

CLAIMS:

1. A gRNA comprising a targeting domain, wherein the targeting domain comprises a
5 sequence of any one of SEQ ID NOs: 21-30 or 48-51.
2. A gRNA comprising a targeting domain which binds a target domain of Table 1, 2, 6,
or 8.
- 10 3. A gRNA comprising a targeting domain capable of directing cleavage or editing of a
target domain of Table 1, 2, 6, or 8.
4. The gRNA of any one of claims 1 to 3, wherein the gRNA comprises a first
complementarity domain, a linking domain, a second complementarity domain which is
15 complementary to the first complementarity domain, and a proximal domain.
5. The gRNA of any one of claims 1 to 4, wherein the gRNA is a single guide RNA
(sgRNA).
- 20 6. The gRNA of any one of claims 1 to 5, wherein the gRNA comprises one or more
2'O-methyl nucleotide.
7. The gRNA of any one of claims 1 to 6, wherein the gRNA comprises one or more
phosphorothioate or thioPACE linkage.
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8. A method of producing a genetically engineered cell, wherein the method comprises:
(i) providing a cell (e.g., a hematopoietic stem or progenitor cell, e.g., a wild-type
hematopoietic stem or progenitor cell), and
(ii) introducing into the cell (a) the gRNA of any of claims 1 to 7; and (b) a Cas9
30 molecule that binds the gRNA,
thereby producing the genetically engineered cell.
9. The method of claim 8, wherein the Cas9 molecule comprises a SpCas9
endonuclease, a SaCas9 endonuclease, or a Cpf1 endonuclease.

10. The method of claim 8 or 9, wherein the gRNA of (a) and the Cas9 molecule of (b) are introduced into the cell as a pre-formed ribonucleoprotein complex.
- 5 11. The method of claim 10, wherein the ribonucleoprotein complex is introduced into the cell via electroporation.
12. A genetically engineered hematopoietic stem or progenitor cell, wherein the genetically engineered hematopoietic stem or progenitor cell is produced by the method of
10 any one of claims 8 to 11.
13. A cell population comprising a plurality of the genetically engineered hematopoietic stem or progenitor cells of claim 12.
- 15 14. The cell population of claim 13, further comprising one or more cells comprising one or more non-engineered CD123 genes.
15. The cell population of claim 13 or 14, wherein the cell population expresses less than 20% of the CD123 expressed by a wild-type counterpart cell population.
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16. The cell population of any one of claims 13 to 15, wherein the cells of the population comprise both hematopoietic stem cells and hematopoietic progenitor cells.
17. The cell population of any one of claims 13 to 16, wherein the cells of the population
25 further comprise a second mutation at a gene encoding the lineage-specific cell surface antigen other than CD123.
18. The cell population of claim 17, wherein the gene encoding a lineage-specific cell surface antigen other than CD123 is CD33 or CLL1.
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19. Use of the cell population of any one of claims 13 to 17 in the manufacture of a medicament for treating a hematopoietic malignancy in a subject.

20. The use of claim 19, wherein the medicament is to be administered to the subject in combination with an effective amount of an agent that targets CD123, wherein the agent comprises an antigen-binding fragment that binds CD123.