multiple myeloma each year and almost 11,000 MM patients die each year. Despite advances in therapy, multiple myeloma remains an incurable disease, see Jemal A, *et al. CA Cancer J Clin.* 2008;58:71-96; Kyle RA, *et al. Mayo Clin Proc.* 2003;778:21-33; Bergsagel DE, *et al. Blood.* 1999, 94:1174-1182.

Summary

In a first aspect, the present invention refers to an isolated BCMA-binding antibody, or a BCMA-binding fragment thereof, wherein the antibody or BCMA-binding fragment thereof comprises a Vh-CDR1 comprising SEQ ID NO:4, a Vh-CDR2 comprising SEQ ID NO:5, a Vh-CDR3 comprising SEQ ID NO:6, a Vl-CDR1 comprising SEQ ID NO:106, a Vl-CDR2 comprising SEQ ID NO:107, and a Vl-CDR3 comprising SEQ ID NO:108. In a second aspect, the present invention refers to a pharmaceutical composition comprising the antibody or fragment of the present invention, a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, and/or a preservative. In a third aspect, the present invention refers to a use of a composition of the present invention in the manufacture of a medicament for treating a disease, wherein the disease is selected from the group consisting of: B-cell cancers, multiple myeloma, malignant plasma cell neoplasms, Kahler's disease and Myelomatosis; Plasma cell leukemia; Plasmacytoma; B-cell prolymphocytic leukemia; Hairy cell leukemia; B-cell non-Hodgkin's lymphoma (NHL); Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML); Acute lymphocytic leukemia (ALL); Chronic lymphocytic leukemia (CLL); Follicular lymphoma (including follicular non-Hodgkin's lymphoma types); Burkitt's lymphoma (Endemic Burkitt's lymphoma; Sporadic Burkitt's lymphoma); Marginal zone lymphoma (Mucosa-Associated Lymphoid Tissue; MALT / MALToma; Monocytoid B cell lymphoma; Splenic lymphoma with villous lymphocytes); Mantle cell lymphoma; Large cell lymphoma (Diffuse large cell; Diffuse Mixed Cell; Immunoblastic Lymphoma; Primary Mediastinal B Cell Lymphoma; Angiocentric Lymphoma - pulmonary B cell); Small lymphocytic lymphoma (SLL); Precursor B-lymphoblastic lymphoma; Myeloid leukemia (granulocytic; myelogenous; Acute myeloid leukemia; Chronic myeloid leukemia; Subacute myeloid leukemia; Myeloid sarcoma; Chloroma; Granulocytic sarcoma; Acute promyelocytic leukemia; Acute myelomonocytic leukemia); Waldenstrom's macroglobulinemia, and other B-cell lymphoma. In a fourth aspect, the present invention refers to an isolated polynucleotide, wherein said polynucleotide encodes the light chain, the heavy chain, or the light chain and the heavy chain of the antibody or fragment of the present invention. In a fifth aspect, the present invention refers to a plasmid, comprising the polynucleotide of the present invention. In a sixth aspect, the present invention refers to an isolated cell, comprising said plasmid of claim 17, wherein said cell is a prokaryotic cell; a eukaryotic cell; a mammalian cell; an insect cell; or a CHO cell. In a seventh aspect, the present invention refers to a method of making a BCMA-binding antibody, or a BCMA-binding fragment thereof, comprising incubating said isolated cell of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the amino acid sequence of human BCMA (SEQ ID NO:285) and cynomolgus (Macaca fascicularis) BCMA (SEQ ID NO:286).

FIGURE 2 is a schematic of one embodiment of an antibody drug conjugate showing the structures of an exemplary linker and toxin.

FIGURE 3 shows that BCMA mRNA is expressed on >99% of multiple myeloma patient samples.

FIGURES 4A and B are schematics of the monoclonal antibody generation, screening, and characterization for the two campaigns.

FIGURES 5A-C are data tables for the monoclonal antibody generation, screening, and characterization for the two campaigns.

FIGURE 6 shows binding of the 2A1 and 1E1 mAbs to the myeloma cell line H929.

FIGURE 7 shows the 2A1 mAb bound BCMA on various myeloma and B-cell lines.

FIGURE 8 is a graph of the ADCC activity for the 2A1 and 1E1 antibodies (EC_{50} of 11 ng/ml for 2A1 and 76 ng/ml for 1E1).

FIGURE 9 shows that the 2A1 antibody was readily internalized following binding to BCMA on H929 cells.

FIGURE 10 is various 2A1-MCC-DM1 ADCs analyzed by mass spectrometry.

FIGURE 11 depicts two different antibodies (2A1 and 1E) that were conjugated with different linkers and maytansine molecules and analyzed for their capacity to kill myeloma cells.

FIGURES 12A-F shows 2A1-MCC-DM1 ADC was tested against various multiple myeloma cell lines, including H929, U266, MMIR, MMIS, the EW36 B-cell lymphoma cell line, and the RAMOS Burkitt's lymphoma cell line.

FIGURE 13 graphically illustrates that various cell lines exposed to free DM1 are in fact killed by free DM1.

FIGURES 14A and B show the Tm for various 2A1 mAb covariance muteins.

FIGURE 15 is a graph showing the binding of various 2A1 mAb covariance muteins to H919 cells.

FIGURES 16A and B show that some 2A1 mutein antibodies retained comparable binding to BCMA relative to parental 2A1 (2A1WT), whereas the 2A1 covariance 3, 8, 9 and 11-19 antibodies had reduced binding to BCMA.

FIGURE 17 shows the comparative ADCC activity of various 2A1 mAb covariance muteins.

We claim:

1. An isolated BCMA-binding antibody, or a BCMA-binding fragment thereof, wherein the antibody or BCMA-binding fragment thereof comprises a Vh-CDR1 comprising SEQ ID NO:4, a Vh-CDR2 comprising SEQ ID NO:5, a Vh-CDR3 comprising SEQ ID NO:6, a Vl-CDR1 comprising SEQ ID NO:106, a Vl-CDR2 comprising SEQ ID NO:107, and a Vl-CDR3 comprising SEQ ID NO:108.

2. The antibody or fragment of claim 1, wherein said antibody or fragment comprises an Ab-1Vl domain comprising SEQ ID NO:240 and an Ab-1Vh domain comprising SEQ ID NO:206.

3. The antibody or fragment of claim 1, wherein said antibody or fragment comprises two Ab-1 light chains comprising SEQ ID NO:280 and two Ab-1 heavy chains comprising SEQ ID NO:274.

4. The antibody or fragment of claim 1, wherein said antibody or fragment:
   a. is human;
   b. is chimeric;
   c. is monoclonal;
   d. specifically binds human BCMA and cross-reacts to cynomolgus BCMA;
   e. does not specifically bind to TACI or BAFF-R;
   f. binds BCMA on the surface of human myeloma cells;
   g. binds BCMA on the surface of human multiple myeloma cells; or
   h. binds BCMA on the surface of human cells and is internalized by said cells.

5. The antibody or fragment of claim 1, wherein said antibody or fragment further comprises a linker wherein said linker is N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate.

6. The antibody or fragment of claim 1, wherein said antibody or fragment further comprises DM1, DM3 or DM4.

7. The antibody or fragment of claim 1, wherein said antibody or fragment is covalently bound to a linker, and said linker is covalently bound to a drug, wherein said linker is N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate and said drug is DM1, DM3, or DM4.

8. The antibody or fragment of claim 7, wherein said antibody or fragment has a drug to antibody ratio of between 1 and 10.

9. The antibody or fragment of claim 8, wherein said antibody or fragment has a drug to antibody ratio of between 2 and 5.

10. A pharmaceutical composition comprising the antibody or fragment of claim 1, a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, and/or ~~a~~ preservative.

11. Use of a composition of claim 10 in the manufacture of a medicament for treating a disease, wherein the disease is selected from the group consisting of: B-cell cancers, multiple myeloma, malignant plasma cell neoplasms, Kahler's disease and Myelomatosis; Plasma cell leukemia; Plasmacytoma; B-cell prolymphocytic leukemia; Hairy cell leukemia; B-cell non-Hodgkin's lymphoma (NHL); Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML); Acute lymphocytic leukemia (ALL); Chronic lymphocytic leukemia (CLL); Follicular lymphoma (including follicular non-Hodgkin's lymphoma types); Burkitt's lymphoma (Endemic Burkitt's lymphoma; Sporadic Burkitt's lymphoma); Marginal zone lymphoma (Mucosa-Associated Lymphoid Tissue; MALT / MALToma; Monocytoid B cell lymphoma; Splenic lymphoma with villous lymphocytes); Mantle cell lymphoma; Large cell lymphoma (Diffuse large cell; Diffuse Mixed Cell; Immunoblastic Lymphoma; Primary Mediastinal B Cell Lymphoma; Angiocentric Lymphoma - pulmonary B cell); Small lymphocytic lymphoma (SLL); Precursor B-lymphoblastic lymphoma; Myeloid leukemia (granulocytic; myelogenous; Acute myeloid leukemia; Chronic myeloid leukemia; Subacute myeloid leukemia; Myeloid sarcoma; Chloroma; Granulocytic sarcoma; Acute promyelocytic leukemia; Acute myelomonocytic leukemia); Waldenstrom's macroglobulinemia, and other B-cell lymphoma.

12. The use of claim 11, wherein the medicament is to be used in combination with one of more of the following: chemotherapy, radiation therapy, surgery, administration of proteasome inhibitors, administration of corticosteroids, or administration of stem cell transplants.

13. An isolated polynucleotide, wherein said polynucleotide encodes the light chain, the heavy chain, or the light chain and the heavy chain of the antibody or fragment of claim 1.

14. The polynucleotide of claim 13, wherein said polynucleotide sequence comprises:
a. a Vh-CDR1 comprising SEQ ID NO:1, a Vh-CDR2 comprising SEQ ID NO:2, and a Vh-CDR3 comprising SEQ ID NO:3~~,~~; and/or
b. a Vl-CDR1 comprising SEQ ID NO:103, a Vl-CDR2 comprising SEQ ID NO:104, and a Vl-CDR3 comprising SEQ ID NO:105.

15. The polynucleotide of claim 13, wherein said polynucleotide sequence comprises an Ab-1Vl comprising SEQ ID NO:239 and/or an Ab-1Vh comprising SEQ ID NO:205.

16. The polynucleotide of claim 13, wherein said polynucleotide sequence comprises a light chain comprising SEQ ID NO:279 and/or a heavy chain comprising SEQ ID NO:273.

17. A plasmid, comprising the polynucleotide of claim 13.

18. The plasmid of claim 13, wherein said plasmid is an expression vector.

19. An isolated cell, comprising said plasmid of claim 17, wherein said cell is:

a. a prokaryotic cell;

b. a eukaryotic cell;

c. a mammalian cell;

d. an insect cell; or

e. a CHO cell.

20. A method of making a BCMA-binding antibody, or a BCMA-binding fragment thereof, comprising incubating said isolated cell of claim 19 to express said antibody or polypeptide.