Claims

1. A polynucleotide, the polynucleotide comprising:

a first nucleotide sequence encoding a chimeric antigen receptor comprising an extracellular domain that specifically binds to a CD19 antigen; and

a second nucleotide sequence encoding either an apoptosis inhibitor selected from the group consisting of SEQ ID NOs: 237 and 238 or an activating mutant consisting of SEQ ID NO. 251.

2. The polynucleotide according to claim 1, further comprising a transposon.

3. A modified T-cell expressing a polynucleotide according to claim 1 or 2.

4. The modified T-cell according to claim 3, wherein:

a persistence of the modified T-cell is increased relative to a persistence of a T-cell that does not comprise the first and second nucleotide sequences; and/or

a proliferation rate of the modified T-cell is increased relative to a proliferation rate of a T-cell that does not comprise the first and second nucleotide sequences.

5. A method for preparing a modified T-cell according to claim 3 or 4, the method comprising introducing the polynucleotide into a T-cell ex-vivo.

6. The method of claim 5, wherein, when the polynucleotide comprises a transposon:

(A) the second nucleotide sequence is operably linked to a heterologous promoter; and

(B) the polynucleotide is flanked by a pair of transposon ends,

wherein a transposase is introduced into the T-cell, and

wherein the polynucleotide is transposable by the transposase.

7. The method of claim 6, wherein the transposon ends have flanking sequences selected from the group consisting of SEQ ID NOs: 6 and 7, SEQ ID NOs: 10 and 11, SEQ ID NOs: 14 and 15, SEQ ID NOs: 20 and 21, SEQ ID NOs: 16 and 17, a sequence at least 90% identical to SEQ ID NO: 24 and a sequence at least 90% identical to SEQ ID NO: 25, or a sequence at least 90% identical to SEQ ID NO: 397 and a sequence at least 90% identical to SEQ ID NO: 398; and

(1) where, when the pair of flanking sequences is SEQ ID NOs: 6 and 7 or SEQ ID NOs: 10 and 11, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 31 or 32;

(2) where, when the pair of flanking sequences is SEQ ID NOs: 14 and 15, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 64;

(3) where, when the pair of flanking sequences is SEQ ID NOs: 20 and 21, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 29;

(4) where, when the pair of flanking sequences is SEQ ID NOs: 16 and 17, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 30;

(5) where, when the pair of flanking sequences is a sequence at least 90% identical to SEQ ID NO: 24 and a sequence at least 90% identical to SEQ ID NO: 25, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 28; and

(6) where, when the pair of flanking sequences is a sequence at least 90% identical to SEQ ID NO: 397 and a sequence at least 90% identical to SEQ ID NO:

398, the transposase is represented by a sequence at least 90% identical to SEQ ID NO: 401.

8. The method of claim 6 or claim 7, wherein the transposase is introduced as a nucleic acid encoding the transposase.

9. The method of claim 8, wherein the nucleic acid encoding the transposase is an mRNA.

10. The method of claim 5, wherein the polynucleotide is integrated into the genome of the modified T-cell.

11. The modified T-cell of claim 3 for use in the treatment of cancer.

12. A pharmaceutical composition comprising a plurality of modified T-cells according to claim 3.

13. The pharmaceutical composition according to claim 12 for use in the treatment of a B cell malignancy.

14. A kit comprising:

(A) the polynucleotide of claim 2;

(B) a transposase capable of transposing the transposon or a nucleic acid encoding a transposase capable of transposing the transposon; and, optionally,

(C) an anti-hCD19-CD3 bispecific T cell engager.

15. The kit according to claim 14, wherein, when the kit comprises a nucleic acid encoding the transposase, the nucleic acid encoding the transposase is an mRNA.