CLAIMS

WHAT IS CLAIMED IS:

1. 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.

2. The hybrid guide nucleic acid of claim 1, wherein the spacer sequence comprises one or more unmodified ribonucleotides.

3. The hybrid guide nucleic acid of claim 1 or 2, wherein the deoxyribonucleotide is located at position 3, 4, 6, 7 or 8 from the 5’ end of the spacer sequence.

4. The hybrid guide nucleic acid of any one of claims 1-3, wherein the spacer sequence comprises deoxyribonucleotides at positions

(i) 3, 4, 6 and 7,
(ii) 3 and 4,
(iii) 6 and 7,
(iv) 3, 4, 6, 7 and 8,
(v) 3, 6, 7, and 8,
(vi) 3, 4, 7, and 8,
(vii) 3, 4, and 6,
(viii) 3, 7, and 8,
(ix) 3, 6, and 8, or
(x) 3, 4, and 8,
from the 5’ end of the spacer sequence.

5. The hybrid guide nucleic acid of any one of claims 1-3, wherein the spacer sequence comprises one to ten deoxyribonucleotides.

6. The hybrid guide nucleic acid of any one of claims 1-5, wherein the spacer sequence comprises at least one phosphorothioate backbone modification (PS).

7. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at least two deoxyribonucleotides.

8. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at least three deoxyribonucleotides.

9. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at least four deoxyribonucleotides.

10. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at least five deoxyribonucleotides.

11. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at most five deoxyribonucleotides.

12. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at most three deoxyribonucleotides.

13. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at most two deoxyribonucleotides.

14. The hybrid guide nucleic acid of any one of claims 1-6, wherein the hybrid guide nucleic acid comprises at least one chemically modified deoxyribonucleotides.

15. The hybrid guide nucleic acid of any one of claims 1-6, wherein at least one ribonucleotide is in between two deoxyribonucleotides.

16. The hybrid guide nucleic acid of any one of claims 1-6, wherein the spacer sequence comprises a 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(RNA)(DNA)(DNA) – 3’ motif.

17. The hybrid guide nucleic acid of claim 16, wherein the 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(RNA)(DNA)(DNA) – 3’ motif is located at the 5’ end of the spacer sequence.

18. The hybrid guide nucleic acid of any one of claims 1-6, wherein the spacer sequence comprises a 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(RNA)(DNA)(DNA)(DNA) – 3’ motif.

19. The hybrid guide nucleic acid of claim 18, wherein the 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(RNA)(DNA)(DNA)(DNA) – 3’ motif is located at the 5’ end of the spacer sequence.

20. The hybrid guide nucleic acid of any one of claims 1-6, wherein the spacer sequence comprises a 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(DNA)(DNA)(DNA) – 3’ motif.

21. The hybrid guide nucleic acid of claim 20, wherein the 5’ – (2’-OMe)PS(2’-OMe)PS(DNA)PS(DNA)(DNA)(DNA)(DNA) – 3’ motif is located at the 5’ end of the spacer sequence.

22. The hybrid guide nucleic acid of any one of claims 1-21, wherein the spacer has 20 nucleotides.

23. The hybrid guide nucleic acid of any one of claims 1-22, wherein the hybrid guide nucleic acid is a CRISPR-Cas hybrid guide nucleic acid.

24. An *in vivo* hybrid guide gene editing system comprising:

(a) the hybrid guide nucleic acid of any one of claims 1-23, and

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

25. The *in vivo* hybrid guide gene editing system of claim 24, wherein the gene editor protein is a fusion protein comprising a deaminase.

26. The *in vivo* hybrid guide gene editing system of claim 24 or 25, wherein the Cas protein is capable of binding to DNA or RNA.

27. The *in vivo* hybrid guide gene editing system of any one of claims 24-26, wherein the Cas protein comprises a nuclease inactive domain.

28. The *in vivo* hybrid guide gene editing system of any one of claims 24-26, wherein the Cas protein is a Cas9 nickase.

29. The *in vivo* hybrid guide gene editing system of claim 28, wherein the Cas9 nickase comprises a D10A mutation.

30. The *in vivo* hybrid guide gene editing system of any one of claims 24-29, wherein the nucleic acid encoding the gene editor protein is an mRNA.

31. The *in vivo* hybrid guide gene editing system of claim 30, wherein the mRNA comprises a sequence having at least 80% sequence identity to SEQ ID NO: 687.

32. The *in vivo* hybrid guide gene editing system of claim 31, wherein the mRNA comprises a sequence set forth in SEQ ID NO: 687.

33. The *in vivo* hybrid guide gene editing system of claim 30, wherein the mRNA comprises a sequence having at least 80% sequence identity to SEQ ID NO: 701.

34. The *in vivo* hybrid guide gene editing system of claim 33, wherein the mRNA comprises a sequence set forth in SEQ ID NO: 701.

35. The *in vivo* hybrid guide gene editing system of any one of claims 24-34, wherein the gene editor protein affects less than about 10% editing on all off-target sites as compared to a gene editing system comprising a corresponding guide nucleic acid without the deoxyribonucleotide.

36. The *in vivo* hybrid guide gene editing system of any one of claims 24-35, wherein the gene editor protein affects over about 50% editing on a target gene as compared to a gene editing system comprising a corresponding guide nucleic acid without the deoxyribonucleotide.

37. Use of the *in vivo* hybrid guide editing system of any one of claims 24-36 in the manufacture of a medicament for treating or preventing an atherosclerotic cardiovascular disease in a subject in need thereof.

38. Use of the *in vivo* hybrid guide editing system of any one of claims 24-36 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.

39. Use of the *in vivo* hybrid guide editing system of any one of claims 24-36 in the manufacture of a medicament for lowering a level of triglyceride in blood of a subject in need thereof.

40. The *in vivo* hybrid guide editing system of any one of claims 24-36 for use in therapy.