

mouse μ gene results in the production of a heavy chain-only antibody, devoid of light chain, in mammalian cell culture. The antibodies produced retained VH binding specificity and effector functions.

[0007] Heavy chain antibodies with a high specificity and affinity can be generated against a variety of antigens through immunization (van der Linden, R. H., et al. *Biochim. Biophys. Acta*. 1431, 37-46 (1999)) and the VHH portion can be readily cloned and expressed in yeast (Frenken, L. G. J., et al. *J. Biotechnol.* 78, 11-21 (2000)). Their levels of expression, solubility and stability are significantly higher than those of classical F(ab) or Fv fragments (Ghahroudi, M. A. et al. *FEBS Lett.* 414, 521-526 (1997)).

[0008] Mice in which the λ (lambda) light (L) chain locus and/or the λ and κ (kappa) L chain loci have been functionally silenced and antibodies produced by such mice are described in U.S. Patent Nos. 7,541,513 and 8,367,888. Recombinant production of heavy chain-only antibodies in mice and rats has been reported, for example, in WO2006008548; U.S. Application Publication No. 20100122358; Nguyen et al., 2003, *Immunology*; 109(1), 93-101; Brüggemann et al., *Crit. Rev. Immunol.*; 2006, 26(5):377-90; and Zou et al., 2007, *J Exp Med*; 204(13): 3271-3283. The production of knockout rats via embryo microinjections of zinc-finger nucleases is described in Geurts et al., 2009, *Science*, 325(5939):433. Soluble heavy chain-only antibodies and transgenic rodents comprising a heterologous heavy chain locus producing such antibodies are described in U. S. Patent Nos. 8,883,150 and 9,365,655. CAR-T structures comprising single-domain antibodies as binding (targeting) domain are described, for example, in Iri-Sofla et al., 2011, *Experimental Cell Research* 317:2630-2641 and Jamnani et al., 2014, *Biochim Biophys Acta*, 1840:378-386.

SUMMARY

[0009] The present disclosure concerns anti-BCMA antibodies.

[0010] Disclosed is a heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising:

(a) a CDR1 having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 1 to 4; and/or

(b) a CDR2 having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 5 to 18 and 54; and/or

(c) a CDR3 having at least 95% sequence identity to SEQ ID NO: 19.

[0010a] In one aspect, there is provided a human idotype heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising: (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1 to 4; and (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5 to 18 and 54; and (c) a CDR3 sequence comprising the sequence of SEQ ID NO: 19.

[0011] In one example, the CDR1, CDR2, and CDR3 sequences are present in a human framework.

[0012] In another example, the anti-BCMA heavy chain-only antibody further comprises a heavy chain constant region sequence in the absence of a CH1 sequence.

[0013] In yet another example, the heavy chain-only antibody comprises:

- (a) a sequence selected from the group consisting of SEQ ID NOs: 1 to 4; and/or
- (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5 to 18 and 54;

and/or

- (c) a CDR3 of SEQ ID NO: 19.

[0014] In a further example, the anti-BCMA heavy chain-only antibody comprises:

- (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1 to 4; and
- (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5 to 18 and 54;

and

- (c) a CDR3 of SEQ ID NO: 19.

[0015] In a still further example, the heavy chain-only anti-BCMA antibody comprises a heavy chain variable region having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 20 to 53.

[0016] In another example, the heavy chain-only anti-BCMA antibody comprises a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 20 to 53.

[0017] Disclosed is a heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising a heavy chain variable comprising

- (a) a CDR1 sequence of the formula:

G F T F X1 X2 Y A (SEQ ID NO: 55)

where

X1 is S or T; and

X2 is S, N or R; and

- (b) CDR2 sequence of the formula:

X3 X4 X5 X6 G X7 X8 X9 (SEQ ID NO: 56)

where

X3 is I or L;

X4 is S, T, I or V;

X5 is G or E;

X6 is S, G, N or D;

X7 is G, D or A;

X8 is S, T or N;

X9 is T or S, and

(c) A CDR3 sequence of SEQ ID NO: 19
in a human VH framework.

[0017a] In another aspect, there is provided a human idiotype heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising: (a) a CDR1 sequence comprising the formula: G F T F X1 X2 Y A (SEQ ID NO: 55) where X1 is S or T; and X2 is S, N or R; and (b) a CDR2 sequence comprising the formula: X3 X4 X5 X6 G X7 X8 X9 (SEQ ID NO: 56) where

X3 is I or L; X4 is S, T, I or V; X5 is G or E; X6 is S, G, N or D; X7 is G, D or A; X8 is S, T or N; X9 is T or S; and (c) a CDR3 comprising the sequence of SEQ ID NO: 19, in a human VH framework.

[0018] Disclosed is a heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework wherein the CDR sequences are a sequence with at least 95% identity to a CDR sequence selected from the group consisting of SEQ ID NOs:1-19 and 54.

[0019] In one example, such antibody comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework wherein the CDR sequences are selected from the group consisting of SEQ ID NOs:1-19 and 54.

[0020] Disclosed is a heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising

(a) a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 5; and a CDR3 of SEQ ID NO: 19;

or

(b) a CDR1 of SEQ ID NO: 2, a CDR2 of SEQ ID NO: 54; and a CDR3 of SEQ ID NO: 19
in a human VH framework.

[0021] In one example, the heavy chain-only antibody is multi-specific, such as bispecific.

[0022] In another example, the heavy chain-only antibody has binding affinity to two different BCMA proteins.

[0023] In yet another example, the heavy chain-only antibody has binding affinity to two different epitopes on the same BCMA protein.

[0024] In a further example, the heavy chain-only antibody has binding affinity to an effector cell.

[0025] In a still further example, the heavy chain-only antibody has binding affinity to a T-cell antigen.

[0026] In another example, the heavy chain-only antibody has binding affinity to CD3.

[0027] In a different example, the heavy chain-only antibody hereinabove described is in a CAR-T format.

[0028] Disclosed is a pharmaceutical composition comprising an anti-BCMA heavy chain-only antibody herein.

[0028a] In another aspect, there is provided a pharmaceutical composition comprising a human idiotype heavy chain-only antibody disclosed herein.

[0029] Disclosed is a method for the treatment of a B-cell disorder characterized by the expression of BCMA comprising administering to a subject with such disorder an anti-BCMA heavy chain-only antibody herein, or a pharmaceutical composition comprising such antibody.

[0029a] In another aspect, there is provided use of a human idiotype heavy chain-only antibody disclosed herein, in the preparation of a medicament for the treatment of a B-cell disorder characterized by the expression of BCMA in an individual. In another aspect, there is provided the human idiotype heavy chain-only antibody disclosed herein, or the pharmaceutical composition disclosed herein, for use the treatment of a B-cell disorder characterized by the expression of BCMA in an individual.

[0030] In various examples, the B-cell disorder may, for example, be multiple myeloma or systemic lupus erythematosus.

[0030a] In another aspect, there is provided a polynucleotide encoding an antibody disclosed herein.

[0031] Disclosed is a polynucleotide encoding an anti-BCMA heavy chain-only antibody herein.

[0031a] In another aspect, there is provided a vector comprising the polynucleotide disclosed herein.

[0032] Disclosed is a vector comprising a polynucleotide encoding an anti-BCMA heavy chain-only antibody herein.

[0032a] In another aspect, there is provided a cell comprising the vector disclosed herein.

[0033] Disclosed is a cell comprising a polynucleotide encoding an anti-BCMA heavy chain-only antibody herein, or a vector comprising such polynucleotide.

[0034] Disclosed is a method of producing an antibody herein, comprising growing a cell as hereinabove described under conditions permissive for expression of the antibody, and isolating the antibody from the cells.

[0034a] In another aspect, there is provided a method of producing a human idiotype heavy chain-only antibody disclosed herein, comprising growing a cell disclosed herein under conditions permissive for expression of the protein, and isolating the antibody from the cell.

[0035] Disclosed is a method of making an anti-BCMA heavy chain-only antibody as described herein, comprising immunizing a UniRat animal with BCMA and identifying BCMA-binding heavy chain sequences.

[0035a] In another aspect, there is provided a method of making a human idiotype heavy chain-only antibody disclosed herein comprising immunizing a transgenic rat expressing heavy chain antibodies with a human VDJ region, with BCMA and identifying BCMA-binding heavy chain sequences.

[0036] These and further aspects will be further explained in the rest of the disclosure, including the Examples.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] FIG. 1 shows the CDR1, CDR2 and CDR3 amino acid sequences of 34 heavy chain-only anti-BCMA antibodies of the invention.

[0038] FIG. 2 shows the heavy chain variable region sequences of 34 heavy chain-only anti-BCMA antibodies of the invention.

[0039] FIG. 3: Heatmap summary of the antibody binding activities of 34 heavy chain-only anti-BCMA antibodies expressed in HEK 293 cells. Red indicates strong binding while blue represents weak or negative binding results. Cell binding assays were run on all 34 antibodies and were shown to bind H929 cells. Two antibodies encoding either VH sequence 308607 or VH sequence 308915 were tested for binding to an untagged human BCMA ECD fragment, and two off-target protein controls including human IgG1 and a baculovirus protein extract (BVP), and BCMA+ MM cell line RPMI8226. Two UniAbs were also evaluated for the ability to block APRIL (ligand)/BCMA (receptor) binding in a recombinant protein ELISA-style assay.

[0040] FIG. 4: Serum binding activity against the immunogen and other on- and off-target proteins. A single 1:500 dilution of d35 serum from a subset of the animals was assayed for binding activity to a series of proteins in a standard ELISA assay. On-target proteins include human BCMA Fc region (huBCMA-Fc), a cyno BCMA ECD fused to a human Fc sequence (cyBCMA), and huBCMA from two

CLAIMS:

1. A human idiotype heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising:
 - (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1 to 4; and
 - (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5 to 18 and 54;and
 - (c) a CDR3 sequence comprising the sequence of SEQ ID NO: 19.
2. The human idiotype heavy chain-only antibody of claim 1, wherein said CDR1, CDR2, and CDR3 sequences are present in a human framework.
3. The human idiotype heavy chain-only antibody of claim 1, further comprising a heavy chain constant region sequence in the absence of a CH1 sequence.
4. The human idiotype heavy chain-only antibody of any one of claims 1-3, comprising a heavy chain variable region having at least 95% sequence identity to any of the sequences of SEQ ID NOs: 20 to 53.
5. The human idiotype heavy chain-only antibody of claim 4, comprising a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 20 to 53.
6. A human idiotype heavy chain-only antibody binding to human B-Cell Maturation Antigen (BCMA) comprising a heavy chain variable region comprising:
 - (a) a CDR1 sequence comprising the formula:

G F T F X1 X2 Y A (SEQ ID NO: 55)

where

X1 is S or T; and

X2 is S, N or R; and

- (b) a CDR2 sequence comprising the formula:

X3 X4 X5 X6 G X7 X8 X9 (SEQ ID NO: 56)

where

X3 is I or L;

X4 is S, T, I or V;

X5 is G or E;

X6 is S, G, N or D;

X7 is G, D or A;

X8 is S, T or N;

X9 is T or S; and

(c) a CDR3 comprising the sequence of SEQ ID NO: 19,
in a human VH framework.

7. The human idiotype heavy chain-only antibody of claim 6, comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, wherein the CDR sequences are selected from the group consisting of SEQ ID NOs: 1-19 and 54.

8. The human idiotype heavy chain-only antibody of claim 6, comprising a heavy chain variable region comprising:

(a) a CDR1 sequence comprising SEQ ID NO: 1, a CDR2 sequence comprising SEQ ID NO: 5; and a CDR3 sequence comprising SEQ ID NO: 19; or

(b) a CDR1 sequence comprising SEQ ID NO: 2, a CDR2 sequence comprising SEQ ID NO: 54; and a CDR3 sequence comprising SEQ ID NO: 19
in a human VH framework; or

(c) a CDR1 sequence comprising SEQ ID NO: 3, a CDR2 sequence comprising SEQ ID NO: 7; and a CDR3 sequence comprising SEQ ID NO: 19.

9. The human idiotype heavy chain-only antibody of any one of claims 1 to 8, which is multi-specific.

10. The human idiotype heavy chain-only antibody of claim 9, which is bispecific.

11. The human idiotype heavy chain-only antibody of claim 10, which has binding affinity to two different epitopes on the same BCMA protein.

12. The human idiotype heavy chain-only antibody of claim 9, having binding affinity to an effector cell.
13. The human idiotype heavy chain-only antibody of claim 9, having binding affinity to a T-cell antigen.
14. The human idiotype heavy chain-only antibody of claim 13, having binding affinity to CD3.
15. The human idiotype heavy chain-only antibody of any one of claims 1 to 11, which is in a CAR-T format.
16. A pharmaceutical composition comprising a human idiotype heavy chain-only antibody of any one of claims 1 to 15.
17. Use of a human idiotype heavy chain-only antibody of any one of claims 1-15, in the preparation of a medicament for the treatment of a B-cell disorder characterized by the expression of BCMA in an individual.
18. The human idiotype heavy chain-only antibody of any one of claims 1-15, or the pharmaceutical composition of claim 16, for use the treatment of a B-cell disorder characterized by the expression of BCMA in an individual.
19. The human idiotype heavy chain-only antibody or the pharmaceutical composition of claim 18 or the use of claim 17, wherein the individual is human.
20. The use of claim 17, the human idiotype heavy chain-only antibody or the pharmaceutical composition of claim 18, or the human idiotype heavy chain-only antibody or the pharmaceutical composition or the use of claim 19, wherein the B-cell disorder is multiple myeloma.
21. The use of claim 17, the human idiotype heavy chain-only antibody or the pharmaceutical composition of claim 18, or the human idiotype heavy chain-only antibody or the pharmaceutical composition or the use of claim 19, wherein the B-cell disorder is systemic lupus erythematosus.
22. A polynucleotide encoding an antibody of any of claims 1 to 15.

23. A vector comprising the polynucleotide of claim 22.
24. A cell comprising the vector of claim 23.
25. A method of producing a human idiotype heavy chain-only antibody of any of claims 1 to 15, comprising growing a cell according to claim 24 under conditions permissive for expression of the protein, and isolating the antibody from the cell.
26. A method of making a human idiotype heavy chain-only antibody of any one of claims 1 to 15 comprising immunizing a transgenic rat expressing heavy chain antibodies with a human VDJ region, with BCMA and identifying BCMA-binding heavy chain sequences.