Claims

1. An engineered immune cell expressing at its cell surface membrane a B-cell maturation antigen (BCMA) specific chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single chain Fv fragment (scFv) comprising a heavy chain variable (VH) region comprising three complementarity determining regions (CDRs) comprising the sequences shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising three CDRs comprising the sequences shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

2. The engineered immune cell of claim 1, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 222.

3. The engineered immune cell of claim 2, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 33 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 34.

4. The engineered immune cell of claim 1, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and wherein the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 225.

5. The engineered immune cell of claim 4, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 112 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 38.

6. The engineered immune cell of claim 1, wherein the BCMA specific CAR comprises the amino acid sequence shown in SEQ ID NO: 344.

7. The engineered immune cell of claim 6, wherein the BCMA specific CAR comprises a CD20 epitope.

8. The engineered immune cell of claim 7, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

9. The engineered immune cell of claim 1, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

10. The engineered immune cell of claim 1, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

11. The engineered immune cell of claim 1, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

12. The engineered immune cell of claim 1, wherein the BCMA specific CAR further comprises a stalk domain between the extracellular ligand-binding domain and the first transmembrane domain.

13. The engineered immune cell of claim 12, wherein the stalk domain is selected from the group consisting of: a human CD8α hinge, an IgG1 hinge, and an FcγRIIIα hinge.

14. The engineered immune cell of claim 1, wherein the BCMA specific CAR further comprises a CD20 epitope.

15. The engineered immune cell of claim 14, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

16. The engineered immune cell of claim 1, wherein the BCMA specific CAR further comprises another extracellular ligand-binding domain that is not specific for BCMA binding.

17. The engineered immune cell of claim 1, further comprising another CAR that is not specific for BCMA.

18. The engineered immune cell of claim 1, further comprising a polynucleotide encoding a suicide polypeptide.

19. The engineered immune cell of claim 1, further comprising a disruption in one or more endogenous genes, wherein the endogenous gene encodes TCRα, TCRβ, CD52, glucocorticoid receptor (GR), deoxycytidine kinase (dCK), or an immune checkpoint protein.

20. The engineered immune cell of claim 19, wherein the engineered immune cell comprises a disruption in an endogenous gene encoding an immune checkpoint protein, wherein the immune checkpoint protein is selected from the group consisting of PD-1, CTLA-4, LAG3, Tim3, BTLA, BY55, TIGIT, B7H5, LAIR1, SIGLEC10 and 2B4.

21. The engineered immune cell of claim 1, wherein the immune cell is selected from the group consisting of: a T cell, a dendritic cell, a killer dendritic cell, a mast cell, an NK-cell, and a B cell.

22. The engineered immune cell of claim 1, wherein the immune cell is an inflammatory T-lymphocyte, a cytotoxic T-lymphocyte, a regulatory T-lymphocyte, or a helper T-lymphocyte.

23. The engineered immune cell of claim 1, wherein the immune cell is an autologous immune cell or an allogeneic immune cell.

24. A pharmaceutical composition comprising a population of the engineered immune cell of claim 1.

25. The pharmaceutical composition of claim 24, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 222.

26. The pharmaceutical composition of claim 25, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 33 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 34.

27. The pharmaceutical composition of claim 24, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and wherein the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 225.

28. The pharmaceutical composition of claim 27, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 112 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 38.

29. The pharmaceutical composition of claim 24, wherein the BCMA specific CAR comprises the amino acid sequence shown in SEQ ID NO: 344.

30. The pharmaceutical composition of claim 29, wherein the BCMA specific CAR comprises a CD20 epitope.

31. The pharmaceutical composition of claim 30, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

32. The pharmaceutical composition of claim 24, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α

hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

33. The pharmaceutical composition of claim 24, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

34. The pharmaceutical composition of claim 24, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

35. A method of engineering an immune cell, the method comprising: a. providing an immune cell; and b. introducing into the cell at least one polynucleotide encoding a B-cell maturation antigen (BCMA) specific chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single chain Fv fragment (scFv) comprising a heavy chain variable (VH) region comprising three complementarity determining regions (CDRs) comprising the sequences shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising three CDRs comprising the sequences shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

36. The method of claim 35, comprising: c. introducing into the cell at least one polynucleotide encoding at least one other CAR which is not specific for BCMA.

37. The method of claim 35, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 222.

38. The method of claim 37, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 33 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 34.

39. The method of claim 35, wherein the VH region of the BCMA specific CAR comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and wherein the VL region of the BCMA specific CAR comprises a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 225.

40. The method of claim 39, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 112 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 38.

41. The method of claim 35, wherein the BCMA specific CAR comprises the amino acid sequence shown in SEQ ID NO: 344.

42. The method of claim 41, wherein the BCMA specific CAR comprises a CD20 epitope.

43. The method of claim 42, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

44. The method of claim 35, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

45. The method of claim 35, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

46. The method of claim 35, wherein the BCMA specific CAR comprises a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.