(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 a BCMA-specific binding protein and a therapeutically effective amount of a γ-secretase inhibitor in the manufacture of a combination therapy for treating (i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or (ii) an autoimmune disease or disorder associated with BCMA expression, in a subject having or suspected having the disease or disorder.

In another aspect, the present disclosure refers to the use of a BCMA-specific binding protein in the manufacture of a medicament for treating (i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or (ii) an

autoimmune disease or disorder associated with BCMA expression, in a subject having or suspected having the disease or disorder, 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 (i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or (ii) an autoimmune disease or disorder associated with BCMA expression, in a subject having or suspected having the disease or disorder, wherein the subject has received a therapeutically effective amount of a BCMA-specific binding protein.

In yet another aspect, the present disclosure refers to a kit for treating a hematologic and/or autoimmune disease or disorder, comprising (a) a unit dosage of a BCMA-specific binding protein, and (b) a unit dosage of a γ-secretase inhibitor.

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 a BCMA-specific binding protein and a therapeutically effective amount of a γ-secretase inhibitor in the manufacture of a combination therapy for treating

(i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or

(ii) an autoimmune disease or disorder associated with BCMA expression,

in a subject having or suspected having the disease or disorder.

2. Use of a BCMA-specific binding protein in the manufacture of a medicament for treating

(i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or

(ii) an autoimmune disease or disorder associated with BCMA expression,

in a subject having or suspected having the disease or disorder, 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

(i) a proliferative disease or disorder associated with BCMA expression, such as a cancer, and/or

(ii) an autoimmune disease or disorder associated with BCMA expression,

in a subject having or suspected having the disease or disorder, wherein the subject has received a therapeutically effective amount of a BCMA-specific binding protein.

4. The use of any one of claims 1 to 3, wherein the BCMA-specific binding protein comprises a BCMA-specific antibody or antigen-binding portion thereof, a

chimeric antigen receptor (CAR), or a tagged chimeric antigen receptor molecule (T-ChARM).

5. The use of claim 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, 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 claim 8, 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 8 to 10, wherein the intracellular component comprises an effector domain or a functional portion thereof, a costimulatory domain or a functional portion thereof, or any combination 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 in any combination thereof.

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

14. The use of any one of claims 8 to 13, wherein the intracellular component comprises 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 8 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 8 to 15, wherein the intracellular component comprises (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 8 to 16, wherein the extracellular component further comprises an immunoglobulin hinge region, a CH2 domain and a CH3 domain, a CH3 domain, or any combination thereof, disposed between the BCMA-specific binding domain and the 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 is encoded by an exogenous polynucleotide and is expressed in a host cell.

21. The use of claim 20, wherein the host cell is a human immune system cell.

22. The use of claim 21, wherein the human immune system cell is a CD4+ T cell, a CD8+ T cell, a CD4- CD8- double negative T cell, a γδ T cell, a natural killer cell, a dendritic cell, or any combination thereof.

23. The use according to claim 22, wherein the human immune system cell is a T cell, wherein the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, bulk T cells, or any combination thereof.

24. The use of any one of claims 1 to 23, wherein the γ-secretase inhibitor comprises LY411575, semagacestat, avagacestat, DAPT, BMS-906024, BMS-986115, MK-0752, PF-03084014, RO4929097, or YO-01027.

25. The use of claim 24, wherein the γ-secretase inhibitor is a nicastrin-specific binding protein.

26. The use of claim 25, wherein the nicastrin-specific binding protein is scFvG9, antibody A5226A, antibody 2H6, or antibody 10C11.

27. The use of any one of claims 1 to 26, 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.

28. The use of any one of claims 1 to 27, wherein the method further comprises pre-conditioning the subject with an immunosuppressive regimen prior to or concurrent with the BCMA-specific binding protein and the γ-secretase inhibitor.

29. The use of claim 28, wherein the immunosuppressive regimen comprises a non-myeloablative treatment or a myeloablative treatment.

30. The use of claim 29, wherein the non-myeloablative treatment comprises cyclophosphamide or cyclophosphamide in combination with fludarabine.

31. The use of any one of claims 1 to 30, wherein the BCMA-specific binding protein and the γ-secretase inhibitor are administered sequentially.

32. The use of any one of claims 1 to 30, wherein the BCMA-specific binding protein and the γ-secretase inhibitor are administered concurrently.

33. The use of claim 32, wherein the BCMA-specific binding protein and the γ-secretase inhibitor are formulated together.

34. The use of any one of claims 1 to 33, wherein the BCMA-specific binding protein is to be administered parenterally and the γ-secretase inhibitor is to be administered orally.

35. The use according to any one of claims 1 to 34, wherein the proliferative disease or disorder is a hematologic cancer or a solid cancer.

36. The use according to claim 35, wherein the hematologic cancer is selected from the group consisting of multiple myeloma, plasmacytoma, plasma cell leukemia, Waldenström's macroglobulinemia, B cell lymphoma, and lymphoplasmactyic lymphoma.

37. The use according to claim 35, wherein the solid cancer is adenocarcinoma of the breast or bronchogenic carcinoma of the lung.

38. The use according to any one of claims 1 to 34, wherein the autoimmune disease is selected from the group consisting of arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, polychondritis, psoriatic arthritis, psoriasis, dermatitis, polymyositis/dermatomyositis, inclusion body myositis, inflammatory myositis, toxic epidermal necrolysis, systemic scleroderma and sclerosis, CREST syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, respiratory distress syndrome, adult respiratory distress syndrome (ARDS), meningitis, encephalitis, uveitis, colitis, glomerulonephritis, allergic conditions, eczema, asthma, conditions involving infiltration of T cells and chronic inflammatory responses, atherosclerosis, autoimmune myocarditis, leukocyte adhesion deficiency, systemic lupus erythematosus (SLE), subacute cutaneous lupus erythematosus, discoid lupus, lupus myelitis, lupus cerebritis, juvenile onset diabetes, multiple sclerosis, allergic encephalomyelitis, neuromyelitis optica, rheumatic fever, Sydenham's chorea, immune

responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, tuberculosis, sarcoidosis, granulomatosis including Wegener's granulomatosis and Churg-Strauss disease, agranulocytosis, vasculitis (including hypersensitivity vasculitis/angiitis, ANCA and rheumatoid vasculitis), aplastic anemia, Diamond Blackfan anemia, immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), pernicious anemia, pure red cell aplasia (PRCA), Factor VIII deficiency, hemophilia A, autoimmune neutropenia, pancytopenia, leukopenia, diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorders, multiple organ injury syndrome, myasthenia gravis, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, anti-phospholipid antibody syndrome, allergic neuritis, Behcet disease, Castleman's syndrome, Goodpasture's syndrome, Lambert-Eaton Myasthenic Syndrome, Reynaud's syndrome, Sjogren's syndrome, Stevens-Johnson syndrome, solid organ transplant rejection, graft versus host disease (GVHD), bullous pemphigoid, pemphigus, autoimmune polyendocrinopathies, seronegative spondyloarthropathies, Reiter's disease, stiff-man syndrome, giant cell arteritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or IgM mediated neuropathy, idiopathic thrombocytopenic purpura (ITP), thrombotic throbocytopenic purpura (TTP), Henoch-Schonlein purpura, autoimmune thrombocytopenia, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, primary hypothyroidism, autoimmune endocrine diseases including autoimmune thyroiditis, chronic thyroiditis (Hashimoto's Thyroiditis), subacute thyroiditis, idiopathic hypothyroidism, Addison's disease, Grave's disease, autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), Type I diabetes also referred to as insulin-dependent diabetes mellitus (IDDM) and Sheehan's syndrome; autoimmune hepatitis, lymphoid interstitial pneumonitis (HIV), bronchiolitis obliterans (non-transplant), non-specific interstitial pneumonia (NSIP), Guillain-Barré Syndrome, large vessel vasculitis (including polymyalgia rheumatica and giant cell (Takayasu's) arteritis), medium vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa), polyarteritis nodosa (PAN) ankylosing spondylitis, Berger's disease (IgA nephropathy), rapidly progressive glomerulonephritis, primary biliary cirrhosis, Celiac sprue (gluten enteropathy),

cryoglobulinemia, cryoglobulinemia associated with hepatitis, amyotrophic lateral sclerosis (ALS), coronary artery disease, familial Mediterranean fever, microscopic polyangiitis, Cogan's syndrome, Whiskott-Aldrich syndrome, and thromboangiitis obliterans.

39. A kit for treating a hematologic and/or autoimmune disease or disorder, comprising (a) a unit dosage of a BCMA-specific binding protein, and (b) a unit dosage of a γ-secretase inhibitor.

40. The kit of claim 39, further comprising: a CD20-specific binding protein such as rituximab, ofatumumab, ocrelizumab; a CD19-specific binding protein; a CD45-specific binding protein; a CD38-specific binding protein; a cytokine; a chemokine; a growth factor; a chemotherapeutic agent; or a radiotherapeutic agent.

41. The use of any one of claims 8-38, wherein the chimeric antigen receptor comprises a T-ChARM and wherein the extracellular domain of the T-ChARM comprises a Strep Tag.

42. The use of claim 41, wherein the extracellular domain of the T-ChARM comprises two, three, four, five, six, seven, eight, or nine tag cassettes.

43. The use of any one of claims 1-38, 41, or 42, wherein the γ-secretase inhibitor is to be administered to the subject at least once subsequent to a first administration of the BCMA-specific binding protein.

44. The use of claim 43, wherein the γ-secretase inhibitor is 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 BCMA-specific binding protein.

45. The use of any one of claims 1-38 and 41-44, wherein the γ-secretase inhibitor is administered at a concentration of about 30 mg/kg.

46. The use of any one of claims 1-7, wherein the BCMA-specific binding protein comprises an antibody or an antigen-binding portion thereof that is coupled to a cytotoxic agent.

47. The use of any one of claims 1-7 or 46, wherein the BCMA-specific binding protein is multispecific.

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