

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:
 - 5 a transmembrane domain;
 - a Janus Kinase (JAK)-binding domain; and
 - a recruiting domain.
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
 - 10 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. The engineered immune cell of claim 2 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
 - 15 version comprises at least one amino acid substitution at the amino acid position selected from H499, S505, and W515.
4. The engineered immune cell of claim 3 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,
 - 20 S505N, and W515K.
5. The engineered immune cell of any one of claims 1-4, wherein the recruiting domain comprises an amino acid sequence that is at least about 90% identical to the STAT-recruiting domain from IL7Ra, IL2Rb, IL12Rb1, IL12Rb2, or IL21R.
6. The engineered immune cell of any one of the preceding claims, wherein the
 - 25 recruiting domain comprises an amino acid sequence that is at least about 90% identical to the STAT-recruiting domain from IL2Rb.
7. 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 to an amino acid sequence that comprises amino acids 339-379, 393-433, and 518-551 of
 - 30 IL2Rb (SEQ ID NO: 78) or an amino acid sequence that is at least about 90% 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. The engineered immune cell of claim 4, wherein the TM/JAK polypeptide
5 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).
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
10 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).
- 15 12. The engineered immune cell of claim 1, wherein the CACCR comprises an amino acid sequence that is at least about 90% 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.
- 20 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.
- 25 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. The engineered immune cell of claim 17, wherein the VH region comprises the
30 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.

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
5 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
10 159; 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.
- 15 21. The engineered immune cell of any one of claims 14-20, wherein the intracellular signaling domain of the BCMA CAR comprises a CD3 ζ (CD3zeta) signaling domain and/or a 4-1BB signaling domain.
22. The engineered immune cell of any one of claims 14-21, wherein the BCMA CAR comprises a safety switch comprising the CD20 mimotope.
- 20 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 25. An engineered immune cell that comprises one or more polynucleotides that encode a BCMA CAR polypeptide that comprises the amino acid sequence of SEQ ID NO: 140, 141 or 166 and a CACCR polypeptide that comprises the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.
26. The engineered immune cell of claim 25, wherein a single polynucleotide encodes
30 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. 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.
- 5 29. The engineered immune cell of claim 28, wherein the promoter comprises an EF-1alpha promoter.
30. The engineered immune cell of any one of claims 1-29, wherein the CACCR does not comprise an extracellular ligand-binding domain.
31. The engineered immune cell of any one of claims 1-30, wherein the engineered
10 immune cell is an engineered T cell.
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
15 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.
- 20 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.
- 25 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 240×10^6 cells/dose, about 320×10^6 cells/dose, about 360×10^6 cells/dose, or about 480×10^6 cells/dose.
- 30 39. At least one isolated polynucleotide encoding a BCMA CAR that 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 and encoding a CACCR that comprises a polypeptide that is at least

about 90% identical to the amino acid sequence of SEQ ID NO: 99, 100, 180, 181, 182, 184, 185 or 186.

40. A vector that comprises the isolated polynucleotide of claim 39.

41. The vector of claim 40, wherein the BCMA CAR comprises the amino acid

5 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. The vector of claim 40 or 41, wherein the vector further comprises a promoter.

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

10 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.

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

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

b) the at least one polynucleotide of claim 39,

c) the vector of claim 40,

20 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,

25 wherein the engineered immune cell expresses a BCMA CAR and a CACCR.

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.

30 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.