

WHAT IS CLAIMED:

1. A chimeric antigen receptor (CAR) comprising a polypeptide comprising:
 - (a) an extracellular antigen binding domain comprising a first BCMA binding moiety and a second BCMA binding moiety, wherein the first BCMA binding moiety is a first anti-BCMA single domain antibody, and the second BCMA binding moiety is a second anti-BCMA sdAb; and wherein each of the first and second sdAb is a VHH domain;
 - (b) a transmembrane domain; and
 - (c) an intracellular signaling domain,wherein:
 - (i) the first anti-BCMA sdAb comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR2 comprising the amino acid sequence of SEQ ID NO: 2; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and
 - (ii) the second anti-BCMA sdAb comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 72; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6.
2. The CAR of claim 1, wherein the first anti-BCMA sdAb comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 7 and SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16, wherein optionally,
 - (1) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 10;
 - (2) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 11;
 - (3) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 12;
 - (4) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 13;
 - (5) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 14;
 - (6) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 15;

(7) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 7, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 16;

(8) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 8;

(9) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 10;

(10) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 11;

(11) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 12;

(12) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 13;

(13) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 14;

(14) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 15; or

(15) the first anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 9, and the second anti-BCMA sdAb comprises an amino acid sequence of SEQ ID NO: 16.

3. The CAR of claim 1 or claim 2, wherein the first anti-BCMA sdAb is at the N-terminus of the second anti-BCMA sdAb; or wherein the first anti-BCMA sdAb is at the C-terminus of the second anti-BCMA sdAb.

4. The CAR of any one of claims 1 to 3, wherein the transmembrane domain is from a molecule selected from the group consisting of CD8 α , CD4, CD28, CD137, CD80, CD86, CD152 and PD1.

5. The CAR of claim 4, wherein the transmembrane domain is from CD8 α or CD28.

6. The CAR of any one of claims 1 to 5, wherein the intracellular signaling domain comprises a primary intracellular signaling domain of an immune effector cell.

7. The CAR of claim 6, wherein the primary intracellular signaling domain is from CD3 ζ .

8. The CAR of any one of claims 1 to 5, wherein the intracellular signaling domain comprises a chimeric signaling domain ("CMSD"), wherein the CMSD comprises a plurality of Immune-receptor Tyrosine-based Activation Motifs ("CMSD ITAMs") optionally connected by one or more linkers ("CMSD linkers"), and wherein optionally the CMSD comprises from N-terminus to C-terminus: optional N-terminal sequence – CD3 δ ITAM – optional first CMSD linker – CD3 ϵ ITAM – optional second CMSD linker – CD3 γ ITAM – optional third linker – DAP12 ITAM – optional C-terminal sequence.
9. The CAR of claim 8, wherein the CMSD comprises an amino acid sequence of SEQ ID NO: 53.
10. The CAR of any one of claims 1 to 9, wherein the intracellular signaling domain comprises a co-stimulatory signaling domain.
11. The CAR of claim 10, wherein the co-stimulatory signaling domain is from a co-stimulatory molecule selected from the group consisting of CD27, CD28, CD137, OX40, CD30, CD40, CD3, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, ligands of CD83 and combinations thereof, wherein optionally the co-stimulatory signaling domain comprises a cytoplasmic domain of CD28 and/or a cytoplasmic domain of CD137.
12. The CAR of any one of claims 1 to 11, further comprising a hinge domain located between the C-terminus of the extracellular antigen binding domain and the N-terminus of the transmembrane domain, wherein optionally the hinge domain is from CD8 α .
13. The CAR of any one of claims 1 to 14, further comprising a signal peptide located at the N-terminus of the polypeptide, wherein optionally the signal peptide is from CD8 α .
14. A chimeric antigen receptor (CAR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23-34.
15. An isolated nucleic acid comprising a nucleic acid sequence encoding the CAR of any one of claims 1 to 14.

16. The isolated nucleic acid of claim 15, wherein the isolated nucleic acid comprises a nucleic acid sequence selected from a group consisting of SEQ ID NOs: 35-46.
17. A vector comprising the isolated nucleic acid of claim 16.
18. An engineered immune effector cell, comprising the CAR of any one of claims 1-14, the isolated nucleic acid of claim 15 or claim 16, or the vector of claim 17.
19. The engineered immune effector cell of claim 18, wherein the immune effector cell is a T cell.
20. The engineered immune effector cell of claim 18 or claim 19, further comprises an exogenous Nef protein.
21. The engineered immune effector cell of claim 20, wherein the exogenous Nef protein is selected from the group consisting of SIV Nef, HIV1 Nef, HIV2 Nef, and subtypes thereof.
22. The engineered immune effector cell of claim 20, wherein the exogenous Nef protein is a wildtype Nef.
23. The engineered immune effector cell of claim 20, wherein the exogenous Nef protein is a mutant Nef.
24. The engineered immune effector cell of claim 23, wherein the mutant Nef comprises one or more mutations in myristoylation site, N-terminal α -helix, tyrosine-based AP recruitment, CD4 binding site, acidic cluster, proline-based repeat, PAK binding domain, COP I recruitment domain, di-leucine based AP recruitment domain, V-ATPase and Raf-1 binding domain, or any combinations thereof.
25. The engineered immune effector cell of claim 24, wherein the mutant Nef is a mutant SIV Nef comprising an amino acid sequence of SEQ ID NO: 51 (mutant SIV Nef M116).
26. A pharmaceutical composition, comprising the engineered immune effector cell of any one of claims 18 to 25, and a pharmaceutically acceptable carrier.

27. A method of treating a disease or disorder in a subject, comprising administering to the subject an effective amount of the engineered immune effector cell of any one of claims 18 to 25, or the pharmaceutical composition of claim 26.
28. The method of claim 27, wherein the disease or disorder is cancer.
29. The method of claim 28, wherein the disease or disorder is multiple myeloma (MM).
30. An anti-BCMA single domain antibody (sdAb) comprising:
- (i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR2 comprising the amino acid sequence of SEQ ID NO: 2; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; or
 - (ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 72; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6.
31. The anti-BCMA sdAb of claim 30, comprising an amino acid sequence selected from a group consisting of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15 and SEQ ID NO: 16.
32. The anti-BCMA sdAb of claim 30, wherein anti-BCMA sdAb comprises or consists of an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more sequence identity with the sequence of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15 and SEQ ID NO: 16.
33. The anti-BCMA sdAb of claim 30, wherein anti-BCMA sdAb is a camelid sdAb.
34. The anti-BCMA sdAb of claim 30, wherein anti-BCMA sdAb is a humanized sdAb.
35. A isolated nucleic acid or a vector comprising a nucleic acid encoding the anti-BCMA sdAb of any one of claims 30 to 34.
36. A chimeric antigen receptor (CAR) comprising a polypeptide comprising:

(a) an extracellular antigen binding domain comprising an anti-BCMA sdAb of any one of claims 30 to 34;

(b) a transmembrane domain; and

(c) an intracellular signaling domain.

37. An isolated nucleic acid or a vector comprising a nucleic acid sequence encoding the CAR of claim 36.

38. An engineered immune effector cell, comprising the CAR of claim 36, the isolated nucleic acid or the vector of claim 37.

39. The engineered immune effector cell of claim 38, wherein the immune effector cell is a T cell.

40. A pharmaceutical composition, comprising the engineered immune effector cell of claim 38 or claim 39, and a pharmaceutically acceptable carrier.

41. A method of treating a disease or disorder in a subject, comprising administering to the subject an effective amount of the engineered immune effector cell of claim 38 or 39, or the pharmaceutical composition of claim 40.