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(54) Title: PRIME EDITOR VARIANTS, CONSTRUCTS, AND METHODS FOR ENHANCING PRIME EDITING EFFICIENCY AND PRECISION

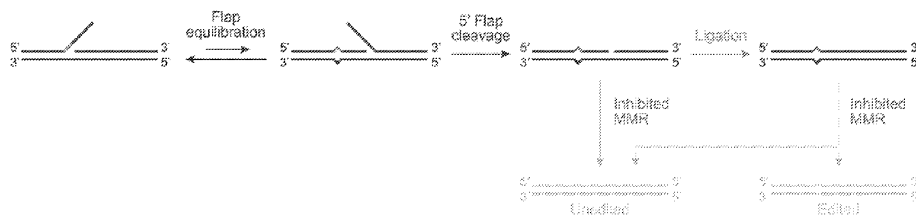


FIG. 9B

(57) Abstract: The present disclosure provides compositions and methods for prime editing with improved editing efficiency and/or reduced indel formation by inhibiting the DNA mismatch repair path way while conducting prime editing of a target site. Accordingly, the present disclosure provides a method for editing a nucleic acid molecule by prime editing that involves contacting a nucleic acid molecule with a prime editor, a pegRNA, and an inhibitor of the DNA mismatch repair pathway, thereby installing one or more modifications to the nucleic acid molecule at a target site with increased editing efficiency and/or lower indel formation. The present disclosure further provides polynucleotides for editing a DNA target site by prime editing comprising a nucleic acid sequence encoding a napDNABp, a polymerase, and an inhibitor of the DNA mismatch repair pathway, wherein the napDNABp and polymerase is capable in the presence of a pegRNA of installing one or more modifications in the DNA target site with increased editing efficiency and/or lower indel formation. The disclosure further provides, vectors, cells, and kits comprising the compositions and polynucleotides of the disclosure. The present disclosure also provides compositions and methods for prime editing with improved editing efficiency and/or reduced indel formation with modified prime editor fusion proteins. The disclosure further provides, vectors, cells, and kits comprising the compositions and polynucleotides of the disclosure.

[Continued on next page]

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