GENE EDITING OF PCSK9 OR ANGPTL3 AND COMPOSITIONS AND METHODS OF USING SAME FOR TREATMENT OF DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119 from Provisional Application Serial No. 63/247,236, filed September 22, 2021; Provisional Application Serial No. 63/255,333, filed October 13, 2021; and Provisional Application Serial No. 63/389,679, filed July 15, 2022, the disclosures of which are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

[0001a] In one aspect, the present disclosure refers to a hybrid guide nucleic acid comprising: (i) a spacer sequence comprising one or more deoxyribonucleotides and a plurality of ribonucleotides, wherein a 2' hydroxyl group of the ribose of at least one ribonucleotide is covalently linked to a methyl group (2'-OMe), and (ii) a binding scaffold.

[0001b] In another aspect, the present disclosure refers to an *in vivo* hybrid guide gene editing system comprising:

(a) the hybrid guide nucleic acid as described herein, and

(b) a gene editor protein comprising a Cas protein, or a nucleic acid encoding the gene editor protein.

[0001c] In another aspect, the present disclosure refers to use of the *in vivo* hybrid guide editing system as described herein in the manufacture of a medicament for treating or preventing an atherosclerotic cardiovascular disease in a subject in need thereof.

[0001d] In another aspect, the present disclosure refers to use of the *in vivo* hybrid guide editing system as described herein in the manufacture of a medicament for lowering a level of low-density lipoprotein cholesterol (LDL-C) in blood of a subject in need thereof.

[0001e] In another aspect, the present disclosure refers to use of the *in vivo* hybrid guide editing system as described herein in the manufacture of a medicament for lowering a level of triglyceride in blood of a subject in need thereof.

[0001f] In another aspect, the present disclosure refers to use of the *in vivo* hybrid guide editing system as described herein for use in therapy.

[0002] Described herein is an *in vivo* hybrid guide gene editing system comprising: (a) a gene editor protein or a component thereof comprising a nucleic acid binding domain, or a nucleic acid encoding the gene editor protein or the component thereof; and (b) a hybrid guide nucleic acid comprising (i) a spacer sequence comprising a deoxyribonucleotide and a ribonucleotide comprising a ribose, wherein a 2' hydroxyl group of the ribose is covalently linked to a methyl

group (2’-OMe), and (ii) a binding scaffold for the gene editor protein or component thereof, wherein (a) and (b) are constituent components of a pharmaceutical composition that comprises a lipid nanoparticle (LNP) containing (a) or (b), wherein the LNP comprises an amino lipid, a phospholipid, a sterol and a PEG lipid. In some embodiments, the spacer sequence corresponds to a protospacer on a target gene, and wherein the target gene is ANGPTL3. In some embodiments, the gene editor protein or the component thereof comprises a deaminase.

[0003] Described herein is an *in vivo* hybrid guide gene editing system comprising: (a) a gene editor protein or a component thereof comprising a nucleic acid binding domain, or a nucleic acid encoding the gene editor protein or the component thereof; and (b) a hybrid guide nucleic acid comprising (i) a spacer sequence comprising a deoxyribonucleotide and a ribonucleotide, wherein the spacer sequence corresponds to a protospacer on an ANGPTL3 gene, and (ii) a binding scaffold for the gene editor protein or component thereof, wherein (a) and (b) are constituent components of a pharmaceutical composition that comprises a lipid nanoparticle (LNP) containing (a) or (b), wherein the LNP comprises an amino lipid, a phospholipid, a sterol and a PEG lipid. In some embodiments, the gene editor protein or the component thereof comprises a deaminase. In some embodiments, the ribonucleotide comprises a ribose, and wherein the ribose comprises a 2’ hydroxyl group covalently linked to a methyl group (2’-OMe).

[0004] Described herein is an *in vivo* hybrid guide gene editing system comprising: (a) a gene editor protein or a component thereof comprising a nucleic acid binding domain and a deaminase, or a nucleic acid encoding the gene editor protein or the component thereof; and (b) a