CLAIMS

What is claimed is:

1. A chimeric antigen receptor (CAR) comprising:

(a) an ectodomain comprising an antigen recognition region, wherein the antigen recognition region comprises at least one VH that specifically binds to B-Cell Maturation Antigen (BCMA);

(b) a transmembrane domain, and

(c) an endodomain comprising at least one costimulatory domain.

2. The CAR of claim 1, wherein the VH comprises or consists of a recombinant or chimeric sequence.

3. The CAR of claim 1, wherein the VH comprises or consists of a human or humanized sequence.

4. The CAR of claim 1, wherein the ectodomain of (a) further comprises a signal peptide.

5. The CAR of claim 1, wherein the ectodomain of (a) further comprises a hinge between the antigen recognition region and the transmembrane domain.

6. The CAR of claim 4, wherein the signal peptide comprises a sequence encoding a human CD2, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD8α, CD19, CD28, 4-1BB or GM-CSFR signal peptide.

7. The CAR of claim 6, wherein the signal peptide comprises a sequence encoding a human CD8α signal peptide.

8. The CAR of claim 7, wherein the human CD8α signal peptide comprises an amino acid sequence of SEQ ID NO: 18012.

9. The CAR of claim 1, wherein the transmembrane domain comprises a sequence encoding a human CD2, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD8α, CD19, CD28, 4-1BB or GM-CSFR transmembrane domain.

10. The CAR of claim 9, wherein the transmembrane domain comprises a sequence encoding a human CD8α transmembrane domain.

11. The CAR of claim 10, wherein the human CD8α transmembrane domain comprises an amino acid sequence of SEQ ID NO: 18014.

12. The CAR of claim 1, wherein the endodomain comprises a human CD3ζ endodomain.

13. The CAR of claim 1, wherein the at least one costimulatory domain comprises a human 4-1BB, CD28, CD40, ICOS, MyD88, OX-40 intracellular segment, or any combination thereof.

14. The CAR of claim 13, wherein the at least one costimulatory domain comprises a human 4-1BB costimulatory domain.

15. The CAR of claim 12, wherein the human CD3ζ endodomain comprises an amino acid sequence of SEQ ID NO: 18016.

16. The CAR of claim 14, wherein the human 4-1BB costimulatory domain comprises an amino acid sequence of SEQ ID NO: 18018.

17. The CAR of claim 5, wherein the hinge comprises a sequence derived from a human CD8α, IgG4, CD4 or any combination thereof.

18. The CAR of claim 17, wherein the hinge comprises a sequence derived from a human CD8α.

19. The CAR of claim 18, wherein the sequence derived from a human CD8α comprises an amino acid sequence of SEQ ID NO: 18020.

20. A composition comprising the CAR of claim 1 and at least one pharmaceutically acceptable carrier.

21. A transposon comprising a nucleic acid sequence encoding the CAR of claim 1.

22. A composition comprising the transposon of claim 21.

23. A vector comprising a nucleic acid sequence encoding the CAR of claim 1.

24. A composition comprising the vector of claim 23.

25. A cell comprising the CAR of claim 1.

26. A cell comprising the transposon of claim 21.

27. A cell comprising the vector of claim 23.

28. The cell of claim 25, wherein the cell is an immune cell.

29. The cell of claim 28, wherein the immune cell is a T-cell, a Natural Killer (NK) cell, a Natural Killer (NK)-like cell, a Cytokine Induced Killer (CIK) cell, a hematopoietic progenitor cell, a peripheral blood (PB) derived T cell or an umbilical cord blood (UCB) derived T-cell.

30. The cell of claim 25, wherein the cell is autologous.

31. The cell of claim 25, wherein the cell is allogeneic.

32. A composition comprising the cell of claim 25.

33. A composition comprising a population of cells, wherein a plurality of cells of the population comprises the cell of claim 25.

34. The composition of claim 33, wherein the plurality of the cells of the population comprises at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or any percentage in between of the cell of claim 25.

35. A method of producing a population of modified T-cells, comprising:

(a) introducing into a plurality of T-cells a composition comprising a nucleic acid sequence encoding the CAR of claim 1, thereby generating a modified T-cell population;

(b) culturing the modified T-cell population under conditions suitable for integration of the nucleic acid sequence encoding the CAR;

(c) expanding and/or selecting at least one cell from the modified T-cell population that expresses the CAR on the cell surface.

36. Use of the composition of claim 33 in the manufacture of a medicament for treating cancer in a subject in need.

37. The use of claim 36, wherein the cancer is multiple myeloma.

38. The use of claim 36, wherein the cell or cell population is autologous.

39. The use of claim 36, wherein the cell or cell population is allogeneic.

40. The CAR of claim 1, wherein the VH comprises:

a complementarity determining region 1 (CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 18056, 18057 and 18058;

a complementarity determining region 2 (CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 18059, 18060, 18061, 18062 and 18063; and

a complementarity determining region 3 (CDR3) comprising an amino acid sequence of SEQ ID NO: 18064.

41. The CAR of claim 1, wherein the VH comprises:

a CDR1 comprising an amino acid sequence of SEQ ID NO: 18056; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18059; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

42. The CAR of claim 1, wherein the VH comprises:
a CDR1 comprising an amino acid sequence of SEQ ID NO: 18056; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18060; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

43. The CAR of claim 1, wherein the VH comprises:
a CDR1 comprising an amino acid sequence of SEQ ID NO: 18057; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18061; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

44. The CAR of claim 1, wherein the VH comprises:
a CDR1 comprising an amino acid sequence of SEQ ID NO: 18057; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18061; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

45. The CAR of claim 1, wherein the VH comprises:
a CDR1 comprising an amino acid sequence of SEQ ID NO: 18058; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18062; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

46. The CAR of claim 1, wherein the VH comprises:
a CDR1 comprising an amino acid sequence of SEQ ID NO: 18056; a CDR2 comprising an amino acid sequence of SEQ ID NO: 18063; and a CDR3 comprising an amino acid sequence of SEQ ID NO: 18064.

47. The CAR of claim 1, wherein the VH comprises an amino acid sequence selected from a group consisting of SEQ ID NOS: 18050, 18051, 18052, 18053, 18054 and 18055.

48. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18050.

49. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18051.

50. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18052.

51. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18053.

52. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18054.

53. The CAR of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18055.

54. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18000.

55. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18002.

56. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18004.

57. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18006.

58. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18008.

59. The CAR of claim 1, comprising the amino acid sequence of SEQ ID NO: 18010.

60. A chimeric antigen receptor (CAR) comprising:

(a) an ectodomain comprising a human CD8α signal peptide and an antigen recognition region, wherein the antigen recognition region comprises at least one VH that specifically binds to BCMA;

(b) a hinge domain comprising a human CD8α hinge domain;

(c) a transmembrane domain comprising a human CD8α transmembrane domain; and

(d) an endodomain comprising a human 4-1BB costimulatory domain and a human CD3ζ endodomain.

61. The CAR of claim 60, wherein the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 18050, 18051, 18052, 18053, 18054 and 18055, wherein the human CD8α signal peptide comprises the amino acid sequence of SEQ ID NO: 18012, wherein the human CD8α hinge domain comprises the amino acid sequence of SEQ ID NO: 18020, wherein the human CD8α transmembrane domain comprises the amino acid sequence of SEQ ID NO: 17505, wherein the human 4-1BB costimulatory domain comprises the amino acid sequence of SEQ ID NO: 17509, and wherein the human CD3ζ endodomain comprises the amino acid sequence of SEQ ID NO: 17507.

62. The CAR of claim 61, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18051, wherein the human CD8α signal peptide comprises the amino acid sequence of SEQ ID NO: 18012, wherein the human CD8α hinge domain comprises the amino acid sequence of SEQ ID NO: 18020, wherein the human CD8α transmembrane domain comprises the amino acid sequence of SEQ ID NO: 17505, wherein the human 4-1BB costimulatory domain comprises the amino acid sequence of SEQ ID NO: 17509, and wherein the human CD3ζ endodomain comprises the amino acid sequence of SEQ ID NO: 17507.

CLAIMS

1. A cell comprising a chimeric antigen receptor (CAR) comprising:

(a) an ectodomain comprising an antigen recognition region, wherein the antigen recognition region comprises at least one VH that specifically binds to B-Cell Maturation Antigen (BCMA);

(b) a transmembrane domain, and

(c) an endodomain comprising at least one costimulatory domain;

wherein the VH comprises:

a complementarity determining region 1 (CDR1) comprising an amino acid sequence of SEQ ID NO: 18056;

a complementarity determining region 2 (CDR2) comprising an amino acid sequence of SEQ ID NO: 18060; and

a complementarity determining region 3 (CDR3) comprising an amino acid sequence of SEQ ID NO: 18064.

2. The cell of claim 1, wherein the VH comprises or consists of a recombinant or chimeric sequence.

3. The cell of claim 1, wherein the VH comprises or consists of a human or humanized sequence.

4. The cell of any one of claims 1-3, wherein the ectodomain of (a) further comprises a signal peptide.

5. The cell of any one of claims 1-4, wherein the ectodomain of (a) further comprises a hinge between the antigen recognition region and the transmembrane domain.

6. The cell of claim 4 or 5, wherein the signal peptide comprises a sequence encoding a human CD2, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD8α, CD19, CD28, 4-1BB or GM-CSFR signal peptide.

7. The cell of claim 6, wherein the signal peptide comprises a sequence encoding a human CD8α signal peptide.

8. The cell of claim 7, wherein the human CD8α signal peptide comprises an amino acid sequence of SEQ ID NO: 18012.

9. The cell of any one of claims 1-8, wherein the transmembrane domain comprises a sequence encoding a human CD2, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD8α, CD19, CD28, 4-1BB or GM-CSFR transmembrane domain.

10. The cell of claim 9, wherein the transmembrane domain comprises a sequence encoding a human CD8α transmembrane domain.

11. The cell of claim 10, wherein the human CD8α transmembrane domain comprises an amino acid sequence of SEQ ID NO: 18014.

12. The cell of any one of claims 1-11, wherein the endodomain comprises a human CD3ζ endodomain.

13. The cell of any one of claims 1-12, wherein the at least one costimulatory domain comprises a human 4-1BB, CD28, CD40, ICOS, MyD88, OX-40 intracellular segment, or any combination thereof.

14. The cell of claim 13, wherein the at least one costimulatory domain comprises a human 4-1BB costimulatory domain.

15. The cell of claim 12, wherein the human CD3ζ endodomain comprises an amino acid sequence of SEQ ID NO: 18016.

16. The cell of claim 14, wherein the human 4-1BB costimulatory domain comprises an amino acid sequence of SEQ ID NO: 18018.

17. The cell of claim 5, wherein the hinge comprises a sequence derived from a human CD8α, IgG4, CD4 or any combination thereof.

18. The cell of claim 17, wherein the hinge comprises a sequence derived from a human CD8α.

19. The cell of claim 18, wherein the sequence derived from a human CD8α comprises an amino acid sequence of SEQ ID NO: 18020.

20. The cell of any one of claims 1-19, wherein the cell is an immune cell.

21. The cell of claim 20, wherein the immune cell is a T-cell, a Natural Killer (NK) cell, a Natural Killer (NK)-like cell, a Cytokine Induced Killer (CIK) cell, a hematopoietic progenitor cell, a peripheral blood (PB) derived T cell or an umbilical cord blood (UCB) derived T-cell.

22. The cell of any one of claims 1-21, wherein the cell is autologous.

23. The cell of any one of claims 1-21, wherein the cell is allogeneic.

24. The cell of any one of claims 1-23, wherein the VH comprises an amino acid sequence of SEQ ID NO: 18051.

25. The cell of any one of claims 1-23, comprising the amino acid sequence of SEQ ID NO: 18006.

26. An isolated cell comprising a CAR comprising:

(a) an ectodomain comprising a human CD8α signal peptide and an antigen recognition region, wherein the antigen recognition region comprises at least one VH that specifically binds to BCMA and wherein the VH comprises an amino acid sequence of SEQ ID NO: 18051;

(b) a hinge domain comprising a human CD8α hinge domain;

(c) a transmembrane domain comprising a human CD8α transmembrane domain; and

(d) an endodomain comprising a human 4-1BB costimulatory domain and a human CD3ζ endodomain.

27. The cell of claim 26, wherein the human CD8α signal peptide comprises the amino acid sequence of SEQ ID NO: 18012, wherein the human CD8α hinge domain comprises the amino acid sequence of SEQ ID NO: 18020, wherein the human CD8α transmembrane domain comprises the amino acid sequence of SEQ ID NO: 18014, wherein the human 4-1BB costimulatory domain comprises the amino acid sequence of SEQ ID NO: 18018, and wherein the human CD3ζ endodomain comprises the amino acid sequence of SEQ ID NO: 18016.

28. A composition comprising the cell of any one of claims 1-27 and at least one pharmaceutically acceptable carrier.

29. A composition comprising a population of cells, wherein a plurality of cells of the population comprises the cell of any one of claims 1-27.

30. Use of the composition of claim 28 or claim 29 in the manufacture of a medicament for the treatment of a BCMA-associated cancer in a subject in need thereof.

31. The use of claim 30, wherein the cancer is multiple myeloma.