(antibody drug conjugate, ADC, such as a radiolabel) can be used to treat some types of B cell malignancies, such as multiple myeloma, but may be limited in efficacy by the number of BCMA molecules expressed on the tumor cell surface and/or the presence of soluble BCMA in the circulation. Low BCMA surface expression on the cancer cells or soluble BCMA can limit and prevent the efficacy of therapeutic agents due to inadequate binding to the BCMA present on the surface of the tumor cells. Low levels of other target molecules on tumor cells (*e.g.*, CD19, CD20) that are targeted with antibody, antibody drug conjugates or chimeric antigen receptor T cells has been shown to limit the efficacy of these therapies, and enable cancer cells that express low levels of the target molecule to escape elimination. In the case of BCMA, the short extracellular portion of the molecule is cleaved from the cell surface and shed through the action of gamma-secretase (γ-secretase), a membrane-localized cellular enzyme involved in protein cleavage. This cleavage lowers the density of BCMA on cells such as myeloma cancer cells that express the molecule and results in elevated levels of soluble BCMA (sBCMA) in the serum of patients with certain autoimmune diseases (*e.g.*, systemic lupus erythomatosis) and cancer (*e.g.*, multiple myeloma).

Currently, there remains a need in the immunotherapy field for alternative or improved compositions and methods for more efficiently treating autoimmune disease and cancer.

SUMMARY

In one aspect, the present disclosure refers to the use of (1) a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM), and (2) a γ-secretase inhibitor in the manufacture of a combination therapy for treating multiple myeloma in a subject.

In another aspect, the present disclosure refers to the use of a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM), in the manufacture of a medicament for treating multiple myeloma

in a subject, wherein the subject has received a therapeutically effective amount of a γ-secretase inhibitor.

In yet another aspect, the present disclosure refers to the use of a γ-secretase inhibitor in the manufacture of a medicament for treating multiple myeloma in a subject, wherein the subject has received a therapeutically effective amount of a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM).

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A – 1P show design and functional testing of exemplary chimeric antigen receptor (CAR) molecules of this disclosure.

(A) Illustrations of exemplary CARs having an extracellular component comprised of a BCMA-specific scFv derived from A7D12.2 antibody ("A7") or C11D5.3 antibody ("C11") and a spacer region (comprised of an IgG4 hinge region), a hydrophobic portion (comprised of a CD28 transmembrane domain), and an intracellular component comprised of a CD3ζ effector domain and a 4-1BB costimulatory domain. The scFvs were constructed with the C-terminal end of the V_H region linked ("G_4S" variable region linker (SEQ ID NO:30)) to the N-terminal end of

CLAIMS

What is claimed is:

1. Use of (1) a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM), and (2) a γ-secretase inhibitor in the manufacture of a combination therapy for treating multiple myeloma in a subject.

2. Use of a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM), in the manufacture of a medicament for treating multiple myeloma in a subject, wherein the subject has received a therapeutically effective amount of a γ-secretase inhibitor.

3. Use of a γ-secretase inhibitor in the manufacture of a medicament for treating multiple myeloma in a subject, wherein the subject has received a therapeutically effective amount of a T cell that expresses a BCMA-specific binding protein, wherein the BCMA-specific binding protein is a chimeric antigen receptor (CAR) or a tagged chimeric antigen receptor molecule (T-ChARM).

4. The use of any one of claims 1 to 3, wherein the BCMA-specific binding protein is a CAR.

5. The use of any one of claims 1 to 4, wherein the BCMA-specific binding protein is human or humanized.

6. The use of any one of claims 1 to 5, wherein the BCMA-specific binding protein comprises a BCMA-specific scFv, a BCMA-specific scTCR, a domain antibody, or a BCMA ligand or binding portion thereof.

7. The use of claim 6, wherein the BCMA-specific binding protein comprises a scFv comprising heavy chain and light chain variable regions based on BCMA antibody J22.0-xi, J22.9-xi, J6M0, J6M1 , J6M2, J9M0, J9M1, J9M2, 11D5-3, CA8, A7D12.2, C11 D5.3, C12A3.2, C13F12.1, 13C2, 17A5, 83A10, 13A4, 13D2, 14B11, 14E1, 29B11, 29F3, 13A7, CA7, S307118G03, SG1, S332121F02, S332126E04, S322110D07, S336105A07, S335115G01, S335122F05, ET140-3, ET140-24, ET140-37, ET140-40, ET140-54, TBL-CLN1, C4.E2.1, Vicky-1, pSCHLI333, pSCHLI372, or pSCHLI373.

8. The use of any one of claims 1 to 7, wherein the BCMA-specific binding protein comprises a chimeric antigen receptor comprising a hydrophobic portion disposed between an extracellular component and an intracellular component, wherein the extracellular component comprises a BCMA-specific binding domain, the BCMA-specific binding domain comprising (a) a BCMA-specific antigen-binding portion from BCMA antibody J22.0-xi, J22.9-xi, J6M0, 11D5-3, CA8, A7D12.2, C11 D5.3, C12A3.2, C13F12.1, 13C2, 17A5, 83A10, 13A4, 13D2, 14B11, 14E1, 29B11, 29F3, 13A7, CA7, SG1, S307118G03, S332121F02, S332126E04, S322110D07, S336105A07, S335115G01, S335122F05, ET140-3, ET140-24, ET140-37, ET140-40, ET140-54, TBL-CLN1, C4.E2.1, Vicky-1, pSCHLI333, pSCHLI372, or pSCHLI373; or (b) a BCMA ligand or binding portion thereof based on or derived from BAFF or APRIL.

9. The use of any one of claims 1 to 8, wherein the BCMA-specific binding protein comprises a hydrophobic portion disposed between an extracellular component and an intracellular component, wherein the hydrophobic portion comprises a transmembrane domain.

10. The use of claim 9, wherein the transmembrane domain comprises a CD4, CD8, CD28, or CD27 transmembrane domain.

11. The use of any one of claims 1 to 10, wherein the BCMA-specific binding protein comprises an intracellular component comprising an effector domain or a functional portion thereof and a costimulatory domain or a functional portion thereof.

12. The use of claim 11, wherein the intracellular component comprises 4-1BB (CD137), CD3ε, CD3δ, CD3ζ, CD25, CD27, CD28, CD79A, CD79B, CARD11, DAP10, FcRα, FcRβ, FcRγ, Fyn, HVEM, ICOS, Lck, LAG3, LAT, LRP, NKG2D, NOTCH1, NOTCH2, NOTCH3, NOTCH4, OX40 (CD134), ROR2, Ryk, SLAMF1, Slp76, pTα, TCRα, TCRβ, TRIM, Zap70, PTCH2, or a functional portion thereof, or any combination thereof.

13. The use of claim 11 or 12, wherein the effector domain comprises CD3ζ or a functional portion thereof.

14. The use of any one of claims 1 to 13, wherein the BCMA-specific binding protein comprises an intracellular component comprising a costimulatory domain or a functional portion thereof selected from CD27, CD28, 4-1BB (CD137), OX40 (CD134), or any combination thereof.

15. The use of any one of claims 11 to 14, wherein the effector domain or effector portion thereof comprises CD3ζ or functional portion thereof, and one or more costimulatory domain, or a functional portion thereof, of 4-1BB (CD137), CD27, CD28, and OX40 (CD134).

16. The use of any one of claims 1 to 15, wherein the BCMA-specific binding protein comprises an intracellular component comprising (a) 4-1BB or a functional portion thereof and CD3ζ, (b) CD27 or a functional portion thereof and CD3ζ, (c) CD28 or a functional portion thereof and CD3ζ, (d) OX40 or a functional portion thereof and CD3ζ, (e) CD28 or a functional portion thereof, 4-1BB or a functional portion thereof, and CD3ζ, (f) OX40 or a functional portion thereof, 4-1BB or a functional portion thereof, and CD3ζ, or (g) CD28 or a functional portion thereof, OX40 or a functional portion thereof, and CD3ζ.

17. The use of any one of claims 1 to 16, wherein the BCMA-specific binding protein comprises an extracellular component comprising (i) an immunoglobulin hinge region, (ii) a CH2 domain and a CH3 domain, (iii) a CH3 domain, or (iv) any combination thereof, disposed between a BCMA-specific binding domain and a hydrophobic portion.

18. The use of claim 17, wherein the immunoglobulin hinge region is an IgG1 hinge region.

19. The use of claim 17 or 18, wherein the CH2 domain is an IgG1 CH2 domain and the CH3 domain is an IgG1 CH3 domain.

20. The use of any one of claims 1 to 19, wherein the BCMA-specific binding protein comprises an extracellular spacer region comprising a hinge, wherein the spacer region has a length of from 15 to 100 amino acids.

21. The use of any one of claims 1 to 20, wherein the BCMA specific binding protein comprises a hinge region comprising a cluster of differentiation molecule stalk region or a functional variant thereof.

22. The use of any one of claims 1 to 21, wherein:

(i) the BCMA-specific binding protein comprises an intracellular component comprising an effector domain from CD3ζ;

(ii) the BCMA-specific binding protein comprises an intracellular component comprising a costimulatory domain from 4-1BB;

(iii) the BCMA-specific binding protein comprises an intracellular component comprising a costimulatory domain from CD28;

(iv) the BCMA-specific binding protein comprises an extracellular component comprising a hinge region comprising a cluster of differentiation molecule stalk region or a functional variant thereof;

(v) the the BCMA-specific binding protein comprises an extracellular component comprising a spacer region comprising a hinge, wherein the spacer region has a length of from 15 to 100 amino acids; or

(vi) any combination of (i)-(v).

23. The use of any one of claims 1 to 22, wherein the T cell comprises a CD4+ T cell, a CD8+ T cell, a CD4- CD8- double negative T cell, a γδ T cell, or any combination thereof.

24. The use of any one of claims 1 to 23, wherein the T cell comprises a naïve T cell, a central memory T cell, an effector memory T cell, bulk T cells, or any combination thereof.

25. The use of any one of claims 1 to 24, wherein the T cell is a human T cell.

26. The use of any one of claims 1 to 25, wherein the γ-secretase inhibitor comprises:

(i) a small molecule or peptidomimetic compound; and/or

(ii) an antibody or antigen-binding fragment that binds to a γ-secretase complex or a γ-secretase complex protein, such as presenilin 1, presenelin 2, nicastrin, anterior-pharynx-defective 1, and presenilin enhancer 2.

27. The use of claim 26, wherein the γ-secretase inhibitor comprises a small molecule.

28. The use of any one of claims 1 to 26, wherein the γ-secretase inhibitor comprises LY411575, semagacestat, avagacestat, DAPT, BMS-906024, BMS-986115, MK-0752, PF-03084014, RO4929097, or YO-01027.

29. The use of claim 26, wherein the γ-secretase inhibitor comprises a nicastrin-specific binding protein.

30. The use of claim 29, wherein the nicastrin-specific binding protein comprises scFvG9, antibody A5226A, antibody 2H6, or antibody 10C11.

31. The use of any one of claims 1 to 30, wherein the BCMA-specific binding protein comprises a variable domain comprising CDR1, CDR2, and CDR3 of the amino acid sequence of any one of SEQ ID NOS.:14-16 and a variable domain comprising CDR1, CDR2, and CDR3 of the amino acid sequence of any one of SEQ ID NOS.:17-21.

32. The use of any one of claims 1 to 31, wherein the method further comprises pre-conditioning the subject with an immunosuppressive regimen prior to or concurrent with the T cell and the γ-secretase inhibitor.

33. The use of claim 32, wherein the immunosuppressive regimen comprises a non-myeloablative treatment or a myeloablative treatment.

34. The use of claim 33, wherein the non-myeloablative treatment comprises cyclophosphamide or cyclophosphamide in combination with fludarabine.

35. The use of any one of claims 1 to 34, wherein the T cell and the γ-secretase inhibitor are to be administered sequentially.

36. The use of any one of claims 1 to 34, wherein the T cell and the γ-secretase inhibitor are to be administered concurrently.

37. The use of claim 36, wherein the T cell and the γ-secretase inhibitor are formulated together.

38. The use of any one of claims 1 to 37, wherein the T cell is to be administered parenterally and the γ-secretase inhibitor is to be administered orally.

39. The use of any one of claims 1 to 38, wherein the BCMA-specific binding protein comprises a BCMA-specific scFv or a BCMA-specific domain antibody.

40. The use of claim 39, wherein the BCMA-specific binding protein comprises an intracellular component comprising: (1) an effector domain from CD3ζ and (2) a costimulatory domain from 4-1BB.

41. The use of claim 39, wherein the BCMA-specific binding protein comprises an intracellular component comprising: (1) an effector domain from CD3ζ and (2) a costimulatory domain from CD28.

42. The use of any one of claims 1 to 40, wherein the BCMA-specific binding protein is a T-ChARM and wherein the extracellular domain of the T-ChARM comprises a Strep Tag.

43. The use of claim 42, wherein the extracellular domain of the T-ChARM comprises two, three, four, five, six, seven, eight, or nine tag cassettes.

44. The use of any one of claims 1 and 3 to 43, wherein the γ-secretase inhibitor is to be administered to the subject at least once subsequent to a first administration of the T cell.

45. The use of claim 44, wherein the γ-secretase inhibitor is to be administered at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50 times subsequent to the first administration of the T cell.

46. The use of any one of claims 1 and 3 to 45, wherein the γ-secretase inhibitor is to be administered at a concentration of about 30 mg/kg.

47. The use of any one of claims 1 to 46, wherein the BCMA-specific binding protein is multispecific.

48. The use of claim 47, wherein the BCMA-specific binding protein is bispecific.

49. The use of any one of claims 1 to 48, wherein the T cell comprises a CD4+ T cell, a CD8+ T cell, naïve T cell, a central memory T cell, an effector memory T cell, bulk T cells, or any combination thereof.

50. The use of any one of claims 1 to 49, wherein a lower amount of the γ-secretase inhibitor and/or of the T cell is used as compared to the amount of the γ-secretase inhibitor and/or of the T cell, respectively, used to prepare a monotherapy comprising the γ-secretase inhibitor or the T cell for treating the multiple myeloma.