CLAIMS

1. A composition comprising:

(i) **an mRNA** encoding a protein comprising a programmable DNA binding domain and **a deaminase**; and

(ii) a guide polynucleotide, wherein the guide polynucleotide comprises a spacer sequence, wherein the spacer sequence comprises at least 13 nucleotide bases of a nucleotide base sequence of a protospacer, wherein the protospacer is on a gene that encodes proprotein convertase subtilisin-kexin type 9 (PCSK9 gene), and wherein uracil is considered the same as thymine.

2. The composition of claim 1, wherein the programmable DNA binding domain is selected from DNA binding domains found in the group consisting of Cas9, CasX, CasY, Cas12a (Cpf1), Cas12b, C2c1, C2c2, C2C3, zinc finger nuclease (ZFN), Transcription activator-like effector nucleases (TALEN), and Argonaute.

3. The composition of claim 1 or 2, wherein the programmable DNA binding domain is selected from DNA binding domains found in the group consisting of a nuclease inactive spCas9 domain and a spCas9 nickase.

4. The composition of any one of claims 1-3, wherein the programmable DNA binding domain comprises a sequence selected from the group consisting of SEQ ID NOs: 40, 2152, 2156 and 2160.

5. The composition of any one of claims 1-4, wherein the deaminase comprises a protein selected from the group consisting of an adenosine deaminase and a cytidine deaminase.

6. The composition of any one of claims 1-5, wherein the deaminase comprises an adenosine deaminase.

7. The composition of any one of claims 1-6, wherein the deaminase comprises a sequence of SEQ ID NO: 2140.

8. The composition of any one of claims 1-7, wherein the spacer sequence has at least 80% identity to any of the following chemically modified sequences:

(a) cscscsGCACCUUGGCGCAGCGG (nucleotides 1 to 20 of SEQ ID NO: 9)

(b) gsgsusGCUAGCCUUGCGUUCCG (nucleotides 1 to 20 of SEQ ID NO: 253), or

(c) ususgsGAAAGACGGAGGCAGCC (nucleotides 1 to 20 of SEQ ID NO: 261), and

wherein 1) the uppercase A, U, G, and C represent adenosine, uridine, guanosine, and cytidine, respectively; 2) the lowercase a, u, g, and c represent 2'-O-Methyl-modified adenosine, uridine, guanosine, and cytidine, respectively, and 3) the lowercase s represents phosphorothioate (PS) linkage.

9. The composition of any one of claims 1-7, wherein the protospacer has at least 80% sequence identity to

(a) CCCGCACCTTGGCGCAGCGG (SEQ ID NO: 13),

(b) GGTGCTAGCCTTGCGTTCCG (SEQ ID NO: 66), or

(c) TTGGAAAGACGGAGGCAGCC (SEQ ID NO: 83), and

wherein the uppercase A, U, G, and C represent adenosine, uridine, guanosine, and cytidine, respectively.

10. The composition of any one of claims 1-9, wherein the guide polynucleotide further comprises a tracr sequence, wherein the tracr sequence has at least 80% identity to any of the following chemically modified sequences:

(a) gUUUUAGagcuaGaaauagcaaGUUaAaAuAaggCUaGUCcGUUAucAAcuuGa aaaaguGgcaccgAgUCggugcusususu,

(b) gUUUUAGagcuagaaauagcaaGUUaAaAuAaggcuaGUccGUUAucAAcuugaaa aagugGcaccgagucggugcusususu, or

(c) gUUUUAGagcuaGaaauagcaaGUUaAaAuAaggcuaGUccGUUAucAAcuuGaa aaagugGcaccgagucggugcusususu, and

wherein 1) the uppercase A, U, G, and C represent adenosine, uridine, guanosine, and cytidine, respectively; 2) the lowercase a, u, g, and c represent 2'-O-Methyl-modified adenosine, uridine, guanosine, and cytidine, respectively, and 3) the lowercase s represents phosphorothioate (PS) linkage.

11. The composition of any one of claims 1-10, wherein the guide polynucleotide is a guide RNA.

12. The composition of any one of claims 1-11, wherein the ratio of the guide nucleotide and the mRNA is from about 1:10 to about 10:1 by weight.

13. The composition of any one of claims 1-12, wherein the ratio of the guide nucleotide and the mRNA is from about 1:3 to about 3:1 by weight.
14. The composition of any one of claims 1-13, wherein the ratio of the guide nucleotide and the mRNA is from about 1:2 to about 2:1 by weight.
15. The composition of any one of claims 1-14, wherein the ratio of the guide nucleotide and the mRNA from about 1:1.5 to about 1.5:1 by weight.
16. The composition of any one of claims 1-15, wherein the ratio of the guide nucleotide and the mRNA is about 1:1 by weight.
17. The composition of any one of claims 1-16, wherein the spacer sequence comprises at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, or at least 24 nucleotide bases of the nucleotide base sequence of the protospacer.
18. The composition of any one of claims 1-17, wherein the guide polynucleotide comprises a chemically modified sequence specified in cscscsGCACCUUGGCGCAGCGGgUUUUAGagcuaGaaauagcaaGUUaAaAuAaggcuaGUccGUUAucAAcuuGaaaaagugGcaccgagucggugcusususu (SEQ ID NO: 9), gsgsusGCUAGCCUUGCGUUCCGGUUUUAGAgcuagaaauagcAAGUUAAAAUAAGGCUAGUCCGUUAUCAacuugaaaaaguggcaccgagucggugcusususu (SEQ ID NO: 253), or ususgsGAAAGACGGAGGCAGCCGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGCUsususu (SEQ ID NO: 261).
19. The composition of any one of claims 1-18, wherein the mRNA comprises a sequence having at least 90% sequence identity to (a) SEQ ID NO: 2148, 2153, or 2192, or (b) the coding sequence of SEQ ID NO: 2148, 2153, or 2192.
20. A pharmaceutical composition, comprising the composition of any one of claims 1-19, for use in treatment or prevention of a condition in a subject in need thereof.