signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and (ii.) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain; wherein the first antigen recognition domain and the second antigen recognition domain are different; wherein the target of the first antigen recognition domain comprises CD33 and the target of the second antigen recognition domain comprises CD123.

In yet another aspect, the present disclosure refers to the use of an engineered cell as described herein in the manufacture of a medicament for treating chronic myeloid leukemia, wherein the target of the first antigen recognition domain comprises CD33; and the target of the second antigen recognition domain comprises CD123. In yet another aspect, the present disclosure refers to the use of an engineered cell as described herein in the manufacture of a medicament for treating multiple myeloma, wherein the target of the first antigen recognition domain is selected from the group consisting of CS1, and BCMA; and the target of the second antigen recognition domain is selected from the group consisting of CS1, and BCMA.

In yet another aspect, the present disclosure refers to an *in vitro* method of reducing the number of target cells, the method comprising the steps of: i. contacting said target cells with an effective amount of an engineered cell as described herein; and ii. optionally, assaying for the reduction in the number of said cells; wherein said target cells comprise at least one cell surface antigen selected from the group consisting of BCMA, CD19, CD33, CD123, and CS1.

In a further aspect, the present disclosure refers to the use of an engineered cell as described herein in the manufacture of a medicament for treating leukemia, wherein the target of the first antigen recognition domain comprises CD33; and the target of the second antigen recognition domain comprises CD123. In a further aspect, the present disclosure refers to the use of an engineered cell as described herein in the manufacture of a medicament for treating multiple myeloma, wherein the target of the first antigen recognition domain comprises BCMA; and the target of the second antigen recognition domain comprises CD19.

CLAIMS

1. An engineered cell comprising:

(i.) a first chimeric antigen receptor polypeptide comprising a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and

(ii.) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain;

wherein the first antigen recognition domain and the second antigen recognition domain are different;

wherein the target of the first and the second antigen recognition domain is a combination selected from the group comprising CD33/CD123, BCMA/CS1 and BCMA/CD19.

2. An engineered cell comprising:

(i.) a first chimeric antigen receptor polypeptide comprising a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and

(ii.) a second chimeric antigen receptor polypeptide comprising a second antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain;

wherein the first antigen recognition domain and the second antigen recognition domain are different;

wherein the target of the first antigen recognition domain comprises CD33 and the target of the second antigen recognition domain comprises CD123.

3. The engineered cell according to claim 1, wherein the first antigen recognition domain comprises CD19 and the second antigen recognition domain comprises BCMA.

4. The engineered cell according to claim 1, wherein the first antigen recognition domain comprises BCMA and the second antigen recognition domain comprises CS1.

5. The engineered cell according to any one of claims 1-4, wherein the first chimeric antigen receptor polypeptide and the second chimeric engineered polypeptide are on a single polypeptide molecule, and wherein an amino acid sequence comprising a high efficiency cleavage site is disposed between the first chimeric antigen receptor polypeptide and the second chimeric antigen receptor polypeptide.

6. The engineered cell according to claim 5, wherein the high efficiency cleavage site is selected from the group consisting of P2A, T2A, E2A, and F2A.

7. The engineered cell according to any one of claims claim 1-6, wherein the first co-stimulatory domain and the second co-stimulatory domain are different.

8. The engineered cell according to any one of claims 1-7, wherein the first co-stimulatory domain comprises CD28, and the second co-stimulatory domain comprises 4-1BB.

9. The engineered cell according to any one of claims 1-8, wherein the engineered cell is a T-cell or Natural Killer cell.

10. The engineered cell according to claim 9, wherein the T-cell is a CD4 T-cell or CD8 T-cell.

11. The engineered cell according to claim 9, wherein the Natural Killer cell is a NKT cell or NK-92 cell.

12. Use of an engineered cell according to any one of claims 1-2, 5-11 in the manufacture of a medicament for treating chronic myeloid leukemia, wherein the target of the first antigen recognition domain comprises CD33; and the target of the second antigen recognition domain comprises CD123.

13. Use of an engineered cell according to any one of claims 1, 4-11 in the manufacture of a medicament for treating multiple myeloma, wherein the target of the first antigen recognition domain is selected from the group consisting of CS1, and BCMA; and the target of the second antigen recognition domain is selected from the group consisting of CS1, and BCMA.

14. An *in vitro* method of reducing the number of target cells, the method comprising the steps of:

i. contacting said target cells with an effective amount of an engineered cell according to any one of claims 1-11; and

ii. optionally, assaying for the reduction in the number of said cells;

wherein said target cells comprise at least one cell surface antigen selected from the group consisting of BCMA, CD19, CD33, CD123, and CS1.

15. The engineered cell according to any one of claims 1, 3 or 4, wherein the BCMA antigen recognition domain comprises APRIL ligand or BAFF ligand or a fragment thereof.

16. The engineered cell according to any one of claims 1-8, wherein the first co-stimulatory domain and the second co-stimulatory domain are same.

17. The engineered cell according to any one of claims 1-8, wherein the first co-stimulatory domain and the second co-stimulatory domain comprise 4-1BB co-stimulatory domain.

18. Use of an engineered cell according to any one of claims 1-2, 5-11 in the manufacture of a medicament for treating leukemia, wherein the target of the first antigen recognition domain comprises CD33; and the target of the second antigen recognition domain comprises CD123.

19. Use of an engineered cell according to any one of claims 1-2, 5-11 in the manufacture of a medicament for treating multiple myeloma, wherein the target of the first antigen recognition domain comprises BCMA; and the target of the second antigen recognition domain comprises CD19.