

aspects above, comprising the polynucleotide encoding the fusion protein, wherein the polynucleotide comprises a sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a sequence selected from the group consisting of SEQ ID NOs: 87, 88, 97, 98, 100, 101, 112, and 113. In some embodiments, the selected sequence is SEQ ID NO 79 or 80. In some embodiments, the selected sequence is SEQ ID NO 87 or 88. In some embodiments, the polynucleotide encoding the fusion protein further comprises a stop codon at the 3' end.

[0026] In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 276-279. In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 282-285. In some embodiments, the prime editing composition further comprising a 5' untranslated region (UTR) and/or a 3' UTR. In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 274, 275, 592, or 593. In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 280, 281, 594, or 595. In some embodiments, the polynucleotide comprises DNA. In some embodiments, the polynucleotide comprises mRNA. In some embodiments, the prime editing composition further comprises a regulatory element sequence, optionally wherein the regulatory element sequence is a promoter.

[0027] In one aspect, provided herein is a prime editing composition comprising a first polynucleotide encoding a DNA binding domain and a second polynucleotide encoding a DNA polymerase domain, wherein the second polynucleotide comprises a sequence having at least 80% identity to a sequence corresponding to nucleotides 100-2130 of a sequence selected from the group consisting of SEQ ID Nos 412-555.

[0028] In one aspect, provided herein is a prime editing composition comprising a first polynucleotide encoding a DNA binding domain and a second polynucleotide encoding a DNA polymerase domain, wherein the second polynucleotide comprises a sequence having at least 80% identity to SEQ ID No 83 or 84.

[0028a] In one aspect, provided herein is a prime editing composition comprising a first polynucleotide encoding a DNA binding domain and a second polynucleotide encoding a DNA polymerase domain, wherein the second polynucleotide comprises a sequence (i) having at least 80% sequence identity to SEQ ID NOs: 83 or 84, or (ii) having at least 80% sequence identity to SEQ ID NOs: 91 or 92.

[0029] In some embodiments, the second polynucleotide comprises a sequence having at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO 83 or 84.

[0030] In one aspect, provided herein is a prime editing composition comprising a first polynucleotide encoding a DNA binding domain and a second polynucleotide encoding a DNA polymerase domain, wherein the second polynucleotide comprises the sequence of SEQ ID No 83 or 84.

[0031] In one aspect, provided herein is a prime editing composition comprising a first polynucleotide encoding a DNA binding domain and a second polynucleotide encoding a DNA polymerase domain, wherein the second polynucleotide comprises a sequence having at least 80% identity to SEQ ID No 91 or 92.

[0032] In some embodiments, the second polynucleotide comprises a sequence having at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO 91 or 92.

[0038] In some embodiments, the fusion polynucleotide comprises a sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity to a sequence selected from the group consisting of SEQ ID NOs: 87, 88, 97, 98, 100, 101, 112, and 113. In some embodiments, the selected sequence is SEQ ID NO: 87 or 88. In some embodiments, the fusion polynucleotide further comprises a stop codon at the 3' end.

[0039] In some embodiments, the fusion polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO 276-279. In some embodiments, the fusion polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO 282-285. In some embodiments, the fusion polynucleotide comprises a 5' untranslated region (UTR) and/or a 3' UTR. In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 274, 275, 592, or 593. In some embodiments, the polynucleotide comprises the sequence of SEQ ID NO 280, 281, 594, or 595. In some embodiments, the first polynucleotide, the second polynucleotide, and/or the fusion polynucleotide comprises DNA. In some embodiments, the first polynucleotide, the second polynucleotide, and/or the fusion polynucleotide comprises mRNA. In some embodiments, the fusion polynucleotide further comprises a regulatory element sequence, optionally wherein the regulatory element sequence is a promoter.

[0040] In some embodiments, the sequence identities are determined by Needleman-Wunsch alignment of two sequences with Gap Costs set to Existence: 11 Extension: 1 where percent identity is calculated by dividing the number of identities by the length of the alignment. In some embodiments, the prime editing composition further comprises a prime editing guide RNA (PEgRNA) or a polynucleotide encoding the PEgRNA. In some embodiments, the prime editing composition further comprises a nick guide RNA (ngRNA) or a polynucleotide encoding the ngRNA.

[0041] In one aspect, provided herein is a vector comprising one or more of the polynucleotides of the prime editing composition of any one of aspects above.

[0041a] In one aspect, provided herein is a vector comprising one or more of the polynucleotides of the prime editing composition as described herein, optionally wherein the vector is an AAV vector.

[0041b] In one aspect, provided herein is a lipid nanoparticle (LNP) comprising the prime editing composition as described herein.

[0042] In some embodiments, the vector is a AAV vector. In some embodiments, the vector is a lipid nanoparticle (LNP).

[0043] In one aspect, provided herein is a pharmaceutical composition comprising the prime editing composition of any one of aspects above or the vector of any one of aspects above, and a pharmaceutically acceptable excipient.

[0043a] In one aspect, provided herein is a pharmaceutical composition comprising the prime editing composition as described herein or the vector as described herein, or the LNP as described herein.

[0044] In one aspect, provided herein is a method of editing a target gene, the method comprising contacting the target gene with the prime editing composition of any one of aspects above.

[0044a] In one aspect, provided herein is an ex vivo or in vitro method of editing a target gene, the method comprising contacting the target gene with the prime editing composition as described herein.

[0045] In some embodiments, the target gene is in a cell. In some embodiments, the cell is a human cell. In some embodiments, the cell is a (CD34+) hematopoietic stem cell or a hematopoietic stem progenitor cell. In some embodiments, the contacting is ex vivo. In some embodiments, the cell is in a subject.