regulatory T cells (Tregs), enhances the efficacy of adoptive T cell therapy,[4,12] as such, the immediate post-autologous transplant period could be an optimal time to administer T cells, and myeloma is one of the few diseases where autologous stem cell transplantation is the standard of care. Third, the immunomodulatory drug lenalidomide may improve CAR based therapy, as has been shown in mice,[13] and lenalidomide is commonly used to treat MM. Fourth, adoptive T cell therapy works best in bone marrow predominant disease such as ALL,[6,7] when compared to solid tumors or extra-medullary CLL,[4] and similar to ALL, myeloma is a disease of the bone marrow.

While there are various reasons to expect that adoptive T cell therapy may work well in MM, expanding adoptive T cell therapy to myeloma also poses unique challenges. Unlike other B-cell malignancies, CD19 expression is seen in only 2% of myeloma patients.[14] Furthermore, unlike CD19, the common extracellular immunophenotypic markers in myeloma (CD138, CD38, and CD56) are all co-expressed on other essential cell types, and we predict CARs to any of these targets would lead to unacceptable "off tumor, on target" toxicity[6] which can be fatal even in targets where antibodies are well tolerated, as was the case with a HER2 targeted CAR.[15] Accordingly, there are needs for novel therapeutic strategies to design CARs targeting antigens that are highly expressed in MM cells and limited expression in normal tissues for treating multiple myeloma, which strategies capable of inducing potent tumor eradication with minimal toxicity and immunogenicity.

SUMMARY

In one aspect, the present disclosure provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that specifically binds to B cell maturation antigen (BCMA), a transmembrane domain, and an intracellular domain, wherein the extracellular antigen-binding domain comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:53, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:54.

In another aspect, the present disclosure provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to B cell maturation antigen (BCMA), a transmembrane domain, and an intracellular domain,

wherein the extracellular antigen-binding domain comprisesa heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 167, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 168, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 169; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 170, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 171, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 172.

In another aspect, the present disclosure provides an immunoresponsive cell comprising the CAR as described herein.

In another aspect, the present disclosure provides a T cell comprising the CAR as described herein.

In another aspect, the present disclosure provides a nucleic acid molecule encoding the CAR as described herein.

In another aspect, the present disclosure provides a vector comprising the nucleic acid molecule as described herein.

In another aspect, the present disclosure provides an immunoresponsive cell comprising the nucleic acid molecule as described herein.

In another aspect, the present disclosure provides a use of the cell as described herein in the manufacture of a medicament for reducing tumor burden in a subject.

In another aspect, the present disclosure provides a use of the cell as described herein in the manufacture of a medicament for increasing or lengthening survival of a subject having a tumor.

In another aspect, the present disclosure provides a method for producing an immunoresponsive cell that binds to B cell maturation antigen (BCMA), comprising introducing into the immunoresponsive cell a nucleic acid sequence that encodes a chimeric antigen receptor (CAR) as described herein.

In another aspect, the present disclosure provides a pharmaceutical composition comprising an effective amount of the cell as described herein and a pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure provides a kit for treating a tumor, comprising the cell as described herein.

In yet another aspect, the present disclosure provides the cell as described herein for use in therapy.

The presently disclosed subject matter generally provides chimeric antigen receptors (CARs) that specifically target B-cell maturation antigen (BCMA), immunoresponsive cells comprising such CARs, and uses of these CARs and immunoresponsive cells for treating multiple myeloma.

The presently disclosed subject matter provides CARs. In one non-limiting example, the CAR comprises an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, where the extracellular antigen-binding domain is a human single-chain variable fragment (scFv) that specifically binds to B cell maturation antigen (BMCA). In certain examples, the human scFv specifically binds to BCMA with a binding affinity (K_D) of from about 1 x 10^{-9} M to

What is claimed is:

1. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that specifically binds to B cell maturation antigen (BCMA), a transmembrane domain, and an intracellular domain, wherein the extracellular antigen-binding domain comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:53, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:54.

2. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to B cell maturation antigen (BCMA), a transmembrane domain, and an intracellular domain, wherein the extracellular antigen-binding domain comprises a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 167, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 168, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 169; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 170, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 171, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 172.

3. The CAR of claim 1 or claim 2, wherein the heavy chain variable region comprises an amino acid sequence that has at least about 90% sequence identity to the sequence set forth in SEQ ID NO:53, and the light chain variable region comprises an amino acid sequence that has at least about 90% sequence identity to the sequence set forth in SEQ ID NO:54.

4. The CAR of any one of claims 1-3, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:53, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:54.

5. The CAR of any one of claims 1-4, wherein the extracellular antigen-binding domain is a single chain variable fragment (scFv), an antigen-binding fragment (Fab), or a $F(ab')_2$.

6. The CAR of any one of claims 1-5, wherein the extracellular antigen-binding domain

comprises the amino acid sequence set forth in SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, or SEQ ID NO: 88.

7. The CAR of any one of claims 1-5, wherein the extracellular antigen-binding domain comprises the amino acid sequence set forth in SEQ ID NO: 77; SEQ ID NO: 88; SEQ ID NO: 87; SEQ ID NO: 86; or SEQ ID NO: 85.

8. The CAR of any one of claims 1-7, wherein the extracellular antigen-binding domain binds to B cell maturation antigen (BCMA) with a binding affinity (K_d) of from 1×10^{-9} M to 3×10^{-6} M or of from 1×10^{-9} M to 1×10^{-8} M.

9. The CAR of any one of claims 1-8, wherein the extracellular antigen-binding domain binds to a non-linear epitope of BCMA.

10. The CAR of any one of claims 1-9, wherein the BCMA comprises the amino acid sequence set forth in SEQ ID NO:71.

11. The CAR of any one of claims 1-10, wherein the transmembrane domain comprises a CD8 polypeptide, a CD28 polypeptide, a CD3ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide , or a combination thereof.

12. The CAR of claim 11, wherein the transmembrane domain comprises a CD8 polypeptide or a CD28 polypeptide.

13. The CAR of any one of claims 1-12, wherein the intracellular domain comprises a CD3ζ polypeptide.

14. The CAR of any one of claims 1-13, wherein the intracellular domain further comprises at least one signaling region.

15. The CAR of claim 14, wherein the at least one signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, a PD-1 polypeptide, a CTLA-4 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide, or a combination thereof.

16. The CAR of claim 14, wherein the at least one signaling region is a co-stimulatory signaling region.

17. The CAR of claim 16, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, or a combination thereof.

18. The CAR of claim 16, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide or a 4-1BB polypeptide.

19. The CAR of any one of claims 14-18, wherein:

(a) the transmembrane domain comprises a CD28 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and the at least one co-stimulatory signaling region that comprises a CD28 polypeptide; or

(b) the transmembrane domain comprises a CD8 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and the at least one co-stimulatory signaling region that comprises a 4-1BB polypeptide.

20. The CAR of any one of claims 14-18, wherein the transmembrane domain comprises a CD28 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and the at least one co-stimulatory signaling region that comprises a 4-1BB polypeptide.

21. The CAR of any one of claims 1-19, wherein the CAR is recombinantly expressed.

22. The CAR of any one of claims 1-21, wherein the CAR is expressed from a γ-retroviral vector or a lentiviral vector.

23. An immunoresponsive cell comprising the CAR of any one of claims 1-22.

24. The immunoresponsive cell of claim 23, wherein the immunoresponsive cell is transduced with the CAR.

25. The immunoresponsive cell of claim 23 or claim 24, wherein the CAR is constitutively expressed on the surface of the immunoresponsive cell.

26. The immunoresponsive cell of any one of claims 23-25, wherein

(a) the immunoresponsive cell is further transduced with at least one co-stimulatory ligand such that the immunoresponsive cell expresses the at least one co-stimulatory ligand, wherein the at least one co-stimulatory ligand is selected from the group consisting of 4-1BBL, CD80, CD86, CD70, OX40L, CD48, TNFRSF14, and combinations thereof; and/or

(b) the immunoresponsive cell is further transduced with at least one cytokine such that the immunoresponsive cell secretes the at least one cytokine, wherein the at least one cytokine is selected from the group consisting of IL-2, IL-3, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, IL-21, and combinations thereof.

27. The immunoresponsive cell of any one of claims 23-26, wherein the immunoresponsive cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a lymphoid progenitor cell, a T cell-precursor cell, and a pluripotent stem cell from which a lymphoid cell may be differentiated.

28. The immunoresponsive cell of claim 27, wherein the immunoresponsive cell is a T cell.

29. A T cell comprising the CAR of any one of claims 1-22.

30. A nucleic acid molecule encoding the CAR of any one of claims 1-22.

31. The nucleic acid molecule of claim 30, comprising the nucleotide sequence set forth in SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, or SEQ ID NO:235.

32. A vector comprising the nucleic acid molecule of claim 30 or claim 31.

33. The vector of claim 32, wherein the vector is a γ-retroviral vector or a lentiviral vector.

34. An immunoresponsive cell comprising the nucleic acid molecule of claim 30 or claim 31.

35. The immunoresponsive cell of claim 34, wherein the immunoresponsive cell is a T cell.

36. Use of the cell of claim 28 or 35 in the manufacture of a medicament for reducing tumor burden in a subject.

37. The use of claim 36, wherein the medicament reduces the number of tumor cells, reduces tumor size, and/or eradicates the tumor in the subject.

38. The use of claim 36 or claim 37 wherein the tumor is selected from the group consisting of multiple myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma, Chronic Lymphocytic Leukemia (CLL), glioblastoma, and Waldenstrom's Macroglobulinemia.

39. The use of any one of claims 36-38, wherein the tumor is multiple myeloma.

40. Use of the cell of claim 28 or 35 in the manufacture of a medicament for increasing or lengthening survival of a subject having a tumor.

41. The use of claim 40, wherein the tumor is selected from the group consisting of multiple myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma, Chronic Lymphocytic Leukemia (CLL), glioblastoma, and Waldenstrom's Macroglobulinemia.

42. The use of claim 40 or claim 41, wherein the tumor is multiple myeloma.

43. The use of any one of claims 40-42, wherein the medicament reduces the number of tumor cells, reduces tumor size, and/or eradicates the tumor in the subject.

44. A method for producing an immunoresponsive cell that binds to B cell maturation antigen (BCMA), comprising introducing into the immunoresponsive cell of claim 28 or 35, a nucleic acid sequence that encodes a chimeric antigen receptor (CAR) of any of claims 1-22.

45. A pharmaceutical composition comprising an effective amount of the cell of any one of claims 23-29, 44, and 45 and a pharmaceutically acceptable excipient.

46. The pharmaceutical composition of claim 45, wherein the pharmaceutical composition is for treating a tumor.

47. The pharmaceutical composition of claim 46, wherein the tumor is selected from the group consisting of multiple myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma, Chronic Lymphocytic Leukemia (CLL), glioblastoma, and Waldenstrom's Macroglobulinemia.

48. The pharmaceutical composition of claim 47, wherein the tumor is multiple myeloma.

49. A kit for treating a tumor, comprising the cell of any one of claims 23-29, 44, and 45.

50. The kit of claim 49, wherein the kit further comprises written instructions for using the cell for treating a subject having the tumor.

51. The kit of claim 49 or claim 50, wherein the tumor is selected from the group consisting of multiple myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma, Chronic Lymphocytic Leukemia (CLL), glioblastoma, and Waldenstrom's Macroglobulinemia.

52. The kit of any one of claims 49-51, wherein the tumor is multiple myeloma.

53. The cell of claim 35 for use in therapy.