Claims

1. An epigenetic-modifying DNA-targeting system comprising a plurality of DNA-targeting modules for repressing transcription of a plurality of genes that regulate low-density lipoprotein (LDL),

wherein the plurality of DNA-targeting modules comprises a first DNA-targeting module for repressing transcription of a first gene of the plurality of genes, and a second DNA-targeting module for repressing transcription of a second gene of the plurality of genes, and

wherein each DNA-targeting module comprises a fusion protein comprising: (a) a DNA-binding domain for targeting to a target site of one of the plurality of genes, and (b) at least one transcriptional repressor domain.

2. The epigenetic-modifying DNA-targeting system of claim 1, wherein the fusion protein of each DNA-targeting module comprises a DNA-binding domain selected from: a Clustered Regularly Interspaced Short Palindromic Repeats associated (Cas) protein or a variant thereof; a zinc finger protein (ZFP); a transcription activator-like effector (TALE); a meganuclease; a homing endonuclease; or an I-SceI enzyme or a variant thereof, optionally wherein the DNA-binding domain comprises a catalytically inactive variant of any of the foregoing.

3. An epigenetic-modifying DNA-targeting system for repressing transcription of a plurality of genes that regulate low-density lipoprotein (LDL) comprising:

(a) a fusion protein comprising a Clustered Regularly Interspaced Short Palindromic Repeats associated (Cas) protein or variant thereof and at least one transcriptional repressor domain; and

(b) a plurality of guide RNAs (gRNAs) comprising at least a first gRNA and a second gRNA, wherein the first gRNA targets a target site of a first gene that regulates low-density lipoprotein (LDL) and the second gRNA targets a target site of a second gene that regulates LDL.

4. The epigenetic-modifying DNA-targeting system of claim 1 , wherein the system further comprises a third DNA-targeting module for repressing transcription of a third gene that regulates low-density lipoprotein (LDL).

5. The epigenetic-modifying DNA-targeting system of claim 3, wherein the system further comprises a third gRNA that targets a target site of a third gene that regulates LDL,

optionally wherein the system further comprises a fourth gRNA that targets a target site of a fourth gene that regulates LDL, optionally a fifth gRNA that targets a target site of a fifth gene that regulates LDL, and/or optionally a sixth gRNA that targets a target site of a sixth gene that regulates LDL.

6. The epigenetic-modifying DNA-targeting system of claim1 or claim 3, wherein the first gene and the second gene are independently selected from the group consisting of PCSK9, LPA, MYLIP, ANGPTL3, APOB, and APOC3.

7. The epigenetic-modifying DNA-targeting system of claim 1 or claim 3, wherein at least one gene is PCSK9 or, at least two genes are PCSK9 and LPA,or at least three genes are PCSK9, LPA, and MYLIP

8. The epigenetic-modifying DNA-targeting system of claim 1 or claim 6, wherein the target site of each of the plurality of genes is in the gene or a regulatory DNA element thereof, wherein the regulatory DNA element is an enhancer or a promoter.

9. The epigenetic-modifying DNA-targeting system of claim 1or claim 3, wherein the target site of the first gene, the second gene, and optionally the third gene, are selected from different members of the group consisting of (a)-(f):

(a) a target site for PCSK9, located within 500bp of human genome assembly GRCh38 (hg38) genomic coordinates chr1:55,039,548;

(b) a target site for LPA, located within 500bp of the hg38 genomic coordinates chr6:160,664,275;

(c) a target site for MYLIP, located within 500bp of the hg38 genomic coordinates chr6:16,129,086;

(d) a target site for ANGPTL3, located within 500bp of the hg38 genomic coordinates chr1:62,597,520;

(e) a target site for APOC3, located within 500bp of the hg38 genomic coordinates chr11:116,829,907; and

(f) a target site for APOB, located within 500bp of the hg38 genomic coordinates chr2:21,044,073.

10. The epigenetic-modifying DNA-targeting system of claim 1 or claim 3, wherein the target site of the first gene, the second gene, and optionally the third gene, are selected from different members of the group consisting of (a)-(f):

(a) a target site for PCSK9 having the sequence set forth in any one of SEQ ID NOS: 3,1, 2,4-13 or 306-317, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing, optionally wherein the target site is (i) set forth in SEQ ID NO:3, (ii) has a contiguous portion of SEQ ID NO:3 of at least 14 nucleotides, or (iii) is a complementary sequence of (i) or (ii);

(b) a target site for LPA having the sequence set forth in any one of SEQ ID NOS:14-23, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(c) a target site for MYLIP having the sequence set forth in any one of SEQ ID NOS:24-33 or 342-351, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(d) a target site for ANGPTL3 having the sequence set forth in any one of SEQ ID NOS:34-43, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(e) a target site for APOC3 having the sequence set forth in any one of SEQ ID NOS:44-53, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing; and

(f) a target site for APOB having the sequence set forth in any one of SEQ ID NOS:54-63 or 372-377, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing.

11. The epigenetic-modifying DNA-targeting system of claim 2 or claim 3, wherein the Cas protein or variant thereof is a variant Cas protein that is a deactivated (dCas) protein.

12. The epigenetic-modifying DNA-targeting system of claim 11, wherein the dCas protein is a dCas9 protein.

13. The epigenetic-modifying DNA-targeting system of claim 12, wherein the dCas9 protein is a *Streptococcus pyogenes* dCas9 (dSpCas9) protein.

14. The epigenetic-modifying DNA-targeting system of claim 3, wherein the first gRNA, the second gRNA, and optionally the third gRNA, are selected from two members of the group consisting of (a)-(f):

(a) a gRNA targeting a target site of PCSK9 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:66, 64, 65, 67-76 or 318-329, or a contiguous portion thereof of at least 14 nt, optionally wherein the gRNA spacer sequence comprises the sequence set forth in SEQ ID NO:66 or a contiguous portion of at least 14 nt;

(b) a gRNA targeting a target site of LPA comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:77-86, or a contiguous portion thereof of at least 14 nt;

(c) a gRNA targeting a target site of MYLIP comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:87-96 or 352-361, or a contiguous portion thereof of at least 14 nt;

(d) a gRNA targeting a target site of ANGPTL3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:97-106, or a contiguous portion thereof of at least 14 nt;

(e) a gRNA targeting a target site of APOC3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:107-116, or a contiguous portion thereof of at least 14 nt; and

(f) a gRNA targeting a target site of APOB comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:117-126 or 378-383, or a contiguous portion thereof of at least 14 nt.

15. The epigenetic-modifying DNA-targeting system of claim 3, wherein the first gRNA, the second gRNA, and optionally the third gRNA, are selected from different members of the group consisting of (a)-(f):

(a) a gRNA targeting a target site in PCSK9 comprising the sequence set forth in any one of SEQ ID NOS:129, 127, 128, 130-139 or 330-341, optionally wherein the gRNA comprises the sequence set forth in SEQ ID NO:129;

(b) a gRNA targeting a target site in LPA comprising the sequence set forth in any one of SEQ ID NOS:140-149;

(c) a gRNA targeting a target site in MYLIP comprising the sequence set forth in any one of SEQ ID NOS:150-159 or 362-371;

(d) a gRNA targeting a target site in ANGPTL3 comprising the sequence set forth in any one of SEQ ID NOS:160-169;

(e) a gRNA targeting a target site in APOC3 comprising the sequence set forth in any one of SEQ ID NOS:170-179; and

(f) a gRNA targeting a target site in APOB comprising the sequence set forth in any one of SEQ ID NOS:180-189 or 384-389.

16. The epigenetic-modifying DNA-targeting system of claim 1 claim 3, wherein:

the at least one transcriptional repressor domain comprises a DNA methyltransferase;

the at least one transcriptional repressor domain comprises a histone methyltransferase, or a repressor domain capable of recruiting heterochromatin-inducing factors, optionally wherein the heterochromatin-inducing factors include a histone methyltransferase;

the at least one transcriptional repressor domain comprises a DNA methyltransferase and a repressor domain capable of recruiting heterochromatin-inducing factors, optionally wherein

the heterochromatin-inducing factors include a histone methyltransferase or the at least one transcriptional repressor domain comprises a DNA methyltransferase and a histone methyltransferase.

17. The epigenetic-modifying DNA-targeting system of claim 1 or claim 3, wherein one or more of the at least one transcriptional repressor domain is selected from the group consisting of a KRAB domain, a DNMT3A domain, a DNMT3L domain, a DNMT3B domain, a DNMT3A-DNMT3L fusion protein domain, an ERF repressor domain, an Mxi1 repressor domain, a SID4X repressor domain, a Mad-SID repressor domain, an LSD1 repressor domain, an EZH2 repressor domain, a SunTag domain, or a variant or portion of any of the foregoing, or a combination of any of the foregoing.

18. The epigenetic-modifying DNA-targeting system of claim 18 or claim 3, wherein the at least one transcriptional repressor domain comprises a KRAB domain or a variant or portion thereof that exhibits transcriptional repressor activity; and/or a DNMT3A-DNMT3L fusion protein domain or a variant thereof that exhibits transcriptional repressor activity.

19. The epigenetic-modifying DNA-targeting system of claim 1or claim 3, wherein at least one transcriptional repressor domain comprises a sequence selected from any one of SEQ ID NOS:193, 195, 197, 199, 201, 220-226, and 283, or a domain thereof, a portion thereof, or an amino acid sequence that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any of the foregoing.

20. The epigenetic-modifying DNA-targeting system of claim 1or claim 3, wherein the fusion protein comprises the sequence set forth in any one of SEQ ID NOS:209, 278, 280, or 282, or an amino acid sequence that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, optionally wherein the fusion protein comprises the sequence set forth in SEQ ID NO:280.

21. An epigenetic-modifying DNA-targeting system for repressing transcription of a gene that regulates low-density lipoprotein (LDL) comprising: (a) a fusion protein comprising a Clustered Regularly Interspaced Short Palindromic Repeats associated (Cas) protein or variant thereof and at least one transcriptional repressor domain; and (b) a gRNA that targets a target site of a gene that regulates low-density lipoprotein (LDL).

22. The epigenetic-modifying DNA-targeting system of claim 21, wherein the target site of the gene is in the gene and/or a regulatory DNA element thereof, wherein the regulatory DNA element is a promoter or enhancer.

23. The epigenetic-modifying DNA-targeting system of claim 21, wherein the gene is selected from the group consisting of: PCSK9, LPA, MYLIP, ANGPTL3, APOB, and APOC3.

24. The epigenetic-modifying DNA-targeting system of claim 21, wherein the target site is selected from:

(a) a target site for PCSK9, located within 500bp of human genome assembly GRCh38 (hg38) genomic coordinates chr1:55,039,548;

(b) a target site for LPA, located within 500bp of the hg38 genomic coordinates chr6:160,664,275;

(c) a target site for MYLIP, located within 500bp of the hg38 genomic coordinates chr6:16,129,086;

(d) a target site for ANGPTL3, located within 500bp of the hg38 genomic coordinates chr1:62,597,520;

(e) a target site for APOC3, located within 500bp of the hg38 genomic coordinates chr11:116,829,907; and

(f) a target site for APOB, located within 500bp of the hg38 genomic coordinates chr2:21,044,073.

25. The epigenetic-modifying DNA-targeting system of claim 21, wherein the target site is selected from:

(a) a target site for PCSK9 having the sequence set forth in any one of SEQ ID NOS: 3,1, 2,4-13 or 306-317, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing, optionally wherein the target site has (i) the sequence set forth in SEQ ID NO:3, (ii) a contiguous portion of at least 14 nucleotides set forth in SEQ ID NO:3; or (iii) a complementary sequence of (i) or (ii);

(b) a target site for LPA having the sequence set forth in any one of SEQ ID NOS:14-23, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(c) a target site for MYLIP having the sequence set forth in any one of SEQ ID NOS:24-33 or 342-351, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(d) a target site for ANGPTL3 having the sequence set forth in any one of SEQ ID NOS:34-43, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(e) a target site for APOC3 having the sequence set forth in any one of SEQ ID NOS:44-53, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing; and

(f) a target site for APOB having the sequence set forth in any one of SEQ ID NOS:54-63 or 372-377, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing.

26. The epigenetic-modifying DNA-targeting system of claim 21, wherein the Cas protein or variant thereof is a variant Cas protein that is a deactivated (dCas) protein.

27. The epigenetic-modifying DNA-targeting system of claim 26, wherein the dCas protein is a dCas9 protein.

28. The epigenetic-modifying DNA-targeting system of claim 27, wherein the dCas9 protein is a *Streptococcus pyogenes* dCas9 (dSpCas9) protein.

29. The epigenetic-modifying DNA-targeting system of claim 21, wherein the gRNA is selected from:

(a) a gRNA targeting a target site of PCSK9 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:66, 64, 65, 67-76 or 318-329, or a contiguous portion thereof of at least 14 nt, optionally wherein the gRNA spacer comprises the sequence set forth in SEQ ID NO:66 or a contiguous portion thereof of at least 14 nt;

(b) a gRNA targeting a target site of LPA comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:77-86, or a contiguous portion thereof of at least 14 nt;

(c) a gRNA targeting a target site of MYLIP comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:87-96 or 352-361, or a contiguous portion thereof of at least 14 nt;

(d) a gRNA targeting a target site of ANGPTL3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:97-106, or a contiguous portion thereof of at least 14 nt;

(e) a gRNA targeting a target site of APOC3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:107-116, or a contiguous portion thereof of at least 14 nt; and

(f) a gRNA targeting a target site of APOB comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:117-126 or 378-383, or a contiguous portion thereof of at least 14 nt.

30. The epigenetic-modifying DNA-targeting system of claim 21 , wherein the gRNA is selected from:

(a) a gRNA targeting a target site in PCSK9 comprising the sequence set forth in any one of SEQ ID NOS:129, 127, 128, 130-139 or 330-341, optionally wherein the gRNA comprises the sequence set forth in SEQ ID NO:129;

(b) a gRNA targeting a target site in LPA comprising the sequence set forth in any one of SEQ ID NOS:140-149;

(c) a gRNA targeting a target site in MYLIP comprising the sequence set forth in any one of SEQ ID NOS:150-159 or 362-371;

(d) a gRNA targeting a target site in ANGPTL3 comprising the sequence set forth in any one of SEQ ID NOS:160-169;

(e) a gRNA targeting a target site in APOC3 comprising the sequence set forth in any one of SEQ ID NOS:170-179; and

(f) a gRNA targeting a target site in APOB comprising the sequence set forth in any one of SEQ ID NOS:180-189 or 384-389.

31. The epigenetic-modifying DNA-targeting system of claim 21, wherein the transcriptional repressor domain is selected from the group consisting of a KRAB domain, a DNMT3A domain, a DNMT3L domain, a DNMT3B domain, a DNMT3A-DNMT3L fusion protein domain, an ERF repressor domain, an Mxi1 repressor domain, a SID4X repressor domain, a Mad-SID repressor domain, an LSD1 repressor domain, an EZH2 repressor domain, a SunTag domain, or a variant or portion of any of the foregoing, or a combination of any of the foregoing.

32. The epigenetic-modifying DNA-targeting system of claim 21, wherein the transcriptional repressor domain comprises a KRAB domain or a variant or portion thereof that exhibits transcriptional repressor activity; and/or a DNMT3A-DNMT3L fusion protein domain or a variant thereof that exhibits transcriptional repressor activity.

33. The epigenetic-modifying DNA-targeting system of claim 21, wherein at least one transcriptional repressor domain comprises a sequence selected from any one of SEQ ID NOS:193, 195, 197, 199, 201, 220-226, and 283, or a domain thereof, a portion thereof, or an amino acid sequence that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any of the foregoing.

34. The epigenetic-modifying DNA-targeting system of claim 21, wherein the fusion protein comprises the sequence set forth in any one of SEQ ID NOs: 280, 209, 278, or 282, or an amino acid sequence that has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, optionally wherein the fusion protein is set forth in SEQ ID NO:280.

35. A combination of epigenetic-modifying DNA-targeting systems comprising at least two of the DNA-targeting systems of any of claims 21-34, wherein each DNA-targeting system represses transcription of a different gene.

36. A guide RNA (gRNA) that targets a target site of a gene that regulates low-density lipoprotein (LDL);

wherein the gene is selected from the group consisting of PCSK9, LPA, MYLIP, ANGPTL3, APOB, and APOC3.

37. The gRNA of claim 36, wherein the target site of the gene is in the gene or a regulatory DNA element thereof; wherein the regulatory DNA element is an enhancer or a promoter.

38. The gRNA of claim 36, wherein the target site is selected from:

(a) a target site for PCSK9 having the sequence set forth in any one of SEQ ID NOS:3, 1, 2, 4-13 or 306-317, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing, optionally wherein the target site has (i) the sequence set forth in SEQ ID NO: 3, (ii) a contiguous portion of SEQ ID NO:3 of at least 14 nt; or (iii) a complementary sequence of (i) or (ii);

(b) a target site for LPA having the sequence set forth in any one of SEQ ID NOS:14-23, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(c) a target site for MYLIP having the sequence set forth in any one of SEQ ID NOS:24-33 or 342-351, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(d) a target site for ANGPTL3 having the sequence set forth in any one of SEQ ID NOS:34-43, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing;

(e) a target site for APOC3 having the sequence set forth in any one of SEQ ID NOS:44-53, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing; and

(f) a target site for APOB having the sequence set forth in any one of SEQ ID NOS:54-63 or 372-377, a contiguous portion thereof of at least 14 nucleotides (nt), or a complementary sequence of any of the foregoing.

39. The gRNA of claim 36, wherein the gRNA is selected from:

(a) a gRNA targeting a target site of PCSK9 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:66, 64, 65, 67-76 or 318-329, or a contiguous portion thereof of at least 14 nt, optionally wherein the gRNA spacer sequence comprises the sequence set forth in SEQ ID NO:66 or a contiguous portion thereof of at least 14 nt;

(b) a gRNA targeting a target site of LPA comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:77-86, or a contiguous portion thereof of at least 14 nt;

(c) a gRNA targeting a target site of MYLIP comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:87-96 or 352-361, or a contiguous portion thereof of at least 14 nt;

(d) a gRNA targeting a target site of ANGPTL3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:97-106, or a contiguous portion thereof of at least 14 nt;

(e) a gRNA targeting a target site of APOC3 comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:107-116, or a contiguous portion thereof of at least 14 nt; and

(f) a gRNA targeting a target site of APOB comprising a gRNA spacer sequence comprising the sequence set forth in any one of SEQ ID NOS:117-126 or 378-383, or a contiguous portion thereof of at least 14 nt.

40. The gRNA of claim 36, wherein the gRNA is selected from:

(a) a gRNA targeting a target site in PCSK9 comprising the sequence set forth in any one of SEQ ID NOS:129, 127, 128, 130-139 or 330-341, optionally wherein the gRNA comprises the sequence set forth in SEQ ID NO:129;

(b) a gRNA targeting a target site in LPA comprising the sequence set forth in any one of SEQ ID NOS:140-149;

(c) a gRNA targeting a target site in MYLIP comprising the sequence set forth in any one of SEQ ID NOS:150-159 or 362-371;

(d) a gRNA targeting a target site in ANGPTL3 comprising the sequence set forth in any one of SEQ ID NOS:160-169;

(e) a gRNA targeting a target site in APOC3 comprising the sequence set forth in any one of SEQ ID NOS:170-179; or

(f) a gRNA targeting a target site in APOB comprising the sequence set forth in any one of SEQ ID NOS:180-189 or 384-389.

41. A plurality of gRNAs comprising two or more gRNAs of any of claims 36-40.

42. A Cas-guide RNA (gRNA) combination comprising:

(a) a Clustered Regularly Interspaced Short Palindromic Repeats associated (Cas) protein or variant thereof; and

(b) the gRNA of any of claims 36-40 or the plurality of gRNAs of claim 41.

43. A polynucleotide encoding the epigenetic-modifying DNA-targeting system of any of claims 1-34, the combination of epigenetic-modifying DNA-targeting systems of claim3 5, the gRNA of any of claims 36-40, the plurality of gRNAs of claim 41, the Cas-gRNA combination of claim 42, or a portion or a component of any of the foregoing.

44. A plurality of polynucleotides comprising:

a polynucleotide encoding the fusion protein of the epigenetic-modifying DNA targeting system of any of claims 3-20; and

the at least first gRNA and second gRNA, and optionally the third gRNA, of the epigenetic-modifying DNA-targeting system of any of claims 3-20.

45. A plurality of polynucleotides comprising:

a polynucleotide encoding the fusion protein of the epigenetic-modifying DNA-targeting system of any of claims 21-34; and

the gRNA of the epigenetic-modifying DNA-targeting system of any of claims 21-34.

46. The plurality of polynucleotides of claim 44 or claim 45, wherein the polynucleotide encoding the fusion protein is mRNA.

47. A vector comprising the polynucleotide of claim 43 or the plurality of polynucleotides of claim 44 or claim 45..

48. The vector of claim 47, wherein the vector is a viral vector or is a non-viral vector.

49. A lipid nanoparticle comprising the polynucleotide of claim 43 or the plurality of polynucleotides of claim 44 or claim 45.

50. A method of decreasing transcription of a gene in a cell or population of cells, wherein the gene regulates low-density lipoprotein (LDL) and the method comprises contacting a cell or population of cells with the epigenetic-modifying DNA-targeting system of any of claims 1-34, the combination of epigenetic-modifying DNA-targeting systems of claim 35, the Cas-gRNA combination of claim 42, the polynucleotide of claim 43, the plurality of polynucleotides of any of claims 44-46, the vector of claim 47 or claim 48,or the lipid nanoparticle of claim 49 .

51. A method of reducing LDL, the method comprising introducing into a cell or population of cells the epigenetic-modifying DNA-targeting system of any of claims 1-34, the combination of epigenetic-modifying DNA-targeting systems of claim 35, the Cas-gRNA

combination of claim 42, the polynucleotide of claim 43, the plurality of polynucleotides of any of claims 44-46, the vector of claim 47 or claim 48 , or the lipid nanoparticle of claim 49 .

52. A pharmaceutical composition for use in reducing low-density lipoprotein (LDL) in a subject comprising the epigenetic-modifying DNA-targeting system of any of claims 1-34, the combination of epigenetic-modifying DNA-targeting systems of claim 35, the Cas-gRNA combination of claim 42, the polynucleotide of claim 43, the plurality of polynucleotides of any of claims 44-46, the vector of claim 47 or claim 48, or the lipid nanoparticle of claim 49.

53. Use of the pharmaceutical composition of claim 52 in the manufacture of a medicament for reducing low-density lipoprotein (LDL) in a subject.

54. The method of claim 50, wherein the contacting is a single dose.

55. The method of claim 50, wherein the contacting is repeated at least once, optionally a plurality of times at regular intervals.

56. The method of 50, wherein the contacting is a multiple dose administration comprising at least a first dose and a second dose.