

CLAIMS:

1. ____ A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of ~~SEQ ID NO: 21~~ any one of SEQ ID NOs: 21-30, 44, 45, 239, or 257.

5

~~2. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 22.~~

10

~~3. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 23.~~

~~4. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 24.~~

15

~~5. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 25.~~

~~6. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 26.~~

20

~~7. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 27.~~

~~8. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 28.~~

25

~~9. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 29.~~

30

~~10. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 30.~~

~~11. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 44.~~

~~12. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 45.~~

~~13. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 257.~~

~~14. A gRNA comprising a targeting domain, wherein the targeting domain comprises a sequence of SEQ ID NO: 239.~~

~~152.~~ 152. A gRNA comprising a targeting domain which binds a target domain of Table 1, 2, 6, or 8.

~~163.~~ 163. A gRNA comprising a targeting domain capable of directing cleavage or editing of a target domain of Table 1, 2, 6, or 8.

~~174.~~ 174. The gRNA of any one of ~~claim 1-16~~claims 1 to 3, ~~which wherein the gRNA~~ comprises a first complementarity domain, a linking domain, a second complementarity domain which is complementary to the first complementarity domain, and a proximal domain.

~~185.~~ 185. The gRNA of any one of claims ~~1-171~~to 4, ~~which wherein the gRNA~~ is a single guide RNA (sgRNA).

~~196.~~ 196. The gRNA of any one of claims ~~1-181~~to 5, ~~which wherein the gRNA~~ comprises one or more 2'O-methyl nucleotide.

~~207.~~ 207. The gRNA of any one of claims ~~1-191~~to 6, ~~which wherein the gRNA~~ comprises one or more phosphorothioate or thioPACE linkage.

~~218.~~ 218. A method of producing a genetically engineered cell, comprising:
(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) ~~a~~the gRNA of any of claims ~~1-17~~1-7; and (b) a Cas9 molecule that binds the gRNA,

thereby producing the genetically engineered cell.

5 ~~229~~. The method of claim ~~21~~8, wherein the Cas~~9~~ molecule comprises a SpCas9 endonuclease, a SaCas9 endonuclease, or a Cpf1 endonuclease.

~~23~~10. The method of claim ~~21~~8 or ~~229~~, wherein the gRNA of (a) and the Cas9 molecule of (b) (i) and (ii) are introduced into the cell as a pre-formed ribonucleoprotein complex.

10

~~24~~11. The method of claim ~~21~~10, wherein the ribonucleoprotein complex is introduced into the cell via electroporation.

~~25~~12. A genetically engineered hematopoietic stem or progenitor cell, ~~which is produced by a method of claim 21 wherein the genetically engineered hematopoietic stem or progenitor cell is produced by the method of any one of claims 8 to 11.~~

15

~~26~~13. A cell population, comprising a plurality of the genetically engineered hematopoietic stem or progenitor cells of claim ~~25~~12.

20

~~27~~14. The cell population of claim ~~26~~13, ~~which further comprises~~comprising one or more cells that comprise one or more non-engineered CLL1 genes.

~~28~~15. The cell population of claim ~~26~~13 or ~~27~~14, ~~which wherein the cell population~~ expresses less than 20% of the CLL1 expressed by a wild-type counterpart cell population.

25

~~29~~16. The cell population of any one of claims ~~26-28~~13 to 15, ~~which wherein the cell population~~ comprises both ~~of~~ hematopoietic stem cells and hematopoietic progenitor cells.

~~30~~17. The cell population of any one of claims ~~26-29~~13 to 16, ~~which wherein the cells of the population~~ further comprises a second mutation at a gene encoding a lineage-specific cell surface antigen other than CLL1.

30

~~31~~18. The cell population of claim ~~30~~17, wherein the gene encoding ~~a~~the lineage-specific cell surface antigen other than CLL1 is CD33 or CD123.

~~32. A method, comprising administering to a subject in need thereof a cell population of any of claims 26-31.~~

~~33. The method of claim 32, wherein the subject has a hematopoietic malignancy.~~

~~34. The method of claim 32 or 33, which further comprises administering to the subject an effective amount of an agent that targets CLL1, wherein the agent comprises an antigen-binding fragment that binds CLL1.~~

19. Use of the cell population of any one of claims 13 to 18 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 CLL1, wherein the agent comprises an antigen-binding fragment that binds CLL1.