

What is claimed is:

1. A TREM comprising a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein:
independently, [L1] and [VL Domain], are optional;
one of [L1], [ASt Domain1], [L2]-[DH Domain], [L3], [ACH Domain], [VL Domain], [TH Domain], [L4], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification, and
the non-naturally occurring modification is present on a nucleotide (e.g., a modified nucleotide) at a position corresponding to a modified position in a row of any of Table 15-22, e.g., described herein.

2. The TREM of claim 1, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region (e.g., a backbone modification).

3. The TREM of claim 2, wherein the non-naturally occurring modification is selected from a 2-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), or 2'deoxy modification.

4. The TREM of claim 3, wherein the non-naturally occurring modification is a 2'OMe modification.

5. The TREM of claim 3, wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

6. The TREM of claim 3, wherein the non-naturally occurring modification is a 2'MOE modification.

7. The TREM of claim 3, wherein the non-naturally occurring modification is a 2'-deoxy modification.
8. The TREM of claim 2, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).
9. The TREM of claim 8, wherein the non-naturally occurring modification is a phosphorothioate modification.
10. The TREM of claim 2, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1-76 of SEQ ID NO: 622, nucleotides 1-85 of SEQ ID NO: 993, or nucleotides 1-75 of SEQ ID NO: 1079.
11. The TREM of claim 2, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1-76 of SEQ ID NO: 622.
12. The TREM of claim 10, wherein the non-naturally occurring modification is present on or within a nucleotide in the [ASt Domain1] or [ASt Domain2].
13. The TREM of claim 10, wherein the non-naturally occurring modification is present on or within a nucleotide in the [DH Domain], [ACH Domain], [VL Domain], or [TH Domain].
14. The TREM of claim 10, wherein the non-naturally occurring modification is present within a linker domain (e.g., [L1], [L2], [L3], or [L4]).
15. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1, 2, 4, 6, 10, 12, 13, 17, 18, 20, 22, 29, 30, 42, 43, 45, 50, 52, 56, 59, 61, 65, 66, 68, 69, 71, 72, and 73 of SEQ ID NO: 622.

16. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 20, 29, 33, 40, 41, 44, 45, 48, 49, 50, 52, 53, 54, 56, 59, 61, 62, 63, 65, 67, 68, 69, 71, 72, 75, and 76 of SEQ ID NO: 622.

17. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1, 4, 14, 15, 16, 17, 20, 29, 44, 45, 47, 49, 50, 52, 54, 56, 57, 59, 65, 72, and 73 of SEQ ID NO: 622.

18. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 3, 4, 5, 6, 14, 15, 16, 20, 22, 23, 33, 54, 59, 62, 63, 72, and 76 of SEQ ID NO: 622.

19. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1, 2, 3, 9, 14, 15, 16, 17, 18, 19, 20, 21, 35, 37, 38, 44, 45, 46, 52, 54, 55, 56, 57, 58, 73, and 74 of SEQ ID NO: 622.

20. The TREM of claim 1, wherein the non-naturally occurring modification is present on or within any one of nucleotides 1, 17, 18, 20, 29, 30, 50, 52, and 73 of SEQ ID NO: 622.

21. A pharmaceutical composition comprising a TREM of claim 1.

22. The pharmaceutical composition of claim 21, further comprising a pharmaceutically acceptable component, e.g., an excipient.

23. A lipid nanoparticle formulation comprising a TREM of claim 1.

24. A lipid nanoparticle formulatin comprising a pharmaceutical composition of claim 21.