ENGINEERED IMMUNE CELL TARGETING BCMA AND USE THEREOF

TECHNICAL FIELD

[0001] The present invention relates to the field of immunotherapy, and more specifically to an engineered immune cell targeting BCMA and use thereof.

BACKGROUND OF THE INVENTION

[0002] Multiple myeloma (MM) is a malignant plasma cell tumor. The tumor cells originate from plasma cells in the bone marrow, and plasma cells are cells that develop to the final functional stage of B lymphocytes. Multiple myeloma is basically an incurable disease with the characteristics of high morbidity and high mortality. In 2017's statistics, there were 30,000 newly diagnosed multiple myeloma patients in the United States, among them, 12,000 might face death. At present, common therapies for multiple myeloma include cytotoxic drug therapy, protease inhibitors (Bortezomib, etc.), lenalidomide, monoclonal antibodies, corticosteroids, and the like. However, the current therapies are all partially effective, have no lasting alleviation effect, and the high risk of recurrence. Therefore, improvement in the therapies of multiple myeloma appears to be particularly important.

[0003] Therefore, there is an urgent need in the art for an effective, low-recurrence rate, and safe therapy for multiple myeloma.

SUMMARY OF THE DISCLOSURE

[0004] An object of the present disclosure is to provide an engineered immune cell targeting BCMA and use thereof.

[0005] Another object of the present disclosure is to provide an engineered immune cell targeting both CD19 and BCMA and use thereof.

[0005a] In one aspect, the present disclosure provides a bispecific chimeric antigen receptor (CAR) comprising: a first antigen binding domain exhibiting specific binding to a first target antigen, comprising (i) a first heavy chain variable region ($V_{H,1}$) and (ii) a first light chain variable region ($V_{L,1}$); and

a second antigen binding domain exhibiting specific binding to BCMA, comprising (i) a second heavy chain variable region ($V_{H,BCMA}$) comprising the polypeptide sequence of SEQ ID NO: 9 and (ii) a second light chain variable region ($V_{L,BCMA}$) comprising the polypeptide sequence of SEQ ID NO: 10,

wherein the bispecific CAR comprises a loop structure as shown in a formula selected from the group consisting of:

$V_{L,1}$-the second antigen binding domain-$V_{H,1}$ (A),

$V_{H,1}$-the second antigen binding domain-$V_{L,1}$ (B),

$V_{L,BCMA}$-the first antigen binding domain-$V_{H,BCMA}$ (C), and

$V_{H,BCMA}$ -the first antigen binding domain-$V_{L,BCMA}$ (D),

wherein "-" is each independently a linker peptide or a peptide bond.

[0005b] In one aspect, the present disclosure provides an engineered immune cell comprising the bispecific CAR as described herein.

[0006] In a first example of the present disclosure, a chimeric antigen receptor (CAR) or TCR is provided, and an antigen binding domain (scFv) of the CAR or TCR comprises an antibody heavy chain variable region as shown in SEQ ID NO: 9 and an antibody light chain variable region as shown in SEQ ID NO: 10.

[0007] In another preferred example, the scFv further comprises a linker peptide located between the heavy chain variable region and the light chain variable region.

[0008] In another preferred example, the scFv is as shown in the following formula A or formula B:

CLAIMS

WHAT IS CLAIMED IS:

1. A bispecific chimeric antigen receptor (CAR) comprising:

a first antigen binding domain exhibiting specific binding to a first target antigen, comprising (i) a first heavy chain variable region ($V_{H,1}$) and (ii) a first light chain variable region ($V_{L,1}$); and

a second antigen binding domain exhibiting specific binding to BCMA, comprising (i) a second heavy chain variable region ($V_{H,BCMA}$) comprising the polypeptide sequence of SEQ ID NO: 9 and (ii) a second light chain variable region ($V_{L,BCMA}$) comprising the polypeptide sequence of SEQ ID NO: 10,

wherein the bispecific CAR comprises a loop structure as shown in a formula selected from the group consisting of:

$V_{L,1}$-the second antigen binding domain-$V_{H,1}$ (A),

$V_{H,1}$-the second antigen binding domain-$V_{L,1}$ (B),

$V_{L,BCMA}$-the first antigen binding domain-$V_{H,BCMA}$ (C), and

$V_{H,BCMA}$ -the first antigen binding domain-$V_{L,BCMA}$ (D),

wherein "-" is each independently a linker peptide or a peptide bond.

2. The bispecific CAR of claim 1,

wherein the first target antigen is selected from the group consisting of CD138, Kappa Light Chain, NKG2D-ligands, TACI, GPRC5D, CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD22, CD25, CD28, CD30, CD33, CD38, CD40, CD44V6, CD47, CD52, CD56, CD57, CD58, CD79b, CD80, CD86, CD81, CD123, CD133, CD137, CD151, CD171, CD276, CLL1, B7H4, VEGFR-2, EGFR, GPC3, PMSA, CEACAM6, c-Met, EGFRvIII, ErbB2/HER2, ErbB3, HER-2, HER3, ErbB4/HER-4, EphA2, IGF1R, GD2, O-acetyl GD2, O-acetyl GD3, GHRHR, GHR, Flt1, KDR, Flt4, Flt3, CEA, CA125, CTLA-4, GITR, BTLA, TGFBR1, TGFBR2, TGFBR1, IL6R, gp130, Lewis, TNFR1, TNFR2, PD1, PD-L1, PD-L2, PSCA, HVEM, MAGE-A, MSLN, NY-ESO-1, PSMA, RANK, ROR1, TNFRSF4, TWEAK-R, LTPR, LIFRP, LRP5, MUC1, MUC16, TCRα, TCRβ, TLR7, TLR9, PTCH1, WT-1, Robol, Frizzled, OX40, Notch-1-4, APRIL, CS1, MAGE3, Claudin 18.2, Folate receptor α, Folate receptor β, GPC2, CD70, BAFF-R, and TROP-2.

3. The bispecific CAR of claim 2, wherein the first target antigen is CD19.

4. The bispecific CAR of claim 3, wherein (a) the $V_{H,1}$ comprises the polypeptide sequence selected from the group consisting of SEQ ID NOs: 11 and 21-30, and (b) the $V_{L,1}$ comprises the polypeptide sequence selected from the group consisting of SEQ ID NOs: 12 and 31-36.

5. The bispecific CAR of claim 4, wherein (a) the $V_{H,1}$ comprises the polypeptide sequence of SEQ ID NO: 11, and (b) the V_{L-1} comprises the polypeptide sequence of SEQ ID NO: 12.

6. The bispecific CAR of claim 1, wherein the bispecific CAR comprises the structure as shown in formula (A).

7. The bispecific CAR of claim 6, wherein the bispecific CAR comprises the structure as shown in formula (A'):

L-$V_{L,1}$-the second antigen binding domain-$V_{H,1}$-H-TM-C-CD3ζ (A')

wherein:

"-" is each independently a linker peptide or a peptide bond;

L is absent or a signal peptide sequence;

H is absent or a hinge region;

TM is a transmembrane domain;

C is a costimulatory signal molecule; and

CD3ζ is a cytoplasmic signaling sequence derived from CD3ζ.

8. The bispecific CAR of claim 1, wherein the bispecific CAR comprises the structure as shown in formula (C).

9. The bispecific CAR of claim 8, wherein the bispecific CAR comprises the structure as shown in formula (C'):

L-$V_{L,BCMA}$-the first antigen binding domain-$V_{H,BCMA}$-H-TM-C-CD3ζ (C')

wherein:

"-" is each independently a linker peptide or a peptide bond;

L is absent or a signal peptide sequence;

H is absent or a hinge region;

TM is a transmembrane domain;

C is a costimulatory signal molecule; and

CD3ζ is a cytoplasmic signaling sequence derived from CD3ζ.

10. The bispecific CAR of claim 1, wherein the bispecific CAR comprises the structure as shown in formula (B).

11. The bispecific CAR of claim 10, wherein the bispecific CAR comprises the structure as shown in formula (B'):

L-$V_{H,1}$-the second antigen binding domain-$V_{L,1}$-H1-TM-C-CD3ζ (B')

wherein:

"-" is each independently a linker peptide or a peptide bond;

L is absent or a signal peptide sequence;

H is absent or a hinge region;

TM is a transmembrane domain;

C is a costimulatory signal molecule; and

CD3ζ is a cytoplasmic signaling sequence derived from CD3ζ.

12. The bispecific CAR of claim 1, wherein the bispecific CAR comprises the structure as shown in formula (D).

13. The bispecific CAR of claim 12, wherein the bispecific CAR comprises the structure as shown in formula (D'):

L-$V_{H,BCMA}$-the first antigen binding domain-$V_{L,BCMA}$-H1-TM-C-CD3ζ (D')

wherein:

"-" is each independently a linker peptide or a peptide bond;

L is absent or a signal peptide sequence;

H is absent or a hinge region;

TM is a transmembrane domain;

C is a costimulatory signal molecule; and

CD3ζ is a cytoplasmic signaling sequence derived from CD3ζ.

14. The bispecific CAR of claim 7, wherein the bispecific CAR comprises the structure as shown in formula (E):

L-$V_{L,1}$-$V_{H,BCMA}$-$V_{L,BCMA}$-$V_{H,1}$-H-TM-C-CD3ζ (E).

15. The bispecific CAR of claim 14, wherein the first target antigen is CD19, and wherein:

L comprises the polypeptide sequence of SEQ ID NO: 16;

$V_{L,1}$ comprises the polypeptide sequence of SEQ ID NO: 12;

$V_{H,BCMA}$ comprises the polypeptide sequence of SEQ ID NO: 9;

$V_{L,BCMA}$ comprises the polypeptide sequence of SEQ ID NO: 10;

$V_{H,1}$ comprises the polypeptide sequence of SEQ ID NO: 11;

H comprises the polypeptide sequence of SEQ ID NO: 38;

TM comprises the polypeptide sequence of SEQ ID NO: 7;

C comprises the polypeptide sequence of SEQ ID NO: 5; and

CD3ζ comprises the polypeptide sequence of SEQ ID NO: 3.

16. An engineered immune cell comprising the bispecific CAR of claim 1.