domain, and an intracellular signaling domain; wherein the extracellular ligand-binding domain specifically recognizes and binds to human BCMA and comprises a single chain variable fragment (scFv); wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region joined by a flexible linker; and

(i) the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 146, 147, or 148; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 149 or 150; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 151; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 152; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 153; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 154; or

ii) the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 157, 158 or 159; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 160 or 161; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 162; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 163; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 164; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 165.

~~2. The engineered immune cell of claim 1 wherein the transmembrane domain and JAK-binding domain are present in a polypeptide (“TM/JAK polypeptide”) that comprises~~

~~an amino acid sequence that is at least about 90% identical to amino acids 478—582 of the naturally occurring TPOR/MPLR receptor (the amino acid sequence of SEQ ID NO: 7).~~

~~3.2.~~ The engineered immune cell of claim ~~2.1~~, wherein the TM/JAK polypeptide comprises a modified version of the sequence of amino acids 478 – 582 of the naturally occurring TPOR/MPLR receptor (the amino acid sequence of SEQ ID NO: 7) wherein the modified version comprises at least one amino acid substitution at the amino acid position selected from H499, S505, and W515.

~~4.3.~~ The engineered immune cell of claim ~~3.2~~, wherein the modified version of the sequence of amino acids 478 – 582 of the naturally occurring TPOR/MPLR receptor comprises at least one amino acid substitution selected from the group consisting of H499L, S505N, and W515K.

~~5.4.~~ The engineered immune cell of any one of claims 1-~~4.3~~, wherein the recruiting domain comprises an amino acid sequence that is at least about 90% identical or 100% identical to the STAT-recruiting domain from IL7Ra, IL2Rb, IL12Rb1, IL12Rb2, or IL21R.

~~6.5.~~ The engineered immune cell of any one of the preceding claims, wherein the recruiting domain comprises an amino acid sequence that is at least about 90% identical or 100% identical to the STAT-recruiting domain from IL2Rb.

~~7.6.~~ The engineered immune cell of any one of the preceding claims, wherein the recruiting domain comprises an amino acid sequence that is at least about 90% identical or 100% identical to an amino acid sequence that comprises amino acids 339-379, 393-433, and 518-551 of IL2Rb (SEQ ID NO: 78) or an amino acid sequence that is at least about 90% identical or 100% identical to an amino acid sequence that comprises amino acids 393-433 and 518-551 of IL2Rb (SEQ ID NO: 77).

~~8. — The engineered immune cell of claim 7, wherein the recruiting domain comprises amino acids 339-379, 393-433, and 518-551 of IL2Rb (SEQ ID NO: 78) or amino acids 393-433 and 518-551 of IL2Rb (SEQ ID NO: 77).~~

~~9.7.~~ The engineered immune cell of claim ~~4.3~~, wherein: the TM/JAK polypeptide comprises the amino acid substitutions S505N and W515K (SEQ ID NO: 13) and further wherein the recruiting domain comprises amino acids 393-433 and 518-551 of IL2Rb (SEQ ID NO: 77); or

the TM/JAK polypeptide comprises the amino acid substitutions H499L, S505N, and W515K (SEQ ID NO: 12) and further wherein the recruiting domain comprises amino acids 339-379, 393-433 and 518-551 of IL2Rb (SEQ ID NO: 78); or

the TM/JAK polypeptide comprises the amino acid substitutions H499L, S505N, and W515K and further wherein the recruiting domain comprises amino acids 393-433 and 518-551 of IL2Rb (SEQ ID NO: 77).

10. — The engineered immune cell of claim 4, wherein the TM/JAK polypeptide comprises the amino acid substitutions H499L, S505N, and W515K (SEQ ID NO: 12) and further wherein the recruiting domain comprises amino acids 339-379, 393-433 and 518-551 of IL2Rb (SEQ ID NO: 78).

11. — The engineered immune cell of claim 4, wherein the TM/JAK polypeptide comprises the amino acid substitutions H499L, S505N, and W515K and further wherein the recruiting domain comprises amino acids 393-433 and 518-551 of IL2Rb (SEQ ID NO: 77).

12.8. — The engineered immune cell of claim 1, wherein the CACCR comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 99, 100, 143, 180, 181, 182, 184, 185 or 186.

13. — The engineered immune cell of claim 1, wherein the CACCR comprises the amino acid sequence of SEQ ID NO: 99, 100, 143, 180, 181, 182, 184, 185 or 186.

14. — The engineered immune cell of any one of claims 1-13, wherein the BCMA CAR comprises an extracellular ligand binding domain, a transmembrane domain, and an intracellular signaling domain.

15. — The engineered immune cell of claim 14, wherein the extracellular ligand binding domain specifically recognizes and binds to human BCMA.

16. — The engineered immune cell of claim 15, wherein the extracellular ligand binding domain comprises a single chain variable fragment (scFv).

17. — The engineered immune cell of claim 16, wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region joined by a flexible linker.

18.9. — The engineered immune cell of any preceding claimclaim 17, wherein the VH region comprises the amino acid sequence of SEQ ID NO: 144 and the VL region comprises the amino acid sequence of SEQ ID NO: 145, or the VH region comprises the amino acid sequence of SEQ ID NO: 155 and the VL region comprises the amino acid sequence of SEQ ID NO: 156; optionally wherein the anti-BCMA CAR comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166.

19. — The engineered immune cell of claim 17 or 18, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 146, 147, or 148; a VH

CDR2 comprising the amino acid sequence of SEQ ID NO: 149 or 150; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 151; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 152; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 153; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 154.

20. — The engineered immune cell of any one of claims 15-18, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 157, 158 or 159; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 160 or 161; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 162; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 163; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 164; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 165.

21.10. The engineered immune cell of any preceding claim, one of claims 14-20, wherein the intracellular signaling domain of the anti-BCMA CAR comprises a CD3ζ (CD3zeta) signaling domain and/or a 4-1BB signaling domain; and/or wherein the BCMA CAR comprises a safety switch comprising the CD20 mimotope.

22. — The engineered immune cell of any one of claims 14-21, wherein the BCMA CAR comprises a safety switch comprising the CD20 mimotope.

23. — The engineered immune cell of any one of claims 1-19, wherein the BCMA CAR comprises an amino acid sequence that is at least about 90% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166.

24. — The engineered immune cell of any one of claims 1-19, wherein the BCMA CAR comprises the amino acid sequence of SEQ ID NO: 140, 141 or 166.

25.11. An engineered immune cell that comprises one or more polynucleotides that encode an anti-BCMA CAR polypeptide that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166 and a CACCR polypeptide that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

26.12. The engineered immune cell of claim 25.11, wherein a single polynucleotide encodes both the polypeptide that comprises the amino acid sequence of SEQ ID NO: 140, 141 or 166 and the polypeptide that comprises the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

~~27.13.~~ An engineered immune cell of claim 1 comprising a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 172 or 176.

~~28.—The engineered immune cell of any one of claims 25-27, wherein the polynucleotide comprises a promoter.~~

~~29.—The engineered immune cell of claim 28, wherein the promoter comprises an EF-1alpha promoter.~~

~~30.14.~~ The engineered immune cell of any one of claims 1-~~29~~13, wherein the CACCR does not comprise an extracellular ligand-binding domain.

~~31.15.~~ The engineered immune cell of any one of claims 1-~~30~~14, wherein the engineered immune cell;

~~(i) is an engineered T cell; optionally wherein the engineered T cell is autologous T cell or allogeneic T cell; and/or~~

~~(ii) further comprises one or more genetic modifications in T cell receptor alpha constant region (TRAC) and/or CD52 gene to reduce or negate the expression of TCR alpha and/or CD52.~~

~~32.—The engineered immune cell of claim 31, wherein the engineered T cell is autologous T cell or allogeneic T cell.~~

~~33.—The engineered immune cell of any one of claims 1-32, further comprising one or more genetic modifications in T cell receptor alpha constant region (TRAC) and/or CD52 gene to reduce or negate the expression of TCR alpha and/or CD52.~~

~~34.—A method of treating a patient suffering from a disease or condition, wherein the method comprises administering an effective amount of the engineered immune cell of any one of claims 1-33 and 46.~~

~~35.—The method of claim 34, wherein the disease or condition is multiple myeloma.~~

~~36.—The method of claim 34 or 35, wherein the engineered immune cell is allogeneic to the patient.~~

~~37.—The method of any one of claims 34-36, wherein the method comprises administering at least one dose of the engineered immune cell to the patient, and further wherein one dose contains between about 7×10^6 cells and about 480×10^6 cells.~~

~~38.—The method of claim 37, wherein the dose ranges from about 20×10^6 cells/dose to about 480×10^6 cells/dose or the at least one dose is about 20×10^6 cells/dose, about 40×10^6 cells/dose, about 80×10^6 cells/dose, about 120×10^6 cells/dose, about $240 \times$~~

~~10⁶ cells/dose, about 320 x 10⁶ cells/dose, about 360 x 10⁶ cells/dose, or about 480 x 10⁶ cells/dose.~~

~~39.16.~~ At least one isolated polynucleotide encoding a BCMA CAR that comprises an amino acid sequence that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 140, 141 or 166 and encoding a CACCR that comprises a polypeptide that is at least about 90% identical or 100% identical to the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

~~40.17.~~ A vector that comprises the isolated polynucleotide of claim ~~39.16~~; optionally wherein the vector is a lentiviral vector.

~~41.~~—The vector of claim 40, wherein the BCMA CAR comprises the amino acid sequence of SEQ ID NO: 140, 141 or 166 and/or the CACCR comprises the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

~~42.18.~~ The engineered immune cell of any one of claims 11-15 or the vector of claim ~~40 or 41.17~~, wherein the polynucleotide~~vector~~ further comprises: a promoter optionally wherein the promoter comprises an EF-1alpha promoter and/or a mutant WPRE.

~~43.~~—The vector of any one of claims 40-42, wherein the promoter comprises an EF-1alpha promoter.

~~44.~~—The vector of any one of claims 40-43, wherein the vector is a lentiviral vector.

~~45.~~—The vector of any one of claims 40-44 further comprising a mutant WPRE.

~~46.~~—An engineered immune cell that comprises the polynucleotide of claim 39 or the vector of any one of claims 40-45.

19. An engineered immune cell of any one of claims 1-15 and 18, for use in treating a patient suffering from a disease or condition.

20. Use of the engineered immune cell of any one of claims 1-15 and 18 in the manufacture of a medicament for treating multiple myeloma in a patient in need thereof.

21. The engineered immune cell for use according to claim 19 or the use according to claim 20, wherein at least one dose of the engineered immune cell is to be administered to the patient, and further wherein one dose contains between about 7 x 10⁶ cells and about 480 x 10⁶ cells; optionally wherein the dose ranges from about 20 x 10⁶ cells/dose to about 480 x 10⁶ cells/dose or the at least one dose is about 20 x 10⁶ cells/dose, about 40 x 10⁶ cells/dose, about 80 x 10⁶ cells/dose, about 120 x 10⁶ cells/dose, about 240 x 10⁶ cells/dose, about 320 x 10⁶ cells/dose, about 360 x 10⁶ cells/dose, or about 480 x 10⁶ cells/dose.

~~47.22.~~ A method of making an engineered immune cell of any one of claims 1-~~33-15~~ and ~~46-18~~ comprising introducing into a cell:

a) at least one polynucleotide that encodes an anti-BCMA CAR and at least one polynucleotide that encodes a CACCR,

b) the at least one polynucleotide of claim ~~39~~16, or

c) the vector of claim ~~40~~17 or 18,

~~d) the vector of claim 41,~~

~~e) the vector of claim 42,~~

~~f) the vector of claim 43,~~

~~g) the vector of claim 44, or~~

~~h) the vector of claim 45,~~

wherein the engineered immune cell expresses an anti-BCMA CAR and a CACCR;

optionally

wherein the immune cell is a T cell, dendritic cell, killer dendritic cell, mast cell, NK-cell,

macrophage, monocyte, B-cell or an immune cell derived from a stem cell; and/or wherein

the cell is autologous or is allogeneic; and

optionally wherein the polynucleotide or vector further encodes at least one selectable

marker; or wherein the polynucleotide or vector is introduced into the cell by

electroporation, transfection and/or viral transduction.

23. The engineered immune cell of any one of claims 1-15 and 18-21, wherein the monomers are capable of spontaneously dimerizing, and can activate signaling in the absence of any exogenous stimulation or ligand.

~~48.—The method of claim 47, wherein the immune cell is a T cell, dendritic cell, killer dendritic cell, mast cell, NK cell, macrophage, monocyte, B cell or an immune cell derived from a stem cell.~~

~~49.—The method of claim 47 or 48, wherein the cell is autologous.~~

~~50.—The method of claim 47 or 48, wherein the cell is allogeneic.~~

~~51.—The method of any one of claims 47-50, wherein the polynucleotide or vector further encodes at least one selectable marker.~~

~~52.—The method of any one of claims 47-50, wherein the polynucleotide or vector is introduced into the cell by electroporation, transfection and/or viral transduction.~~