

Claims

1. A pharmaceutical composition comprising:
 - (a) a plurality of hematopoietic cells (HCs), wherein the plurality of HCs comprises
 - (i) a genetically engineered gene encoding CD33 that is engineered to have reduced or eliminated expression of CD33, and
 - (ii) a genetically engineered gene encoding CLL1 that is engineered to have reduced or eliminated expression of CLL1; and
 - (b) a therapeutically effective amount of at least one agent comprising an anti-CD33 binding domain or an anti-CLL1 binding domain.
2. The pharmaceutical composition according to claim 1 for use in therapy.
3. Use of the pharmaceutical composition according to claim 1 in the manufacture of a medicament for treating a hematopoietic malignancy in a subject.
4. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the at least one agent comprises an anti-CLL1 binding domain.
5. The pharmaceutical composition or the use according to claim 4, wherein the at least one agent comprises a T cell comprising a CAR comprising the anti-CLL1 binding domain, or an antibody or fragment thereof comprising the anti-CLL1 binding domain.
6. The pharmaceutical composition or the use according to claim 5, wherein the at least one agent further comprises an anti-CD33 binding domain.
7. The pharmaceutical composition or the use according to claim 6, wherein the at least one agent comprises a T cell comprising a CAR comprising the anti-CD33 binding domain, or an antibody or fragment thereof comprising the anti-CD33 binding domain.
8. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the genetically engineered gene encoding CLL1 or CD33 comprises a frameshift mutation.

9. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the genetically engineered HCs are genetically engineered using a CRISPR system comprising a guide nucleic acid.
10. The pharmaceutical composition or the use according to claim 9, wherein the guide nucleic acid comprises a sequence according to SEQ ID NO: 67 or a complement thereof.
11. The pharmaceutical composition or the use according to claim 9, wherein the guide nucleic acid comprises a sequence according to SEQ ID NO: 137 or a complement thereof.
12. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein exon 3 of the genetically engineered gene encoding CD33 is genetically engineered.
13. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein exon 4 of the genetically engineered gene encoding CLL1 is genetically engineered.
14. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the plurality of genetically engineered HCs retains the capacity to differentiate normally compared to a population of HCs that are not genetically engineered.
15. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein each cell of the plurality of genetically engineered HCs comprises the genetically engineered gene encoding CD33 and the genetically engineered gene encoding CLL1.
16. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the plurality of genetically engineered HCs comprises HCs with reduced or no binding to the anti-CD33 binding domain and reduced or no binding to the anti-CLL1 binding domain.

17. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the plurality of genetically engineered HCs is capable of expanding by at least 2-fold over 8 days in culture.
18. The use according to claim 3, wherein the plurality of HCs is obtained from a method comprising providing HCs from a biological sample from the subject, and genetically engineering the HCs from the biological sample from the subject, thereby forming the plurality of genetically engineered HCs.
19. The pharmaceutical composition according to claim 1 or claim 2, or the use according to claim 3, wherein the plurality of HCs comprises HCs obtained from a healthy donor, or descendants thereof.
20. A method of preparing a population of genetically engineered hematopoietic cells (HCs), the method comprising:
 - (a) providing a population of HCs obtained from a human subject, wherein the population of HCs or descendants thereof express CD33 and CLL1; and
 - (b) genetically modifying the population of HCs such that
 - (i) a gene encoding CD33 is engineered to have reduced or eliminated expression of CD33; and
 - (ii) a gene encoding CLL1 is engineered to have reduced or eliminated expression of CLL1.