

What is claimed is:

1. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):
[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),
wherein:
independently, [L1] and [VL Domain], are optional; and
a nucleotide within [L1]-[ASt Domain1]-[L2] comprises a nucleotide having a non-naturally occurring modification.
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.
3. The TREM of any one of the preceding claims, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.
4. The TREM of any one of the preceding claims, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.
5. The TREM of any one of the preceding claims, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 1-9 of SEQ ID NO: 622 or one or more of nucleotides 1-9 according to the CtNS.
6. The TREM of any one of the preceding claims, wherein:
 - (i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 1-9 of SEQ ID NO: 622; and/or
 - (ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

7. The TREM of any one of claims 1-6, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.
8. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):
[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),
wherein:
independently, [L1] and [VL Domain], are optional; and
a nucleotide within [DH Domain], or [L3] comprises a nucleotide having a non-naturally occurring modification.
9. The TREM of claim 8, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region.
10. The TREM of any one of claims 8-9, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.
11. The TREM of any one of claims 8-10, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.
12. The TREM of any one of claims 8-11, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 10-26 of SEQ ID NO: 622 or one or more of nucleotides 10-26 according to the CtNS.
13. The TREM of any one of claims 8-12, wherein:
(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 10-26 of SEQ ID NO: 622; and/or
(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

14. The TREM of any one of claims 8-13, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.
15. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):
[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),
wherein:
independently, [L1] and [VL Domain], are optional; and
a nucleotide within [ACH Domain] comprises a nucleotide having a non-naturally occurring modification.
16. The TREM of claim 15, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region.
17. The TREM of any one of claims 15-16, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.
18. The TREM of any one of claims 15-17, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.
19. The TREM of any one of claims 15-18, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 27-43 of SEQ ID NO: 622 or one or more of nucleotides 27-43 according to the CtNS.
20. The TREM of any one of claims 15-19, wherein:
(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 27-43 of SEQ ID NO: 622; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

21. The TREM of any one of claims 15-20, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.

22. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):
[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),
wherein:
independently, [L1] and [VL Domain], are optional; and
a nucleotide within [VL Domain] comprises a nucleotide having a non-naturally occurring modification.

23. The TREM of claim 22, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region.

24. The TREM of any one of claims 22-23, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.

25. The TREM of any one of claims 22-24, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.

26. The TREM of any one of claims 22-25, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 44-48 of SEQ ID NO: 622 or one or more of nucleotides 44-48 according to the CtNS.

27. The TREM of any one of claims 22-26, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 44-48 of SEQ ID NO: 622; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

28. The TREM of any one of claims 22-27, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.

29. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),

wherein:

independently, [L1] and [VL Domain], are optional; and

a nucleotide within [TH Domain] comprises a nucleotide having a non-naturally occurring modification.

30. The TREM of claim 29, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region .

31. The TREM of any one of claims 29-30, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.

32. The TREM of any one of claims 29-31, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.

33. The TREM of any one of claims 29-32, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 49-65 of SEQ ID NO: 622 or one or more of nucleotides 49-65 according to the CtNS.

34. The TREM of any one of claims 29-33, wherein:
- (i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 49-65 of SEQ ID NO: 622; and/or
 - (ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.
35. The TREM of any one of claims 29-34, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.
36. A tRNA effector molecule (TREM) comprising a sequence of Formula (I):
[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (I),
wherein:
independently, [L1] and [VL Domain], are optional; and
a nucleotide within [L4] or [ASt Domain 2] comprises a nucleotide having a non-naturally occurring modification.
37. The TREM of claim 36, wherein the non-naturally occurring modification is present on the 2'-position of a nucleotide sugar or within the internucleotide region.
38. The TREM of any one of claims 36-37, wherein the non-naturally occurring modification is selected from a 2'-O-methyl (2-OMe), 2'-halo (2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), 2'deoxy, and a phosphorothioate modification.
39. The TREM of any one of claims 36-38, wherein the TREM comprises a sequence selected from a sequence provided in FIG. 2 or a sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a sequence provided in FIG. 2.
40. The TREM of any one of claims 36-39, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 66-76 of SEQ ID NO: 622 or one or more of nucleotides 66-76 according to the CtNS.

41. The TREM of any one of claims 36-40, wherein:
- (i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 66-76 of SEQ ID NO: 622; and/or
 - (ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 622 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.
42. The TREM of any one of claims 36-41, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 622, SEQ ID NO: 623, or SEQ ID NO: 624.
43. A TREM, according to Design Guidance 1, Design Guidance 2, Design Guidance 3, Design Guidance 4, Design Guidance 5, or Design Guidance 6.
44. A TREM, according to any two, three, four, five, or all of Design Guidances 1, 2, 3, 4, 5, and 6.
45. A pharmaceutical composition comprising a TREM of any one of the preceding claims.
46. A lipid nanoparticle formulation comprising a TREM of any one of claims 1-44 or the pharmaceutical composition of claim 45.
47. Use of a TREM, TREM core fragment, or TREM fragment described in any one of the preceding claims, in the manufacture of a medicament for treating a subject having a disease or disorder associated with a PTC.
48. The use of claim 47, wherein the disease or disorder associated with a PTC comprises Hemophilia B, Fabry disease, Usher syndrome, or CLN2 disease.