

CLAIMS

1. A single guide RNA (sgRNA) comprising a targeting sequence comprising a sequence that is: at least 95%, 90%, 85%, or 80% identical to or complementary to the nucleotide sequence of SEQ ID NO: 9, 14, or 18; identical to or complementary to at least 17, 18, 19, or 20 contiguous nucleotides of the nucleotide sequence of SEQ ID NO: 9, 14, or 18; or identical to the nucleotide sequence of SEQ ID NO: 9, 14, or 18.
2. The sgRNA of claim 1, wherein the targeting sequence comprises SEQ ID NO: 9, 14, or 18.
3. The sgRNA of claim 1, wherein the targeting sequence comprises SEQ ID NO: 9.
4. The sgRNA of any one of claims 1-3, wherein the sgRNA further comprises at the 3' end a nucleotide sequence comprising the sequence
GUUUUAGAGCUAGAAAUAGCAAGUUA AAAUAAGGCUAGUCCGUUAUCACGAA
AGGGCACCGAGUCGGUGCU (SEQ ID NO: 309).
5. The sgRNA of claim 4, wherein one or more of the first three, four, or five nucleotides at the 5' terminus of the targeting sequence, and one or more of the last three, four, or five nucleotides at the 3' terminus of SEQ ID NO: 309 are modified, wherein the modification is a 2'-O-Me group or a phosphorothioate (PS) bond.
6. The sgRNA of claim 5, wherein the first four nucleotides at the 5' terminus of the targeting sequence and the last four nucleotides at the 3' terminus of SEQ ID NO: 309 are linked with a PS bond.
7. The sgRNA of claim 4, wherein SEQ ID NO: 309 is modified according to the pattern
GUUUUAGAmGmCmUmAmGmAmAmUmAmGmCAAGUUA AAAUAAGGCUAGU
CCGUUAUCACGAAAGGGCACCGAGUCGGmU*mG*mC*mU (SEQ ID NO: 512),
wherein "m" indicates a 2'-O-methyl-modified nucleotide and * indicates a phosphorothioate linkage to the adjacent nucleotide residue.

8. The sgRNA of claim 7, wherein the sgRNA consists of
mC*mG*mU*GCUCAACUGCCAAGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCG
GmU*mG*mC*mU (SEQ ID NO: 221).
9. A pharmaceutical composition comprising the sgRNA of any one of claims 1-8.
10. The pharmaceutical composition of claim 9, further comprising an RNA-guided DNA binding agent or a messenger RNA (mRNA) comprising an open reading frame (ORF) encoding an RNA-guided DNA binding agent.
11. The pharmaceutical composition of claim 10, wherein the RNA-guided DNA binding agent is a *Streptococcus pyogenes* (*S. pyogenes*) Cas9 nuclease.
12. The pharmaceutical composition of claim 11, wherein the *S. pyogenes* Cas9 nuclease comprises an amino acid sequence having at least 90% identity to SEQ ID NO: 1001, 1004, 1007, or 1010, or the mRNA comprises an ORF encoding an *S. pyogenes* Cas9 nuclease having at least 90% identity to SEQ ID NO: 1003, 1006, or 1009.
13. The pharmaceutical composition of any one of claims 10-12, wherein the ORF is modified such that each uridine is replaced with N1-methyl-pseudouridine.
14. The pharmaceutical composition of any one of claims 9-13, wherein the sgRNA consists of
mC*mG*mU*GCUCAACUGCCAAGGGAGUUUUAGAmGmCmUmAmGmAmAmAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCACGAAAGGGCACCGAGUCG
GmU*mG*mC*mU (SEQ ID NO: 221).
15. The pharmaceutical composition of any one of claims 9-14, wherein the sgRNA is associated with a lipid nanoparticle (LNP) comprising an ionizable lipid.
16. The pharmaceutical composition of claim 15, wherein the ionizable lipid is (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-

((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate.

17. The pharmaceutical composition of claim 15 or 16, wherein the LNP further comprises a helper lipid, a neutral lipid, and a stealth lipid.

18. The pharmaceutical composition of claim 17, wherein the helper lipid is cholesterol, the neutral lipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and the stealth lipid is 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2k-DMG).

19. The pharmaceutical composition of claim 15, wherein the ionizable lipid is (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate, and the LNP further comprises DSPC, cholesterol, and PEG2k-DMG.

20. The pharmaceutical composition of any one of claims 9-19 for use in therapy.

21. Use of the pharmaceutical composition of any one of claims 9-19 in the manufacture of a medicament for the treatment of a lipidemia in a human subject.

22. The use of claim 21, wherein the lipidemia is hypercholesterolemia or hypertriglyceridemia.