

CLAIMS

1. A chimeric antigen receptor (CAR) which binds B cell maturation antigen (BCMA), in which the CAR comprises a Fab antigen binding domain.

2. A CAR according to Claim 1, in which the Fab antigen-binding domain comprises:

5 (a) a heavy chain variable region (VH) having complementarity determining regions (CDRs) with the following sequences:

CDR1 - GFIFSDYN (SEQ ID NO: 79)

CDR2 - IYDGSST (SEQ ID NO: 80)

CDR3 - ATRPGPFAY (SEQ ID NO: 81); and

10 (b) a light chain variable region (VL) having complementarity determining regions (CDRs) with the following sequences:

CDR1 - QSLHSNGNTY (SEQ ID NO: 82)

CDR2 - LVS (SEQ ID NO: 83)

CDR3 - VHGTHAWT (SEQ ID NO: 84).

15 3. A CAR according to Claim 2, in which the Fab antigen-binding domain comprises a VH domain having the sequence shown as SEQ ID NO: 29; and a VL domain having the sequence shown as SEQ ID NO: 30.

4. A CAR according to Claim 1, 2 or 3, in which the Fab antigen-binding domain comprises a first binding domain which binds a first target antigen and a second binding
20 domain which binds a second target antigen.

5. A nucleic acid sequence which encodes a CAR according to any preceding claim.

6. A nucleic acid construct which encodes a CAR according to Claim 1, 2 or 3 and has one of the following general structures:

VH-CH-spacer-TM-endo-coexpr-VL-CL;

25 VL-CL-coexpr-VH-CH-spacer-TM-endo;

VL-CL-spacer-TM-endo-coexpr-VH-CH; or

VH-CH-coexpr-VL-CL-spacer-TM-endo;

in which:

VH is a nucleic acid sequence encoding a heavy chain variable region;

CH is a nucleic acid sequence encoding a heavy chain constant region

spacer is a nucleic acid encoding a spacer;

5 TM is a a nucleic acid sequence encoding a transmembrane domain;

endo is a nucleic acid sequence encoding an endodomain;

coexpr is a nucleic acid sequence enabling co-expression of the first and second polypeptides;

VL is a nucleic acid sequence encoding a light chain variable region; and

10 CL is a nucleic acid sequence encoding a light chain constant region.

7. A nucleic acid construct which encodes a CAR according to Claim 4, 5 or 6 and has one of the following general structures:

VH1-L1-VH2-CH-spacer-TM-endo-coexpr-VL1-L2-VL2-CL;

VL1-L1-VL2-CL-coexpr-VH1-L2-VH2-CH-spacer-TM-endo;

15 VL1-L1-VL2-CL-spacer-TM-endo-coexpr-VH1-L2-VH2-CH; or

VH1-L1-VH2-CH-coexpr-VL1-L2-VL2-CL-spacer-TM-endo

in which:

VH1 is a nucleic acid sequence encoding a heavy chain variable region of the first binding domain;

20 L1 and L2, which may be the same or different, are cleavable linkers;

VH2 is a nucleic acid sequence encoding a heavy chain variable region of the second binding domain;

CH is a nucleic acid sequence encoding a heavy chain constant region;

spacer is a nucleic acid encoding a spacer;

25 TM is a nucleic acid sequence encoding a transmembrane domain;

endo is a nucleic acid sequence encoding an endodomain;

coexpr is a nucleic acid sequence enabling co-expression of the first and second polypeptides;

VL1 is a nucleic acid sequence encoding a light chain variable region of the first binding domain;

5 VL2 is a nucleic acid sequence encoding a light chain variable region of the second binding domain; and

CL is a nucleic acid sequence encoding a light chain constant region.

8. A nucleic acid construct according to Claim 12 or 13 which also encodes a second chimeric antigen receptor which binds CD19.

10 9. A vector which comprises a nucleic acid sequence according to Claim 5 or a nucleic acid construct according to Claim 6, 7 or 8.

10. A cell which expresses a CAR according to any of Claims 1 to 4.

11. A cell which expresses a first CAR according to any of Claims 1 to 4, and a second chimeric antigen receptor which binds CD19.

15 12. A method for making a cell according to Claim 10 or 11, which comprises the step of introducing a nucleic acid sequence according to Claim 5; a nucleic acid construct according to Claim 6, 7 or 8; or a vector according to Claim 9 into a cell *ex vivo*.

13. A pharmaceutical composition which comprises a plurality of cells according to Claim 10 or 11, together with a pharmaceutically acceptable carrier, diluent or excipient.

20 14. A pharmaceutical composition according to Claim 13 for use in treating cancer.

15. A pharmaceutical composition for use according to Claim 14, in which the cancer is multiple myeloma.

CLAIMS

1. A chimeric antigen receptor (CAR) which binds B cell maturation antigen (BCMA), in which the CAR comprises a Fab antigen binding domain comprising:

(a) a heavy chain variable region (VH) having complementarity determining regions (CDRs) with the following sequences:

CDR1 - GFIFSDYN (SEQ ID NO: 79)

CDR2 - IYDGSST (SEQ ID NO: 80)

CDR3 - ATRPGPFAY (SEQ ID NO: 81); and

(b) a light chain variable region (VL) having complementarity determining regions (CDRs) with the following sequences:

CDR1 - QSLLSNGNTY (SEQ ID NO: 82)

CDR2 - LVS (SEQ ID NO: 83)

CDR3 - VHGTHAWT (SEQ ID NO: 84).

2. A CAR according to Claim 1, in which the Fab antigen-binding domain comprises a VH domain having the sequence shown as SEQ ID NO: 29; and a VL domain having the sequence shown as SEQ ID NO: 30.

3. A CAR according to Claim 1 or 2, in which the Fab antigen-binding domain comprises a first binding domain which binds a first target antigen and a second binding domain which binds a second target antigen.

4. A nucleic acid sequence which encodes a CAR according to any preceding claim.

5. A nucleic acid construct which encodes a CAR according to Claim 1 or 2 and has one of the following general structures:

VH-CH-spacer-TM-endo-coexpr-VL-CL;

VL-CL-coexpr-VH-CH-spacer-TM-endo;

VL-CL-spacer-TM-endo-coexpr-VH-CH; or

VH-CH-coexpr-VL-CL-spacer-TM-endo;

in which:

VH is a nucleic acid sequence encoding a heavy chain variable region;

CH is a nucleic acid sequence encoding a heavy chain constant region

spacer is a nucleic acid encoding a spacer;

TM is a a nucleic acid sequence encoding a transmembrane domain;

5 endo is a nucleic acid sequence encoding an endodomain;

coexpr is a nucleic acid sequence enabling co-expression of the first and second polypeptides;

VL is a nucleic acid sequence encoding a light chain variable region; and

CL is a nucleic acid sequence encoding a light chain constant region.

10 6. A nucleic acid construct which encodes a CAR according to Claim 3, 4 or 5 and has one of the following general structures:

VH1-L1-VH2-CH-spacer-TM-endo-coexpr-VL1-L2-VL2-CL;

VL1-L1-VL2-CL-coexpr-VH1-L2-VH2-CH-spacer-TM-endo;

VL1-L1-VL2-CL-spacer-TM-endo-coexpr-VH1-L2-VH2-CH; or

15 VH1-L1-VH2-CH-coexpr-VL1-L2-VL2-CL-spacer-TM-endo

in which:

VH1 is a nucleic acid sequence encoding a heavy chain variable region of the first binding domain;

L1 and L2, which may be the same or different, are cleavable linkers;

20 VH2 is a nucleic acid sequence encoding a heavy chain variable region of the second binding domain;

CH is a nucleic acid sequence encoding a heavy chain constant region;

spacer is a nucleic acid encoding a spacer;

TM is a nucleic acid sequence encoding a transmembrane domain;

25 endo is a nucleic acid sequence encoding an endodomain;

coexpr is a nucleic acid sequence enabling co-expression of the first and second polypeptides;

VL1 is a nucleic acid sequence encoding a light chain variable region of the first binding domain;

VL2 is a nucleic acid sequence encoding a light chain variable region of the second binding domain; and

5 CL is a nucleic acid sequence encoding a light chain constant region.

7. A nucleic acid construct according to Claim 11 or 12 which also encodes a second chimeric antigen receptor which binds CD19.

8. A vector which comprises a nucleic acid sequence according to Claim 4 or a nucleic acid construct according to Claim 5, 6 or 7.

10 9. A cell which expresses a CAR according to Claim 1, 2 or 3.

10. A cell which expresses a first CAR according to Claim 1, 2 or 3, and a second chimeric antigen receptor which binds CD19.

11. A method for making a cell according to Claim 9 or 10, which comprises the step of introducing a nucleic acid sequence according to Claim 4; a nucleic acid construct according to Claim 5, 6 or 7; or a vector according to Claim 8 into a cell *ex vivo*.
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12. A pharmaceutical composition which comprises a plurality of cells according to Claim 9 or 10, together with a pharmaceutically acceptable carrier, diluent or excipient.

13. A pharmaceutical composition according to Claim 12 for use in treating cancer.

14. A pharmaceutical composition for use according to Claim 13, in which the cancer is multiple myeloma.
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