TREM COMPOSITIONS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/255,420, filed on October 13, 2021; U.S. Provisional Application No. 63/255,426, filed on October 13, 2021; U.S. Provisional Application No. 63/284,934, filed on December 1, 2021; and U.S. Provisional Application No. 63/284,946, filed on December 1, 2021; the entire contents of each of the foregoing applications is hereby incorporated by reference.

BACKGROUND

Transfer RNAs (tRNAs) are complex, naturally occurring RNA molecules that possess a number of functions including initiation and elongation of proteins.

SUMMARY

The present disclosure features modified tRNA-based effector molecules (TREMs, e.g., a TREM or TREM fragment), as well as related compositions and uses thereof. As provided herein, TREMs are complex molecules which can mediate a variety of cellular processes. The TREMs disclosed herein comprise at least one modification (e.g., a non-naturally occurring modification), e.g., on a component nucleotide (e.g., a nucleobase or sugar) or within an internucleotide region, e.g., the TREM backbone. In one aspect, provided herein is 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; and one of [L1], [ASt Domain1], [L2]-[DH Domain], [L3], [ACH Domain], [VL Domain], [TH Domain], [L4], and [ASt Domain2] comprises a nucleotide comprising a non-naturally occurring modification.

In an embodiment, the TREM: (a) has the ability to: (i) support protein synthesis, (ii) be charged by a synthetase, (iii) be bound by an elongation factor, (iv) introduce an amino acid into a peptide chain, (v) support elongation, or (vi) support initiation; (b) comprises at least X contiguous nucleotides without a non-naturally occurring modification, wherein X is greater than 3, 4, 5, 6, 7, 8, 9, or 10; (c) comprises at least 3, but less than all of the nucleotides of a type (e.g., A, T, C, G or U) comprise the same non-naturally occurring modification; (d) comprises at least

X nucleotides of a type (e.g., A, T, C, G or U) that do not comprise a non-naturally occurring modification, wherein X= than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, or 80; (e) comprises no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, or 80 nucleotides of a type (e.g., A, T, C, G or U) that comprise a non-naturally occurring modification; and/or (f) comprises no more than than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, or 80 nucleotides of a type (e.g., A, T, C, G or U) that do not comprise a non-naturally occurring modification.

In an embodiment, the TREM comprises feature (a)(i). In an embodiment, the TREM comprises feature (a)(ii). In an embodiment, the TREM comprises feature (a)(iii). In an embodiment, the TREM comprises feature (a)(iv). In an embodiment, the TREM comprises feature (a)(v). In an embodiment, the TREM comprises feature (a)(vi). In an embodiment, the TREM comprises feature (b). In an embodiment, the TREM comprises feature (c). In an embodiment, the TREM comprises feature (d). In an embodiment, the TREM comprises feature (e). In an embodiment, the TREM comprises feature (f). In an embodiment, the TREM comprises all of features (a)-(f) or a combination thereof.

In an embodiment, the TREM Domain comprising the non-naturally occurring modification has a function, e.g., a domain function described herein.

In an aspect, provided herein is a TREM core fragment comprising a sequence of Formula B:

$[L1]_y$-[ASt Domain1]$_x$-$[L2]_y$-[DH Domain]$_y$-$[L3]_y$-[ACH Domain]$_x$-[VL Domain]$_y$-[TH Domain]$_y$-$[L4]_y$-[ASt Domain2]$_x$,

wherein x=1 and y=0 or 1; and one of [ASt Domain1], [ACH Domain], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM has the ability to support protein synthesis. In an embodiment, the TREM has the ability to be able to be charged by a synthetase. In an embodiment, the TREM has the ability to be bound by an elongation factor. In an embodiment, the TREM has the ability to introduce an amino acid into a peptide chain. In an embodiment, the

TREM has the ability to support elongation. In an embodiment, the TREM has the ability to support initiation.

In an embodiment, the [ASt Domain 1] and/or [ASt Domain 2] comprising the non-naturally occurring modification has the ability to initiate or elongate a polypeptide chain.

In an embodiment, the [ACH Domain] comprising the non-naturally occurring modification has the ability to mediate pairing with a codon.

In an embodiment, y=1 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

In an embodiment, y=0 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

In an embodiment, y=1 for linker [L1], and L1 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for linker [L2], and L2 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [DH Domain (DHD)], and DHD comprises a nucleotide having a non-naturally occurring modification. In an embodiment, the DHD comprising the non-naturally occurring modification has the ability to mediate recognition of aminoacyl-tRNA synthetase.

In an embodiment, y=1 for linker [L3], and L3 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [VL Domain (VLD)], and VLD comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [TH Domain (THD)], and THD comprises a nucleotide having a non-naturally occurring modification. In an embodiment, the THD comprising the non-naturally occurring modification has the ability to mediate recognition of the ribosome.

In an embodiment, y=1 for linker [L4], and L4 comprises a nucleotide having a non-naturally occurring modification.

In another aspect, the disclosure provides a TREM fragment comprising a portion of a TREM, wherein the TREM comprises a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein the TREM fragment comprises a non-naturally occurring modification.

In an embodiment, the TREM fragment comprises one, two, three or all or any combination of the following: (a) a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half); (b) a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain); (c) a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or (d) an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain).

In an embodiment, the TREM fragment comprise (a) a TREM half which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (b) a 5' fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (c) a 3' fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (d) an internal fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM Domain comprises a plurality of nucleotides each having a non-naturally occurring modification. In an embodiment, the non-naturally occurring modification comprises a nucleobase modification, a sugar (e.g., ribose) modification, or a backbone modification. In an embodiment, tbe non-naturally occurring modification is a sugar (e.g., ribose) modification. In an embodiment, tbe non-naturally occurring modification is 2'-ribose modification, e.g., a 2'-OMe, 2'-halo (e.g., 2'-F), 2'-MOE, or 2'-deoxy modification. In an embodiment, tbe non-naturally occurring modification is a backbone modification, e.g., a phosphorothioate modification.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM sequence comprises a CCA sequence on a terminus, e.g., the 3' terminus. In an embodiment, the TREM sequence does not comprise a CCA sequence on a terminus, e.g., the 3' terminus.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a modification in a base or a backbone of a nucleotide, e.g., a modification chosen from any one of Tables 5, 6, 7, 8 or or 9.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 5.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 6.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 7.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a backbone modification chosen from a modification listed in Table 8.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a backbone modification chosen from a modification listed in Table 9.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is encoded by a sequence provided in Table 1, e.g., any one of SEQ ID NOs 1-451.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is encoded by a consensus sequence chosen from any one of SEQ ID NOs: 562-621.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is encoded by a sequence provided in FIG. 2, e.g., any one of SEQ ID NOs: 622-9757. In an embodiment, the TREM, TREM core fragment, or TREM fragment comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2, e.g., any one of SEQ ID NOs: 622-9757. In an embodiment, the TREM, TREM core fragment, or TREM fragment comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

nucleotides from a TREM provided in FIG. 2, e.g., any one of SEQ ID NOs: 622-3284. In an embodiment, the TREM, TREM core fragment, or TREM fragment comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM, TREM core fragment, or TREM fragment provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications), e.g., any one of SEQ ID NOs: 622-9757.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is a TREM provided in FIG. 2, e.g., any one of TREM NOs: 1-9757. In an embodiment, the TREM, TREM core fragment, or TREM fragment comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications), e.g., any one of TREM NOs. 1-2663.

In another aspect, the disclosure provides a pharmaceutical composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein.

In another aspect, a TREM or a related composition thereof can be used, *inter alia,* to modulate a production parameter (e.g., an expression parameter and/or a signaling parameter) of an RNA corresponding to, or a polypeptide encoded by, a nucleic acid sequence comprising an endogenous open reading frame (ORF) having a premature termination codon (PTC).

In another aspect, provided herein is a method of modulating a production parameter of an mRNA corresponding to, or polypeptide encoded by, an endogenous open reading frame (ORF) in a subject, which ORF comprises a premature termination codon (PTC), contacting the subject with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein in an amount and/or for a time sufficient to modulate the production parameter of the mRNA or polypeptide, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with the codon having the first sequence, thereby modulating the production parameter in the subject. In an embodiment, the production parameter comprises a signaling parameter and/or an expression parameter, e.g., as described herein.

In another aspect, disclosed herein is a method of modulating expression of a protein in a cell, wherein the protein is encoded by a nucleic acid comprising an endogenous open reading frame (ORF), which ORF comprises a premature termination codon (PTC), comprising

contacting the cell with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein in an amount and/or for a time sufficient to modulate expression of the encoded protein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with the PTC, thereby modulating expression of the protein in the cell. In an embodiment, the PTC comprises UAA, UGA or UAG.

In another aspect, provided herein is a method of increasing expression of a protein in a subject wherein the protein is encoded by a nucleic acid comprising an endogenous open reading frame (ORF), which ORF comprises a premature termination codon (PTC), comprising contacting the subject, in an amount and/or for a time sufficient to increase expression of the protein, with a TREM composition that (i) has an anticodon that pairs with the PTC, (ii) recognizes an aminoacyl-tRNA synthetase specific for Trp, Tyr, Cys, Glu, Lys, Gln, Ser, Leu, Arg, or Gly, (iii) comprises a sequence of Formula A, or (iv) comprises a non-naturally occurring modification. In an embodiment, the PTC comprises UAA, UGA or UAG. In an embodiment, the TREM composition comprises (i). In an embodiment, the TREM composition comprises (ii). In an embodiment, the TREM composition comprises (iii). In an embodiment, the TREM composition comprises (iv). In an embodiment, the TREM composition comprises two of (i)-(iv). In an embodiment, the TREM composition comprises three of (i)-(iv). In an embodiment, the TREM composition comprises each of (i)-(iv).

In another aspect, the disclosure provides a method of treating a subject having an endogenous open reading frame (ORF) which comprises a premature termination codon (PTC), comprising providing a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein, wherein the TREM comprises an anticodon that pairs with the PTC in the ORF; contacting the subject with the composition comprising a TREM, TREM core fragment or TREM fragment in an amount and/or for a time sufficient to treat the subject, thereby treating the subject. In an embodiment, the PTC comprises UAA, UGA or UAG.

In another aspect, the disclosure provides a method of treating a subject having an disease or disorder associated with a premature termination codon (PTC), comprising providing a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein; contacting the subject with the composition comprising a TREM, TREM core fragment or TREM fragment in an amount and/or for a time sufficient to treat the subject, thereby treating the subject. In an embodiment, the PTC comprises UAA, UGA or UAG. In an embodiment, the

disease or disorder associated with a PTC is a disease or disorcer described herein, e.g., a cancer or a monogenic disease.

In an embodiment of any of the methods disclosed herein, the codon having the first sequence comprises a mutation (e.g., a point mutation, e.g., a nonsense mutation), resulting in a premature termination codon (PTC) chosen from UAA, UGA or UAG. In an embodiment, the codon having the first sequence or the PTC comprises a UAA mutation. In an embodiment, the codon having the first sequence or the PTC comprises a UGA mutation. In an embodiment, the codon having the first sequence or the PTC comprises a UAG mutation

In another aspect, the disclosure provides a method of making a TREM, a TREM core fragment, or a TREM fragment disclosed herein, comprising linking a first nucleotide to a second nucleotide to form the TREM.

In an embodiment, the TREM, TREM core fragment or TREM fragment is non-naturally occurring (e.g., synthetic).

In an embodiment, the TREM, TREM core fragment or TREM fragment is made by cell-free solid phase synthesis.

In another aspect, the disclosure provides a method of modulating a tRNA pool in a cell comprising: providing a TREM, a TREM core fragment, or a TREM fragment disclosed herein, and contacting the cell with the TREM, TREM core fragment or TREM fragment, thereby modulating the tRNA pool in the cell.

In an aspect, the disclosure provides a method of contacting a cell, tissue, or subject with a TREM, a TREM core fragment, or a TREM fragment disclosed herein, comprising: contacting the cell, tissue or subject with the TREM, TREM core fragment or TREM fragment, thereby contacting the cell, tissue, or subject with the TREM, TREM core fragment or TREM fragment.

In another aspect, the disclosure provides a method of delivering a TREM, TREM core fragment or TREM fragment to a cell, tissue, or subject, comprising: providing a cell, tissue, or subject, and contacting the cell, tissue, or subject, a TREM, a TREM core fragment, or a TREM fragment disclosed herein.

In an aspect, the disclosure provides a method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the cell, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell;

contacting the cell with a TREM, a TREM core fragment, or a TREM fragment disclosed herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: the codon having the first sequence; or the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the cell,

thereby modulating the tRNA pool in the cell.

In another aspect, the disclosure provides a method of modulating a tRNA pool in a subject having an ORF, which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the subject, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the subject;

contacting the subject with a TREM, a TREM core fragment, or a TREM fragment disclosed herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: the codon having the first sequence; or the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the subject,

thereby modulating the tRNA pool in the subject.

In an aspect, the disclosure provides a method of modulating a tRNA pool in a subject having an endogenous ORF comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the subject with the composition in an amount and/or for a time sufficient to modulate the tRNA pool in the subject,

thereby modulating the tRNA pool in the subject.

In another aspect, the disclosure provides a method of modulating a tRNA pool in a cell comprising an endogenous ORF comprising a codon comprising a SMC, comprising:

providing a composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the cell with the composition comprising a TREM in an amount and/or for a time sufficient to modulate the tRNA pool in the cell,

thereby modulating the tRNA pool in the cell.

In an aspect, the disclosure provides a method of modulating expression of a protein in a cell, wherein the protein is encoded by a nucleic acid comprising an ORF, which ORF comprises a codon having a mutation, comprising:

contacting the cell with a composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein in an amount and/or for a time sufficient to modulate expression of the encoded protein,

wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with the codon having the mutation,

thereby modulating expression of the protein in the cell.

In another aspect, the disclosure provides a method of modulating expression of a protein in a subject, wherein the protein is encoded by a nucleic acid comprising an endogenous ORF, which ORF comprises a codon having a mutation, comprising:

contacting the subject with a composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein, in an amount and/or for a time sufficient to modulate expression of the encoded protein,

wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with the codon having the mutation,

thereby modulating expression of the protein in the subject.

In an embodiment of any of the methods disclosed herein, the mutation in the ORF is a nonsense mutation, e.g., resulting in a premature stop codon chosen from UAA, UGA or UAG. In an embodiment, the stop codon is UAA. In an embodiment, the stop codon is UGA. In an embodiment, the stop codon is UAG.

In an embodiment of any of the methods disclosed herein, the TREM comprises an anticodon that pairs with a stop codon.

TREMs of the disclosure include TREMs, TREM core fragments and TREM fragments. TREMs, TREM core fragments or TREM fragments can be modified with non-naturally occurring modifications to, e.g., increase the level and/or activity (e.g., stability) of the TREM. Pharmaceutical TREM compositions, e.g., comprising TREMs having a non-naturally occurring modification, can be administered to cells, tissues or subjects to modulate these functions, *e.g.*, *in vitro* or *in vivo*. Disclosed herein are TREMs, TREM core fragments or TREM fragments comprising non-naturally occurring modifications, TREM compositions, preparations, methods of making TREM compositions and preparations, and methods of using the same.

In an embodiment, the TREM, TREM core fragment, and TREM fragments comprise a non-naturally occurring modification that improves stability or enhances activity of the TREM, TREM core fragment, or TREM fragment.

Additional features of any of the aforesaid TREMs, TREM core fragments, TREM fragments, TREM compositions, preparations, methods of making TREM compositions and preparations, and methods of using TREM compositions and preparations include one or more of the features in the Enumerated Embodiments, Figures, Description, Examples, or Claims.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following Enumerated Embodiments, Drawings, Description, Examples, or Claims.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a depiction of a representative TREM with a summary of a design guidances (e.g., Design Guidance 1-6) described herein.

FIG. 2 is a table summarizing exemplary TREMs, TREM core fragments, and TREM fragments described herein. The sequence of each TREM, TREM core fragment, and TREM

fragment is provided, and the chemical modification profile is annotated as follows: : r: ribonucleotide; m: 2'-OMe; *: PS linkage; f: 2'-fluoro; moe: 2'-moe; d: deoxyribonucleotide; 5MeC: 5-methylcytosine. Thus, for example, mA represents 2'-O-methyl adenosine, moe5MeC represents 2'-MOE nucleotide with 5-methylcytosine nucleobase, and dA represents an adenosine deoxyribonucleotide. The table also provides mass spectrometric characterization of each TREM, TREM core fragment, and TREM fragment, along with results from the activity screens described in Examples 6 and 7. The results from the activity screens are in the columns titled "A" (described in Example 6), "B," "C," and "D" (all three described in Example 7).

FIG. 3 is an image showing PTC readthrough activity of exemplary TREMs described herein in four cell lines as outlined in both Examples 6 and 7. Activity is shown as log2 fold change over a control unmodified TREM.

FIG. 4 is an image showing Western blot analysis of full-length GLA protein rescue in Fabry patient fibroblasts and normal healthy fibroblasts upon administration of exemplary TREMs described herein, as described in Example 11.

FIGS. 5A-5E depict the results of time course and dose-response studies in Fabry patient fibroblasts and normal healthy fibroblasts upon administration of exemplary TREMs described herein, as described in Example 11.

FIG. 6 is a graph illustrating the rescue of GLA activity in Fabry patient fibroblasts upon administration of exemplary TREMs described herein, as outlined in Example 11.

FIG. 7 is a set of graphs illustrating *in vivo* PTC readthrough and target engagement of a TREM. **FIG. 7A** is a graph depicting dose-dependent expression of luciferase in the liver from a plasmid following hydrodynamic delivery. **FIG. 7B** is a graph illustrating rescue of a luciferase gene with a PTC mutation with a plasmid expressing the corresponding TREM.

ENUMERATED EMBODIMENTS

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 any one of (i) [L1]-[ASt Domain1]-[L2], (ii) [DH Domain]-[L3]; (iii) [ACH Domain]; (iv) [VL Domain]; (v) [TH Domain]; and [L4]-[ASt Domain2] comprises a nucleotide having a non-naturally occurring modification.

2. The TREM of embodiment 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 any one of the preceding embodiments, 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 any one of the preceding embodiments, wherein the non-naturally occurring modification is a 2'OMe modification.

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

6. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is a 2'MOE modification.

7. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is a 2'-deoxy modification.

8. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

9. The TREM of embodiment 8, wherein the non-naturally occurring modification is a phosphorothioate modification.

11. The TREM of any one of the preceding embodiments, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

12. The TREM of any one of the preceding embodiments, wherein the TREM is a TREM provided in FIG. 2.

13. The TREM of any one of the preceding embodiments, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

14. The TREM of any one of the preceding embodiments, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

15. The TREM of any one of the preceding embodiments, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

16. The TREM of any one of the preceding embodiments, wherein the TREM is selected from TREM NOs. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2.

17. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 1-500 in FIG. 2.

18. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 501-1000 in FIG. 2.

19. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 1001-2000 in FIG. 2.

20. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 2001-3000 in FIG. 2.

21. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 3001-4000 in FIG. 2.

22. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 4001-5000 in FIG. 2.

23. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 5001-6000 in FIG. 2.

24. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 6001-7000 in FIG. 2.

25. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 7001-8000 in FIG. 2.

26. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 8001-9000 in FIG. 2.

27. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of TREM NOs. 9001-9136 in FIG. 2.

28. The TREM of any one of the preceding embodiments, wherein the TREM is selected from TREM NOs. 1-100, 101-200, 201-300, 301-400, 401-500, 501-600, 601-700, 701-800, 801-900, 901-1000, 1001-1100, 1101-1200, 1201-1300, 1301-1400, 1401-1500, 1501-1600, 1601-1700, 1701-1800, 1801-1900, 1901-2000, 2001-2100, 2101-2200, 2201-2300, 2301-2400, 2401-2500, 2501-2600, and 2601-2663 in FIG. 2.

29. The TREM of any one of the preceding embodiments, wherein the TREM is selected from SEQ ID NOs. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, 9001-9500, and 9501-9757.

30. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 1-500.

31. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 501-1000.

32. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 1001-2000.

33. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 2001-3000.

34. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 3001-4000.

35. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 4001-5000.

36. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 5001-6000.

37. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 6001-7000.

38. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 7001-8000.

39. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 8001-9000.

40. The TREM of any one of the preceding embodiments, wherein the TREM has at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to one of SEQ ID NOs. 9001-9757.

41. The TREM of any one of the preceding embodiments, wherein the TREM is selected from SEQ ID NOs. 1-100, 101-200, 201-300, 301-400, 401-500, 501-600, 601-700, 701-800, 801-900, 901-1000, 1001-1100, 1101-1200, 1201-1300, 1301-1400, 1401-1500, 1501-1600, 1601-1700, 1701-1800, 1801-1900, 1901-2000, 2001-2100, 2101-2200, 2201-2300, 2301-2400, 2401-2500, 2501-2600, 2601-2700, 2701-2800, 2801-2900, 2901-3000, 3001-3100, 3101-3200, and 3201-3284.

42. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 622.

43. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides 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.

44. The TREM of any one of the preceding embodiments, wherein:

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

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 622.

45. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 622.

46. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

47. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

48. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

49. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 622.

50. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

51. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

52. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [DH Domain].

53. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 622.

54. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

55. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo

(e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

56. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [ACH Domain].

57. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 622.

58. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

59. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

60. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [VL Domain].

61. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 622.

62. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

63. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

64. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [TH Domain].

65. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 622.

66. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

67. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

68. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 622 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

69. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 623.

70. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 623; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 623by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

71. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 623; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

72. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 623.

73. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

74. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe)

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

75. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

76. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 623.

77. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

78. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

79. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [DH Domain].

80. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 623.

81. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

82. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

83. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [ACH Domain].

84. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 623.

85. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

86. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

87. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [VL Domain].

88. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 623.

89. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

90. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

91. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [TH Domain].

92. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 623.

93. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

94. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

95. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 623 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

96. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 624.

97. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 624; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 624 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

98. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 624; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

99. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 624.

100. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

101. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

102. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

103. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 624.

104. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

105. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

106. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [DH Domain].

107. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 624.

108. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

109. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

110. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [ACH Domain].

111. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 624.

112. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

113. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

114. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [VL Domain].

115. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 624.

116. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

117. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

118. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [TH Domain].

119. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 624.

120. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

121. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

122. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 624 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

123. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6967.

124. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6967; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 6967 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

125. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6967; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 6967.

126. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 6967.

127. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

128. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

129. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

130. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 6967.

131. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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), 2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

132. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

133. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [DH Domain].

134. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 6967.

135. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

136. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

137. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [ACH Domain].

138. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 6967.

139. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

140. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

141. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [VL Domain].

142. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 6967.

143. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

144. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-

halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

145. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [TH Domain].

146. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 6967.

147. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

148. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

149. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6967 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

150. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4386.

151. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4386; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 4386 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

152. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4386; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 4386.

153. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 4386.

154. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

155. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

166. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

167. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 4386.

168. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

169. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

170. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [DH Domain].

171. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 4386.

172. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

173. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-

halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

174. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [ACH Domain].

175. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 4386.

176. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

177. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

178. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [VL Domain].

179. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 4386.

180. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

181. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

182. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [TH Domain].

183. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 4386.

184. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

185. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

186. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

187. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4834.

188. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4834; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 4834 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

189. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4386; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 4386.

190. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 4834.

191. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

192. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe)

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

193. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

194. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 4834.

195. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

196. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

197. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [DH Domain].

198. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 4834.

199. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

200. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

201. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [ACH Domain].

202. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 4834.

203. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

204. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

205. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [VL Domain].

206. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 4834.

207. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4386, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

208. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

209. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [TH Domain].

210. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 4834.

211. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

212. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

213. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4834 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

214. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6749.

215. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6749; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 6749 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

216. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6749; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 6749.

217. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 6749.

218. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

219. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

220. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

221. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 6749.

222. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

223. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

224. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [DH Domain].

225. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 6749.

226. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

227. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

228. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [ACH Domain].

229. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 6749.

230. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

231. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

232. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [VL Domain].

233. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 6749.

234. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

235. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

236. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [TH Domain].

237. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 6749.

238. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

239. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

240. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

241. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 8051.

242. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 8051; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 8051by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

243. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 8051; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 8051.

244. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 8051.

245. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

246. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

247. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

248. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6749 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 8051.

249. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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), 2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

250. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

251. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [DH Domain].

252. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 8051.

253. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

254. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

255. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [ACH Domain].

256. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 8051.

257. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

258. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

259. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [VL Domain].

260. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 8051.

261. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

262. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-

halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

263. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [TH Domain].

264. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 8051.

265. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

266. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

267. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 8051 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

268. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6707.

269. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6707; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 6707 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

270. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6707; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 6707.

271. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 6707.

272. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

273. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

274. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

275. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 6707.

276. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

277. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

278. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [DH Domain].

279. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 6707.

280. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

281. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-

halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

282. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [ACH Domain].

283. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 6707.

284. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

285. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

286. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [VL Domain].

287. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 6707.

288. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

289. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

290. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [TH Domain].

291. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 6707.

292. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

293. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

294. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 6707 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

295. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 5630.

296. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 5630; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 5630 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

297. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 5630; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 5630.

298. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 5630.

299. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

300. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe)

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

301. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

302. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 5630.

303. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

304. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

305. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [DH Domain].

306. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 5630.

307. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

308. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

309. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [ACH Domain].

310. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 5630.

311. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

312. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

313. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [VL Domain].

314. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 5630.

315. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

316. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

317. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [TH Domain].

318. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 5630.

319. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

320. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

321. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 5630 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

322. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4249.

323. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4249; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 4249 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides.

324. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 4249; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 4249.

325. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1] of SEQ ID NO: 4249.

326. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

327. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain1].

328. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [ASt Domain1].

329. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain] of SEQ ID NO: 4249.

330. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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), 2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

331. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [DH Domain].

332. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [DH Domain].

333. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain] of SEQ ID NO: 4249.

334. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

335. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ACH Domain].

336. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [ACH Domain].

337. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain] of SEQ ID NO: 4249.

338. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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'MOE2'deoxy, or phosphorothioate

modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

339. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [VL Domain].

340. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [VL Domain].

341. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain] of SEQ ID NO: 4249.

342. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

343. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [TH Domain].

344. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [TH Domain].

345. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2] of SEQ ID NO: 4249.

346. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, 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'MOE2'deoxy, or phosphorothioate modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

347. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249, the non-naturally occurring modification is a 2'-O-methyl (2-OMe) or 2'-halo (e.g., 2'F or 2'Cl) modification, and the non-naturally occurring modification is present at a nucleotide position within in the [ASt Domain2].

348. The TREM of any one of the preceding embodiments, wherein the TREM comprises SEQ ID NO: 4249 and does not contain a non-naturally occurring modification within in the [ASt Domain2].

349. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula I_{ALA} (SEQ ID NO: 562):

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}, wherein R is a ribonucleotide residue and the consensus for Ala is: R_0= absent; R_{14}, R_{57}=are independently A or absent; R_{26}= A, C, G or absent; R_5, R_6, R_{15}, R_{16}, R_{21}, R_{30}, R_{31}, R_{32}, R_{34}, R_{37}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{48}, R_{49}, R_{50}, R_{58}, R_{59}, R_{63}, R_{64}, R_{66}, R_{67}= are independently N or absent; R_{11}, R_{35}, R_{65}= are independently A, C, U or absent; R_1, R_9, R_{20}, R_{38}, R_{40}, R_{51}, R_{52}, R_{56}= are independently A, G or absent; R_7, R_{22}, R_{25}, R_{27}, R_{29}, R_{46}, R_{53}, R_{72}= are independently A, G, U or absent; R_{24}, R_{69}= are independently A, U or absent; R_{70}, R_{71}=are independently C or absent; R_3, R_4= are independently C, G or absent; R_{12}, R_{33}, R_{36}, R_{62}, R_{68}= are

independently C, G, U or absent; R_{13}, R_{17}, R_{28}, R_{39}, R_{55}, R_{60}, R_{61}= are independently C, U or absent; R_{10}, R_{19}, R_{23}= are independently G or absent; R_2= G, U or absent; R_8, R_{18}, R_{54}= are independently U or absent; $[R_{47}]_x$ = N or absent; wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

350. The TREM of embodiment 349, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

351. The TREM of embodiment 350, 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), 2'deoxy, or phosphorothioate modification.

352. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula II_{ALA} (SEQ ID NO: 563),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_6, R_{18}= are absent;

R_{14}, R_{24}, R_{57}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}, R_{59}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_{1}, R_{5}, R_{9}, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_{7}, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}, R_{72}= are independently A, G, U or absent;

R_{6}, R_{35}, R_{69}= are independently A, U or absent;

R_{55}, R_{60}, R_{70}, R_{71}= are independently C or absent;

R_{3}= C, G or absent;

R_{12}, R_{36}, R_{48}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{61}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_{4}, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_{2}, R_{8}, R_{33}= are independently G, U or absent;

R_{21}, R_{54}= are independently U or absent;

$[R_{47}]_{x}$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

353. The TREM of embodiment 352, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

354. The TREM of embodiment 353, 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), 2'deoxy, or phosphorothioate modification.

355. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula III_{ALA} (SEQ ID NO: 564),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0, R_{18}= are absent;

R_{14}, R_{24}, R_{57}, R_{72}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_5, R_9, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}= are independently A, G, U or absent;

R_6, R_{35}= are independently A, U or absent;

R_{55}, R_{60}, R_{61}, R_{70}, R_{71}= are independently C or absent;

R_{12}, R_{48}, R_{59}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_1, R_2, R_3, R_4, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_{33}, R_{36}= are independently G, U or absent;

R_8, R_{21}, R_{54}, R_{69}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1,

x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

356. The TREM of embodiment 355, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

357. The TREM of embodiment 356, 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), 2'deoxy, or phosphorothioate modification.

358. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula I_{ARG} (SEQ ID NO: 565),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{57}=A or absent;

R_9,R_{27}=are independently A,C,G or absent;

R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_{11},R_{12},R_{16},R_{21},R_{22},R_{23},R_{25},R_{26},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{42},R_{44},R_{45}, R_{46},R_{48},R_{49},R_{50},R_{51},R_{58},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70},R_{71}=are independently N or absent;

R_{13},R_{17},R_{41}=are independently A,C,U or absent;

R_{19},R_{20},R_{24},R_{40},R_{56}=are independently A,G or absent;

R_{14},R_{15},R_{72}=are independently A,G,U or absent;

R_{18}= A,U or absent;

R_{38}= C or absent;

R_{35},R_{43},R_{61}=are independently C,G,U or absent;

R_{28},R_{55},R_{59},R_{60}=are independently C,U or absent;

R_0,R_{10},R_{52}=are independently G or absent;

R_8,R_{39}=are independently G,U or absent;

R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

359. The TREM of embodiment 358, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

360. The TREM of embodiment 359, 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), 2'deoxy, or phosphorothioate modification.

361. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula II $_{ARG}$ (SEQ ID NO: 566),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}= absent;

R_{24},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_3,R_7,R_{34},R_{50}=are independently A,C,G or absent;

R_2,R_5,R_6,R_{12},R_{26},R_{32},R_{37},R_{44},R_{58},R_{66},R_{67},R_{68},R_{70}=are independently N or absent;

R_{49},R_{71}=are independently A,C,U or absent;

R_1,R_{15},R_{19},R_{25},R_{27},R_{40},R_{45},R_{46},R_{56},R_{72}=are independently A,G or absent;

R_{14},R_{29},R_{63}=are independently A,G,U or absent;

R_{16},R_{21}=are independently A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_{33},R_{48}=are independently C,G or absent;

R_4,R_9,R_{11},R_{43},R_{62},R_{64},R_{69}=are independently C,G,U or absent;

R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{55},R_{60},R_{65}=are independently C,U or absent;

R_0,R_{10},R_{20},R_{23},R_{51},R_{52}=are independently G or absent;

R_8,R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

362. The TREM of embodiment 361, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

363. The TREM of embodiment 362, 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), 2'deoxy, or phosphorothioate modification.

364. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of Formula III $_{ARG}$ (SEQ ID NO: 567),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}=is absent;

R_{15},R_{21},R_{24},R_{41},R_{57}=are independently A or absent;

R_{34},R_{44}=are independently A,C or absent;

R_3,R_5,R_{58}=are independently A,C,G or absent;

R_2,R_6,R_{66},R_{70}=are independently N or absent;

R_{37},R_{49}=are independently A,C,U or absent;

R_1,R_{25},R_{29},R_{40},R_{45},R_{46},R_{50}=are independently A,G or absent;

R_{14},R_{63},R_{68}=are independently A,G,U or absent;

R_{16}= A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_7,R_{11},R_{12},R_{26},R_{48}=are independently C,G or absent;

R_{64},R_{67},R_{69}=are independently C,G,U or absent;

R_4,R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{43},R_{55},R_{60},R_{62},R_{65},R_{71}=are independently C,U or absent;

R_0,R_{10},R_{19},R_{20},R_{23},R_{27},R_{33},R_{51},R_{52},R_{56},R_{72}=are independently G or absent;

R_8,R_9,R_{32},R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

365. The TREM of embodiment 364, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

366. The TREM of embodiment 365, 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), 2'deoxy, or phosphorothioate modification.

367. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula I_{ASN} (SEQ ID NO: 568),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

R_0,R_{18}=are absent;

R_{41}= A or absent;

R_{14},R_{48},R_{56}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_{12},R_{17},R_{26},R_{29},R_{30},R_{31},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65},R_{66},R_{67},R_{68},R_{70},R_{71}= are independently N or absent;

R_{11},R_{13},R_{22},R_{42},R_{55},R_{59}=are independently A,C,U or absent;

R_9,R_{15},R_{24},R_{27},R_{34},R_{37},R_{51},R_{72}=are independently A,G or absent;

R_1,R_7,R_{25},R_{69}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_{60}= C or absent;

R_{33}= C,G or absent;

R_{21},R_{32},R_{43},R_{64}=are independently C,G,U or absent;

R_3,R_{16},R_{28},R_{35},R_{36},R_{61}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{52}=are independently G or absent;

R_{54}= G,U or absent;

R_8,R_{23},R_{38},R_{39},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

368. The TREM of embodiment 367, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

369. The TREM of embodiment 368, 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), 2'deoxy, or phosphorothioate modification.

370. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula II $_{ASN}$ (SEQ ID NO: 569),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

$R_{0,}R_{18}$=are absent

R_{24},R_{41},R_{46},R_{62}=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{17},R_{29}=are independently N or absent;

R_{11},R_{26},R_{42},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{12},R_{15},R_{25},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70},R_{72}=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_5,R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{21},R_{43},R_{71}=are independently C,G,U or absent;

R_3,R_6,R_{13},R_{22},R_{32},R_{35},R_{36},R_{61},R_{63},R_{64}=are independently C,U or absent;

R_7,R_{10},R_{19},R_{20},R_{27},R_{49},R_{52}=are independently G or absent;

R_{54}= G,U or absent;

R_2,R_4,R_8,R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13,

x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

371. The TREM of embodiment 370, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

372. The TREM of embodiment 371, 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), 2'deoxy, or phosphorothioate modification.

373. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula III $_{ASN}$ (SEQ ID NO: 570),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

R_0,R_{18}=are absent

R_{24},R_{40},R_{41},R_{46},R_{62}=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{11},R_{26},R_{42},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{12},R_{15},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70}=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{57}= A,U or absent;

R_5,R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{17},R_{21},R_{29}=are independently C,G,U or absent;

R_3,R_6,R_{13},R_{22},R_{32},R_{35},R_{36},R_{43},R_{61},R_{63},R_{64},R_{71}=are independently C,U or absent;

R_7,R_{10},R_{19},R_{20},R_{25},R_{27},R_{49},R_{52},R_{72}=are independently G or absent;

R_{54}= G,U or absent;

R_2,R_4,R_8,R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

374. The TREM of embodiment 373, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

375. The TREM of embodiment 374, 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), 2'deoxy, or phosphorothioate modification.

376. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula I_{ASP} (SEQ ID NO: 571),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0=absent

R_{24},R_{71}=are independently A,C or absent;

R_{33},R_{46}=are independently A,C,G or absent;

R_2,R_3,R_4,R_5,R_6,R_{12},R_{16},R_{22},R_{26},R_{29},R_{31},R_{32},R_{44},R_{48},R_{49},R_{58},R_{63},R_{64},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{13},R_{21},R_{34},R_{41},R_{57},R_{65}=are independently A,C,U or absent;

R_9,R_{10},R_{14},R_{15},R_{20},R_{27},R_{37},R_{40},R_{51},R_{56},R_{72}=are independently A,G or absent;

R_7,R_{25},R_{42}=are independently A,G,U or absent;

R_{39}= C or absent;

R_{50},R_{62}=are independently C,G or absent;

R_{30},R_{43},R_{45},R_{55},R_{70}=are independently C,G,U or absent;

R_8,R_{11},R_{17},R_{18},R_{28},R_{35},R_{53},R_{59},R_{60},R_{61}=are independently C,U or absent;

R_{19},R_{52}=are independently G or absent;

R_1= G,U or absent;

R_{23},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

377. The TREM of embodiment 376, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

378. The TREM of embodiment 377, 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), 2'deoxy, or phosphorothioate modification.

379. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula II $_{ASP}$ (SEQ ID NO: 572),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0,R_{17},R_{18},R_{23}=are independently absent;

R_9,R_{40}=are independently A or absent;

R_{24},R_{71}=are independently A,C or absent;

R_{67},R_{68}=are independently A,C,G or absent;

R_2,R_6,R_{66}=are independently N or absent;

R_{57},R_{63}=are independently A,C,U or absent;

R_{10},R_{14},R_{27},R_{33},R_{37},R_{44},R_{46},R_{51},R_{56},R_{64},R_{72}=are independently A,G or absent;

R_7,R_{12},R_{26},R_{65}=are independently A,U or absent;

R_{39},R_{61},R_{62}=are independently C or absent;

R_3,R_{31},R_{45},R_{70}=are independently C,G or absent;

R_4,R_5,R_{29},R_{43},R_{55}=are independently C,G,U or absent;

R_8,R_{11},R_{13},R_{30},R_{32},R_{34},R_{35},R_{41},R_{48},R_{53},R_{59},R_{60}=are independently C,U or absent;

R_{15},R_{19},R_{20},R_{25},R_{42},R_{50},R_{52}=are independently G or absent;

R_1,R_{22},R_{49},R_{58},R_{69}=are independently G,U or absent;

R_{16},R_{21},R_{28},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

380. The TREM of embodiment 379, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

381. The TREM of embodiment 380, 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), 2'deoxy, or phosphorothioate modification.

382. The TREM of any one of the preceding embodiments, wherein the TREM comprises the sequence of of Formula III $_{ASP}$ (SEQ ID NO: 573),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

$R_{0,}R_{17,}R_{18,}R_{23}$=are absent

R_9,R_{12},R_{40},R_{65},R_{71}=are independently A or absent;

R_2,R_{24},R_{57}=are independently A,C or absent;

R_6,R_{14},R_{27},R_{46},R_{51},R_{56},R_{64},R_{67},R_{68}=are independently A,G or absent;

R_3,R_{31},R_{35},R_{39},R_{61},R_{62}=are independently C or absent;

R_{66}= C,G or absent;

R_5,R_8,R_{29},R_{30},R_{32},R_{34},R_{41},R_{43},R_{48},R_{55},R_{59},R_{60},R_{63}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{20},R_{25},R_{33},R_{37},R_{42},R_{44},R_{45},R_{49},R_{50},R_{52},R_{69},R_{70},R_{72}=are independently G or absent;

R_{22},R_{58}=are independently G,U or absent;

R_1,R_4,R_7,R_{11},R_{13},R_{16},R_{21},R_{26},R_{28},R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

383. The TREM of embodiment 382, wherein the TREM comprises a non-naturally occurring modification present at a nucleotide position within one of the [ASt Domain1], [DH Domain], [ACH Domain], [VL Domain], [TH Domain], or [ASt Domain2].

384. The TREM of embodiment 383, 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), 2'deoxy, or phosphorothioate modification.

385. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 701; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 701 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 80; and/or

(iv) the TREM differs from the sequence of TREM NO: 80 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

386. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 701; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 701.

387. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 701.

388. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 2951; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 2951 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 2330; and/or

(iv) the TREM differs from the sequence of TREM NO: 2330 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

388. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 2951; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 2951.

389. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 2951.

390. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 6047; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 6047 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 5426; and/or

(iv) the TREM differs from the sequence of TREM NO: 5426 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

391. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6047; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 6047.

392. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 6047.

393. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 9364; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 9364 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 8743; and/or

(iv) the TREM differs from the sequence of TREM NO: 8743 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

394. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 9364; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 9364.

395. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 9364.

396. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 3795; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 3795 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 3174; and/or

(iv) the TREM differs from the sequence of TREM NO: 3174 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

397. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 3795; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 3795.

398. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 3795.

399. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 8524; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 8524 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 7903; and/or

(iv) the TREM differs from the sequence of TREM NO: 7903 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring

modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

400. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 8524; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 8524.

401. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 8524.

402. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 6725; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 6725 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 6104; and/or

(iv) the TREM differs from the sequence of TREM NO: 6104 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

403. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 6725; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 6725.

404. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 6725.

405. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 8712; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 8712 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 8091; and/or

(iv) the TREM differs from the sequence of TREM NO: 8091 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

406. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 8712; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 8712.

407. The TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 8712.

408. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 9488; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 9488 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 8867; and/or

(iv) the TREM differs from the sequence of TREM NO: 8867 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

409. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 9488; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 9488.

410. 9488 TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 8712.

411. The TREM of any one of the preceding embodiments, wherein:

(i) the TREM comprises the nucleotide sequence of SEQ ID NO: 5397; and/or

(ii) the TREM differs from the nucleotide sequence of SEQ ID NO: 5397 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides; and/or

(iii) the TREM comprises the sequence of TREM NO.: 4776; and/or

(iv) the TREM differs from the sequence of TREM NO: 4776 by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 non-naturally occurring modifications, e.g., a non-naturally occurring modification selected from a 2'-O-methyl (2-OMe), 2'-halo (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE2'deoxy, or phosphorothioate modification.

412. The TREM of any one of the preceding embodiments, wherein:

(i) the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of the nucleotides of SEQ ID NO: 5397; and/or

(ii) the TREM comprises the nucleotide sequence of SEQ ID NO: 5397.

413. 9488 TREM of any one of the preceding embodiment, having the sequence of SEQ ID NO: 8712.

414. The TREM of any one of the preceding embodiments, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides according to the CtNS.

415. A pharmaceutical composition comprising a TREM of embodiments 1-414.

416. The pharmaceutical composition of embodiment 415, comprising a pharmaceutically acceptable component, *e.g.*, an excipient.

417. A lipid nanoparticle formulation comprising a TREM of embodiments 1-414.

418. A method of making a TREM of embodiments 1-414, comprising linking a first nucleotide to a second nucleotide to form the TREM.

419. The method of embodiment 418, wherein the TREM, TREM core fragment or TREM fragment is synthetic (e.g, non-naturally occurring).

420. The method of embodiment 418-419, wherein the synthesis is performed in vitro.

421. The method of embodiment 419, wherein the TREM, TREM core fragment or TREM fragment is made by cell-free solid phase synthesis.

422. A cell comprising a TREM of embodiments 1-414.

423. A cell comprising a TREM, TREM core fragment or TREM fragment made according to the method of embodiment 418.

424.. A method of modulating a tRNA pool in a cell comprising:
providing a TREM of embodiments 1-414, and
contacting the cell with the TREM,
thereby modulating the tRNA pool in the cell.

425. A method of contacting a cell, tissue, or subject with a TREM of embodiments 1-414, comprising
contacting the cell, tissue or subject with the TREM,
thereby contacting the cell, tissue, or subject with the TREM.

426. A method of presenting a TREM, comprising
contacting the cell, tissue or subject with a TREM of embodiments 1-414, thereby presenting the TREM to a cell, tissue, or subject.

427. A method of forming a TREM-contacted cell, tissue, or subject, comprising
contacting the cell, tissue or subject with a TREM of embodiments 1-414,
thereby forming a TREM-contacted cell, tissue, or subject.

428. A method of using a TREM comprising,
contacting the cell, tissue or subject with a TREM of embodiments 1-414,
thereby using the TREM.

429. A method of applying a TREM to a cell, tissue, or subject, comprising
contacting the cell, tissue or subject with a TREM of embodiments 1-414,
thereby applying a TREM to a cell, tissue, or subject.

430. A method of exposing a cell, tissue, or subject to a TREM, comprising
contacting the cell, tissue or subject with a TREM of embodiments 1-414,
thereby exposing a cell, tissue, or subject to a TREM.

431. A method of forming an admixture of a TREM and a cell, tissue, or subject, comprising
contacting the cell, tissue or subject with a TREM of embodiments 1-414,
thereby forming an admixture of a TREM and a cell, tissue, or subject.

432. A method of delivering a TREM to a cell, tissue, or subject, comprising:
providing a cell, tissue, or subject, and contacting the cell, tissue, or subject, a TREM of embodiments 1-414.

433. A method, e.g., an ex vivo method, of modulating the metabolism, *e.g.*, the translational capacity of an organelle, comprising:
providing a preparation of an organelle, *e.g.*, mitochondria or chloroplasts, and contacting the organelle with a TREM of embodiments 1-414.

434. A method of treating a subject, *e.g.*, modulating the metabolism, *e.g.*, the translational capacity of a cell, in a subject, comprising:

providing, *e.g.*, administering to the subject a TREM of embodiments 1-414,

thereby treating the subject.

435. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the cell, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell;

contacting the cell with a TREM of embodiments 1-414, wherein the TREM has an anticodon that pairs with: the codon having the first sequence; or the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the cell,

thereby modulating the tRNA pool in the cell.

436. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the subject, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the subject;

contacting the subject with a TREM of embodiments 1-414, wherein the TREM has an anticodon that pairs with: the codon having the first sequence; or the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the subject,

thereby modulating the tRNA pool in the subject.

437. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a composition comprising a TREM of embodiments 1-414, wherein the TREM comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the subject with the composition in an amount and/or for a time sufficient to modulate the tRNA pool in the subject,

thereby modulating the tRNA pool in the subject.

438. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a composition comprising a TREM of embodiments 1-414, wherein the TREM comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the cell with the composition comprising a TREM in an amount and/or for a time sufficient to modulate the tRNA pool in the cell,

thereby modulating the tRNA pool in the cell.

439. A method of modulating expression of a protein in a cell, wherein the protein is encoded by a nucleic acid comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a mutation, comprising:

contacting the cell with a composition comprising a TREM of embodiments 1-414 in an amount and/or for a time sufficient to modulate expression of the encoded protein,

wherein the TREM has an anticodon that pairs with the codon having the mutation,

thereby modulating expression of the protein in the cell.

440. A method of modulating expression of a protein in a subject, wherein the protein is encoded by a nucleic acid comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a mutation, comprising:

contacting the subject with a composition comprising a TREM of embodiments 1-414, in an amount and/or for a time sufficient to modulate expression of the encoded protein,

wherein the TREM has an anticodon that pairs with the codon having the mutation,

thereby modulating expression of the protein in the subject.

441. The method of embodiment 439-440, wherein the mutation in the ORF is a nonsense mutation, e.g., resulting in a premature stop codon chosen from UAA, UGA or UAG.

442. The method of embodiment 439-441, wherein the TREM comprises an anticodon that pairs with a stop codon.

443. The method of any one of the preceding embodiments, wherein the TREM comprises an anticodon that pairs with a stop codon.

Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

The present disclosure features tRNA-based effector molecules (TREMs) comprising a non-naturally occurring modification and methods relating thereto. As disclosed herein, TREMs are complex molecules which can mediate a variety of cellular processes. Pharmaceutical TREM compositions, e.g., TREMs comprising a non-naturally occurring modification, can be administered to a cell, a tissue, or to a subject to modulate these functions. Also disclosed herein are methods of modulating expression of a protein in a subject or cell, wherein the protein is encoded by a nucleic acid comprising an endogenous open reading frame (ORF) having a first sequence, e.g., a mutation, e.g., a premature termination codon (PTC), and methods of treating a

subject having an endogenous open reading frame (ORF) which comprises a premature termination codon (PTC). Further disclosed herein are TREMs comprising a non-naturally occurring modification, methods of making the same and compositions thereof.

Definitions

"Acquire" or "acquiring" as the terms are used herein, refer to obtaining possession of a value, *e.g.*, a numerical value, by "directly acquiring" or "indirectly acquiring" the physical entity or value. "Directly acquiring" refers to performing a process (*e.g.*, performing an analytical method) to obtain the value. "Indirectly acquiring" refers to receiving the value from another party or source (*e.g.*, a third party laboratory that directly acquired the or value).

A "disease or disorder associated with a PTC" as that term is used herein includes, but is not limited to, a disease or disorder in which cells express, or at one time expressed, a polypeptide encoded by an ORF comprising a PTC. In some embodiments, a disease associated with a PTC is chosen from: a proliferative disorder (e.g., a cancer), a genetic disorder, a metabolic disorder, an immune disorder, an inflammatory disorder or a neurological disorder. Exemplary diseases or disorders associated with a PTC are provided in any one of Tables 15, 16 and 17. In an embodiment, the disease associated with a PTC is a cancer. In an embodiment, the disease associated with a PTC is a monogenic disease.

An "isoacceptor," as that term is used herein, refers to a plurality of tRNA molecule or TREMs wherein each molecule of the plurality comprises a different naturally occurring anticodon sequence and each molecule of the plurality mediates the incorporation of the same amino acid and that amino acid is the amino acid that naturally corresponds to the anticodons of the plurality.

A "modification," as that term is used herein with reference to a nucleotide, refers to a modification of the chemical structure, e.g., a covalent modification, of the subject nucleotide. The modification can be naturally occurring or non-naturally occurring. In an embodiment, the modification is non-naturally occurring. In an embodiment, the modification is naturally occurring. In an embodiment, the modification is a synthetic modification. In an embodiment, the modification is a modification provided in Tables 5, 6, 7 , 8 or 9.

A "naturally occurring nucleotide," as that term is used herein, refers to a nucleotide that does not comprise a non-naturally occurring modification. In an embodiment, it includes a naturally occurring modification.

A "non-naturally occurring modification," as that term is used herein with reference to a nucleotide, refers to a modification that: (a) a cell, e.g., a human cell, does not make on an endogenous tRNA; or (b) a cell, e.g., a human cell, can make on an endogenous tRNA but wherein such modification is in a location in which it does not occur on a native tRNA, e.g., the modification is in a domain, linker or arm, or on a nucleotide and/or at a position within a domain, linker or arm, which does not have such modification in nature. In either case, the modification is added synthetically, e.g., in a cell free reaction, e.g., in a solid state or liquid phase synthetic reaction. In an embodiment, the non-naturally occurring modification is a modification that is not present (in identity, location or position) if a sequence of the TREM is expressed in a mammalian cell, e.g., a HEK293 cell line. Exemplary non-naturally occurring modifications are found in Tables 5, 6, 7, 8 or 9.

A "non-naturally modified nucleotide," as that term is used herein, refers a nucleotide comprising a non-naturally occurring modification on or of a sugar, nucleobase, or phosphate moiety.

A "nucleotide," as that term is used herein, refers to an entity comprising a sugar, typically a pentameric sugar; a nucleobase; and a phosphate linking group. In an embodiment, a nucleotide comprises a naturally occurring, e.g., naturally occurring in a human cell, nucleotide, e.g., an adenine, thymine, guanine, cytosine, or uracil nucleotide.

A "premature termination codon" or "PTC" as those terms are used herein, refer to a stop codon that occurs in an open reading frame (ORF) of a DNA or mRNA. In an embodiment, a PTC occurs at a position upstream of a naturally occurring stop codon in an ORF. In an embodiment, a PTC that occurs upstream of a naturally occurring stop codon, e.g., in an ORF, results in modulation of a production parameter of the corresponding mRNA or polypeptide encoded by the ORF. In an embodiment, a PTC can differ (or arise) from a pre-mutation sequence by a point mutation, e.g., a nonsense mutation. In an embodiment, a PTC can differ (or arise) from a pre-mutation sequence by a genetic change, e.g., abnormality, other than a point mutation, e.g., a frameshift, a deletion, an insertion, a rearrangement, an inversion, a translocation, a duplication, or a transversion. In an embodiment, a PTC results in the production

of a truncated protein which lacks a native activity or which is associated with a mutant, disease, or other unwanted phenotype. In an embodiment, the ORF comprising the PTC is an ORF from a tumor suppressor gene. In an embodiment, the mutation giving rise to the PTC is a driver mutation, e.g., a mutation that provides a growth advantage to a tumor cell.

A "production parameter," refers to an expression parameter and/or a signaling parameter. In an embodiment a production parameter is an expression parameter. An expression parameter includes an expression parameter of a polypeptide or protein encoded by the endogenous ORF having a first sequence or PTC; or an expression parameter of an RNA, *e.g.*, messenger RNA, encoded by the endogenous ORF having a first sequence or PTC. In an embodiment, an expression parameter can include:

(a) protein translation;

(b) expression level (*e.g.*, of polypeptide or protein, or mRNA);

(c) post-translational modification of polypeptide or protein;

(d) folding (*e.g.*, of polypeptide or protein, or mRNA),

(e) structure (*e.g.*, of polypeptide or protein, or mRNA),

(f) transduction (*e.g.*, of polypeptide or protein),

(g) compartmentalization (*e.g.*, of polypeptide or protein, or mRNA),

(h) incorporation (*e.g.*, of polypeptide or protein, or mRNA) into a supermolecular structure, *e.g.*, incorporation into a membrane, proteasome, or ribosome,

(i) incorporation into a multimeric polypeptide, *e.g.*, a homo or heterodimer, and/or

(j) stability.

In an embodiment, a production parameter is a signaling parameter. A signaling parameter can include:

(1) modulation of a signaling pathway, *e.g.*, a cellular signaling pathway which is downstream or upstream of the protein encoded by the endogenous ORF having a first sequence or PTC;

(2) cell fate modulation;

(3) ribosome occupancy modulation;

(4) protein translation modulation;

(5) mRNA stability modulation;

(6) protein folding and structure modulation;

(7) protein transduction or compartmentalization modulation; and/or

(8) protein stability modulation.

An "ORF having a PTC" as that phrase is used herein, refers to an open reading frame (ORF) which comprises a premature termination codon (PTC). In an embodiment, the ORF having the PTC is associated with a disease or disorder associated with a PTC, e.g., as described herein, e.g., a disease or disorder listed in any one of Tables 15, 16 and 17. In an embodiment, the ORF having the PTC is not associated with a disease or disorder associated with a PTC.

A "stop codon" as that term is used herein, refers to a three nucleotide contiguous sequence within messenger RNA that specifies a termination of translation. For example, UAG, UAA, UGA (in RNA) and TAG, TAA or TGA (in DNA) are stop codons. The stop codons are also known as amber (UAG), ochre (UAA), and opal (UGA).

A "tRNA-based effector molecule" or "TREM," as that term is used herein, refers to an RNA molecule comprising a structure or property from (a)-(v) below, and which is a recombinant TREM, a synthetic TREM, or a TREM expressed from a heterologous cell. The TREMs described in the present invention are synthetic molecules and are made, e.g., in a cell free reaction, e.g., in a solid state or liquid phase synthetic reaction. TREMs are chemically distinct, e.g., in terms of primary sequence, type or location of modifications from the endogenous tRNA molecules made in cells, e.g., in mammalian cells, e.g., in human cells. A TREM can have a plurality (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9) of the structures and functions of (a)-(v).

In an embodiment, a TREM is non-native, as evaluated by structure or the way in which it was made.

In an embodiment, a TREM comprises one or more of the following structures or properties:

(a') an optional linker region of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 1 region;

(a) an amino acid attachment domain that binds an amino acid, *e.g.*, an acceptor stem domain (AStD), wherein an AStD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, acceptance of an amino acid, *e.g.*, its cognate amino acid or a non-cognate amino acid, and transfer of the amino acid (AA) in the initiation or elongation of a polypeptide chain. Typically, the AStD comprises a 3'-end adenosine (CCA) for acceptor stem charging which is part of synthetase recognition. In an embodiment the AStD has at least

75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring AStD, *e.g.*, an AStD encoded by a nucleic acid in Table 1. In an embodiment, the TREM can comprise a fragment or analog of an AStD, *e.g.*, an AStD encoded by a nucleic acid in Table 1, which fragment in embodiments has AStD activity and in other embodiments does not have AStD activity. (One of ordinary skill can determine the relevant corresponding sequence for any of the domains, stems, loops, or other sequence features mentioned herein from a sequence encoded by a nucleic acid in Table 1. *E.g.*, one of ordinary skill can determine the sequence which corresponds to an AStD from a tRNA sequence encoded by a nucleic acid in Table 1.)

In an embodiment the AStD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(a'-1) a linker comprising residues R_8-R_9 of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 2 region;

(b) a dihydrouridine hairpin domain (DHD), wherein a DHD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of aminoacyl-tRNA synthetase, *e.g.*, acts as a recognition site for aminoacyl-tRNA synthetase for amino acid charging of the TREM. In embodiments, a DHD mediates the stabilization of the TREM's tertiary structure. In an embodiment the DHD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring DHD, *e.g.*, a DHD encoded by a nucleic acid in Table 1. In an embodiment, the TREM can comprise a fragment or analog of a DHD, *e.g.*, a DHD encoded by a nucleic acid in Table 1, which fragment in embodiments has DHD activity and in other embodiments does not have DHD activity.

In an embodiment the DHD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(b'-1) a linker comprising residue R_{29} of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 3 region;

(c) an anticodon that binds a respective codon in an mRNA, *e.g.*, an anticodon hairpin domain (ACHD), wherein an ACHD comprises sufficient sequence, *e.g.*, an anticodon triplet, to mediate, *e.g.*, when present in an otherwise wildtype tRNA, pairing (with or without wobble) with a codon; In an embodiment the ACHD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring ACHD, *e.g.*, an ACHD encoded by a nucleic acid in Table 1. In an embodiment, the TREM can comprise a fragment or analog of an ACHD, *e.g.*, an ACHD encoded by a nucleic acid in Table 1, which fragment in embodiments has ACHD activity and in other embodiments does not have ACHD activity.

In an embodiment the ACHD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(d) a variable loop domain (VLD), wherein a VLD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of aminoacyl-tRNA synthetase, *e.g.*, acts as a recognition site for aminoacyl-tRNA synthetase for amino acid charging of the TREM. In embodiments, a VLD mediates the stabilization of the TREM's tertiary structure. In an embodiment, a VLD modulates, *e.g.*, increases, the specificity of the TREM, *e.g.*, for its cognate amino acid, *e.g.*, the VLD modulates the TREM's cognate adaptor function. In an embodiment the VLD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring VLD, *e.g.*, a VLD encoded by a nucleic acid in Table 1. In an embodiment, the TREM can comprise a fragment or analog of a VLD, *e.g.*, a VLD encoded by a nucleic acid in Table 1, which fragment in embodiments has VLD activity and in other embodiments does not have VLD activity.

In an embodiment the VLD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section.

In an embodiment, the VLD comprises residue -$[R_{47}]_x$ of a consensus sequence provided in the "Consensus Sequence" section, wherein x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271);

(e) a thymine hairpin domain (THD), wherein a THD comprises sufficient RNA sequence, to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of the ribosome, *e.g.*, acts as a recognition site for the ribosome to form a TREM-ribosome complex during translation. In an embodiment the THD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring THD, *e.g.*, a THD encoded by a nucleic acid in Table 1. In an

embodiment, the TREM can comprise a fragment or analog of a THD, *e.g.*, a THD encoded by a nucleic acid in Table 1, which fragment in embodiments has THD activity and in other embodiments does not have THD activity.

In an embodiment the THD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(e'1) a linker comprising residue R_{72} of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 4 region;

(f) under physiological conditions, it comprises a stem structure and one or a plurality of loop structures, *e.g.*, 1, 2, or 3 loops. A loop can comprise a domain described herein, *e.g.*, a domain selected from (a)-(e). A loop can comprise one or a plurality of domains. In an embodiment, a stem or loop structure has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring stem or loop structure, *e.g.*, a stem or loop structure encoded by a nucleic acid in Table 1. In an embodiment, the TREM can comprise a fragment or analog of a stem or loop structure, *e.g.*, a stem or loop structure encoded by a nucleic acid in Table 1, which fragment in embodiments has activity of a stem or loop structure, and in other embodiments does not have activity of a stem or loop structure;

(g) a tertiary structure, *e.g.*, an L-shaped tertiary structure;

(h) adaptor function, i.e., the TREM mediates acceptance of an amino acid, *e.g.*, its cognate amino acid and transfer of the AA in the initiation or elongation of a polypeptide chain;

(i) cognate adaptor function wherein the TREM mediates acceptance and incorporation of an amino acid (*e.g.*, cognate amino acid) associated in nature with the anti-codon of the TREM to initiate or elongate a polypeptide chain;

(j) non-cognate adaptor function, wherein the TREM mediates acceptance and incorporation of an amino acid (*e.g.*, non-cognate amino acid) other than the amino acid associated in nature with the anti-codon of the TREM in the initiation or elongation of a polypeptide chain;

(k) a regulatory function, *e.g.*, an epigenetic function (*e.g.*, gene silencing function or signaling pathway modulation function), cell fate modulation function, mRNA stability modulation function, protein stability modulation function, protein transduction modulation function, or protein compartmentalization function;

(l) a structure which allows for ribosome binding;

(m) a post-transcriptional modification, e.g., a naturally occurring post-trasncriptional modification;

(n) the ability to inhibit a functional property of a tRNA, *e.g.*, any of properties (h)-(k) possessed by a tRNA;

(o) the ability to modulate cell fate;

(p) the ability to modulate ribosome occupancy;

(q) the ability to modulate protein translation;

(r) the ability to modulate mRNA stability;

(s) the ability to modulate protein folding and structure;

(t) the ability to modulate protein transduction or compartmentalization;

(u) the ability to modulate protein stability; or

(v) the ability to modulate a signaling pathway, *e.g.*, a cellular signaling pathway.

In an embodiment, a TREM comprises a full-length tRNA molecule or a fragment thereof.

In an embodiment, a TREM comprises the following properties: (a)-(e).

In an embodiment, a TREM comprises the following properties: (a) and (c).

In an embodiment, a TREM comprises the following properties: (a), (c) and (h).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (b).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (b) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (b), (e) and (g).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (m).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), and (g).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m) and (b).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), (g), (b) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), (g), (b), (e) and (q).

In an embodiment, a TREM comprises:

(i) an amino acid attachment domain that binds an amino acid (*e.g.*, an AStD, as described in (a) herein; and

(ii) an anticodon that binds a respective codon in an mRNA (*e.g.*, an ACHD, as described in (c) herein).

In an embodiment the TREM comprises a flexible RNA linker which provides for covalent linkage of (i) to (ii).

In an embodiment, the TREM mediates protein translation.

In an embodiment a TREM comprises a linker, *e.g.*, an RNA linker, *e.g.*, a flexible RNA linker, which provides for covalent linkage between a first and a second structure or domain. In an embodiment, an RNA linker comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 ribonucleotides. A TREM can comprise one or a plurality of linkers, *e.g.*, in embodiments a TREM comprising (a), (b), (c), (d) and (e) can have a first linker between a first and second domain, and a second linker between a third domain and another domain.

In an embodiment, the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2].

In an embodiment, a TREM comprises an RNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with, or which differs by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 ribonucleotides from, an RNA sequence encoded by a DNA sequence listed in Table 1, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises an

RNA sequence encoded by a DNA sequence listed in Table 1, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises an RNA sequence encoded by a DNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with a DNA sequence listed in Table 1, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical with, or which differs by no more than 1, 2, 3, 4, 5, 10, or 15, ribonucleotides from, an RNA encoded by a DNA sequence listed in Table 1, or a fragment or a functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising an RNA sequence encoded by DNA sequence listed in Table 1, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising an RNA sequence encoded by DNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with a DNA sequence listed in Table 1, or a fragment or functional fragment thereof.

In an embodiment, a TREM is 76-90 nucleotides in length. In embodiments, a TREM or a fragment or functional fragment thereof is between 10-90 nucleotides, between 10-80 nucleotides, between 10-70 nucleotides, between 10-60 nucleotides, between 10-50 nucleotides, between 10-40 nucleotides, between 10-30 nucleotides, between 10-20 nucleotides, between 20-90 nucleotides, between 20-80 nucleotides, 20-70 nucleotides, between 20-60 nucleotides, between 20-50 nucleotides, between 20-40 nucleotides, between 30-90 nucleotides, between 30-80 nucleotides, between 30-70 nucleotides, between 30-60 nucleotides, or between 30-50 nucleotides.

In an embodiment, a TREM is aminoacylated, *e.g.*, charged, with an amino acid by an aminoacyl tRNA synthetase.

In an embodiment, a TREM is not charged with an amino acid, *e.g.*, an uncharged TREM (uTREM).

In an embodiment, a TREM comprises less than a full length tRNA. In embodiments, a TREM can correspond to a naturally occurring fragment of a tRNA, or to a non-naturally occurring fragment. Exemplary fragments include: TREM halves (*e.g.*, from a cleavage in the ACHD, *e.g.*, in the anticodon sequence, *e.g.*, 5'halves or 3' halves); a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DHD or the ACHD); a 3' fragment

(*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the THD); or an internal fragment (*e.g.*, from a cleavage in one or more of the ACHD, DHD or THD).

A "TREM core fragment," as that term is used herein, refers to a portion of the sequence of Formula B: $[L1]_y$-[ASt Domain1]$_x$-$[L2]_y$-[DH Domain]$_y$-$[L3]_y$-[ACH Domain]$_x$-[VL Domain]$_y$-[TH Domain]$_y$-$[L4]_y$-[ASt Domain2]$_x$, wherein: x=1 and y=0 or 1.

A "TREM fragment," as used herein, refers to a portion of a TREM, wherein the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2].

A "cognate adaptor function TREM," as that term is used herein, refers to a TREM which mediates initiation or elongation with the AA (the cognate AA) associated in nature with the anti-codon of the TREM.

"Decreased expression," as that term is used herein, refers to a decrease in comparison to a reference, *e.g.*, in the case where altered control region, or addition of an agent, results in a decreased expression of the subject product, it is decreased relative to an otherwise similar cell without the alteration or addition.

An "exogenous nucleic acid," as that term is used herein, refers to a nucleic acid sequence that is not present in or differs by at least one nucleotide from the closest sequence in a reference cell, *e.g.*, a cell into which the exogenous nucleic acid is introduced. In an embodiment, an exogenous nucleic acid comprises a nucleic acid that encodes a TREM.

An "exogenous TREM," as that term is used herein, refers to a TREM that:

(a) differs by at least one nucleotide or one post transcriptional modification from the closest sequence tRNA in a reference cell, *e.g.*, a cell into which the exogenous nucleic acid is introduced;

(b) has been introduced into a cell other than the cell in which it was transcribed;

(c) is present in a cell other than one in which it naturally occurs; or

(d) has an expression profile, *e.g.*, level or distribution, that is non-wildtype, *e.g.*, it is expressed at a higher level than wildtype. In an embodiment, the expression profile can be mediated by a change introduced into a nucleic acid that modulates expression or by addition of an agent that modulates expression of the RNA molecule. In an embodiment an exogenous TREM comprises 1, 2, 3 or 4 of properties (a)-(d).

A "GMP-grade composition," as that term is used herein, refers to a composition in compliance with current good manufacturing practice (cGMP) guidelines, or other similar requirements. In an embodiment, a GMP-grade composition can be used as a pharmaceutical product.

As used herein, the terms "increasing" and "decreasing" refer to modulating that results in, respectively, greater or lesser amounts of function, expression, or activity of a particular metric relative to a reference. For example, subsequent to administration to a cell, tissue or subject of a TREM described herein, the amount of a marker of a metric (*e.g.*, protein translation, mRNA stability, protein folding) as described herein may be increased or decreased by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98%, 2X, 3X, 5X, 10X or more relative to the amount of the marker prior to administration or relative to the effect of a negative control agent. The metric may be measured subsequent to administration at a time that the administration has had the recited effect, *e.g.*, at least 12 hours, 24 hours, one week, one month, 3 months, or 6 months, after a treatment has begun.

"Increased expression," as that term is used herein, refers to an increase in comparison to a reference, *e.g.*, in the case where altered control region, or addition of an agent, results in an increased expression of the subject product, it is increased relative to an otherwise similar cell without the alteration or addition.

A "non-cognate adaptor function TREM," as that term is used herein, refers to a TREM which mediates initiation or elongation with an AA (a non-cognate AA) other than the AA associated in nature with the anti-codon of the TREM. In an embodiment, a non-cognate adaptor function TREM is also referred to as a mischarged TREM (mTREM).

A "non-naturally occurring sequence," as that term is used herein, refers to a sequence wherein an Adenine is replaced by a residue other than an analog of Adenine, a Cytosine is replaced by a residue other than an analog of Cytosine, a Guanine is replaced by a residue other than an analog of Guanine, and a Uracil is replaced by a residue other than an analog of Uracil. An analog refers to any possible derivative of the ribonucleotides, A, G, C or U. In an embodiment, a sequence having a derivative of any one of ribonucleotides A, G, C or U is a non-naturally occurring sequence.

A "pharmaceutical TREM composition," as that term is used herein, refers to a TREM composition that is suitable for pharmaceutical use. Typically, a pharmaceutical TREM composition comprises a pharmaceutical excipient. In an embodiment the TREM will be the only active ingredient in the pharmaceutical TREM composition. In embodiments the pharmaceutical TREM composition is free, substantially free, or has less than a pharmaceutically acceptable amount, of host cell proteins, DNA, *e.g.*, host cell DNA, endotoxins, and bacteria.

A "post-transcriptional processing," as that term is used herein, with respect to a subject molecule, *e.g.*, a TREM, RNA or tRNAs, refers to a covalent modification of the subject molecule. In an embodiment, the covalent modification occurs post-transcriptionally. In an embodiment, the covalent modification occurs co-transcriptionally. In an embodiment the modification is made *in vivo, e.g.*, in a cell used to produce a TREM. In an embodiment the modification is made *ex vivo*, *e.g.*, it is made on a TREM isolated or obtained from the cell which produced the TREM. In an embodiment, the post-transcriptional modification is selected from a post-transcriptional modification listed in Table 2.

A "synthetic TREM," as that term is used herein, refers to a TREM which was synthesized other than in or by a cell having an endogenous nucleic acid encoding the TREM, *e.g.*, a synthetic TREM is synthetized by cell-free solid phase synthesis. A synthetic TREM can have the same, or a different, sequence, or tertiary structure, as a native tRNA.

A "recombinant TREM," as that term is used herein, refers to a TREM that was expressed in a cell modified by human intervention, having a modification that mediates the production of the TREM, *e.g.*, the cell comprises an exogenous sequence encoding the TREM, or a modification that mediates expression, *e.g.*, transcriptional expression or post-transcriptional modification, of the TREM. A recombinant TREM can have the same, or a different, sequence, set of post-transcriptional modifications, or tertiary structure, as a reference tRNA, *e.g.*, a native tRNA.

A "tRNA", as that term is used herein, refers to a naturally occurring transfer ribonucleic acid in its native state.

A "TREM composition," as that term is used herein, refers to a composition comprising a plurality of TREMs, a plurality of TREM core fragments and/or a plurality of TREM fragments. A TREM composition can comprise one or more species of TREMs, TREM core fragments or TREM fragments. In an embodiment, the composition comprises only a single species of

TREM, TREM core fragment or TREM fragment. In an embodiment, the TREM composition comprises a first TREM, TREM core fragment or TREM fragment species; and a second TREM, TREM core fragment or TREM fragment species. In an embodiment, the TREM composition comprises X TREM, TREM core fragment or TREM fragment species, wherein X=2, 3, 4, 5, 6, 7, 8, 9, or 10. In an embodiment, the TREM, TREM core fragment or TREM fragment has at least 70, 75, 80, 85, 90, or 95, or has 100%, identity with a sequence encoded by a nucleic acid in Table 1. A TREM composition can comprise one or more species of TREMs, TREM core fragments or TREM fragments. In an embodiment, the TREM composition is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 or 99% dry weight TREMs (for a liquid composition dry weight refers to the weight after removal of substantially all liquid, *e.g.*, after lyophilization). In an embodiment, the composition is a liquid. In an embodiment, the composition is dry, *e.g.*, a lyophilized material. In an embodiment, the composition is a frozen composition. In an embodiment, the composition is sterile. In an embodiment, the composition comprises at least 0.5 g, 1.0 g, 5.0 g, 10 g, 15 g, 25 g, 50 g, 100 g, 200 g, 400 g, or 500 g (*e.g.*, as determined by dry weight) of TREM.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a selected position, and X is 80, 90, 95, 96, 97, 98, 99, or 99.5.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a first position and a non-naturally occurring modification at a second position, and X, independently, is 80, 90, 95, 96, 97, 98, 99, or 99.5. In embodiments, the modification at the first and second position is the same. In embodiments, the modification at the first and second position are different. In embodiments, the nucleiotide at the first and second position is the same, e.g., both are adenine. In embodiments, the nucleiotide at the first and second position are different, e.g., one is adenine and one is thymine.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a first position and less than Y% have a non-naturally occurring modification at a second position, wherein X is 80, 90, 95, 96, 97, 98, 99, or 99.5 and Y is 20, 20, 5, 2, 1, .1, or .01. In embodiments, the nucleotide at the first and second position is the same, e.g., both are adenine. In embodiments the nucleotide at the first and second position are different, e.g., one is adenine and one is thymine.

TREM, TREM core fragment and TREM fragment

A "tRNA-based effector molecule" or "TREM" refers to an RNA molecule comprising one or more of the properties described herein. A TREM can comprise a non-naturally occurring modification, e.g., as provided in Tables 4, 5, 6 or 7.

In an embodiment, a TREM includes a TREM comprising a sequence of Formula A; a TREM core fragment comprising a sequence of Formula B; or a TREM fragment comprising a portion of a TREM which TREM comprises a sequence of Formula A.

In an embodiment, a TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2]. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

In an embodiment, a TREM core fragment comprises a sequence of Formula B: $[L1]_y$-$[ASt\ Domain1]_x$-$[L2]_y$-$[DH\ Domain]_y$-$[L3]_y$-$[ACH\ Domain]_x$-$[VL\ Domain]_y$-$[TH\ Domain]_y$-$[L4]_y$-$[ASt\ Domain2]_x$, wherein: x=1 and y=0 or 1. In an embodiment, y=0. In an embodiment, y=1.;

In an embodiment, a TREM fragment comprises a portion of a TREM, wherein the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein the TREM fragment comprises: one, two, three or all or any combination of the following: a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half); a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain); a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain). Exemplary TREM fragments include TREM halves (*e.g.*, from a cleavage in the ACHD, *e.g.*, 5'TREM halves or 3' TREM halves), a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DHD or the ACHD), a 3' fragment (*e.g.*, a fragment comprising the 3' end of a TREM, *e.g.*, from a cleavage in the THD), or an internal fragment (*e.g.*, from a cleavage in one or more of the ACHD, DHD or THD).

In an embodiment, a TREM, a TREM core fragment or a TREM fragment can be charged with an amino acid (*e.g.*, a cognate amino acid); charged with a non-cognate amino acid (*e.g.*, a mischarged TREM (mTREM)); or not charged with an amino acid (*e.g.*, an uncharged TREM

(uTREM)). In an embodiment, a TREM, a TREM core fragment or a TREM fragment can be charged with an amino acid selected from alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, methionine, leucine, lysine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

In some embodiments, a non-extended anticodon is an anticodon of no more than three nucleotides. In an embodiment, a non-extended codon pairs with no more than three codon nucleotides on a nucleic acid being translated.

In an embodiment, the TREM, TREM core fragment or TREM fragment is a cognate TREM. In an embodiment, the TREM, TREM core fragment or TREM fragment is a non-cognate TREM. In an embodiment, the TREM, TREM core fragment or TREM fragment recognizes a codon provided in Table 2 or Table 3.

Table 2: List of codons

AAA	CGC	UAG
AAC	CGG	UAU
AAG	CGU	UCA
AAU	CUA	UCC
ACA	CUC	UCG
ACC	CUG	UCU
ACG	CUU	UGA
ACU	GAA	UGC
AGA	GAC	UGG
AGC	GAG	UGU
AGG	GAU	UUA
AGU	GCA	UUC
AUA	GCC	UUG
AUC	GCG	UUU
AUG	GCU	
AUU	GGA	
CAA	GGC	
CAC	GGG	
CAG	GGU	
CAU	GUA	
CCA	GUC	
CCC	GUG	
CCG	GUU	
CCU	UAA	
CGA	UAC	

Table 3: Amino acids and corresponding codons

Amino Acid	**mRNA codons**
Alanine	GCU, GCC, GCA, GCG
Arginine	CGU, CGC, CGA, CGG, AGA, AGG
Asparagine	AAU, AAC
Aspartate	GAU, GAC
Cysteine	UGU, UGC
Glutamate	GAA, GAG
Glutamine	CAA, CAG
Glycine	GGU, GGC, GGA, GGG
Histidine	CAU, CAC
Isoleucine	AUU, AUC, AUA
Leucine	UUA, UUG, CUU, CUC, CUA, CUG
Lysine	AAA, AAG
Methionine	AUG
Phenylalanine	UUU, UUC
Proline	CCU, CCC, CCA, CCG
Serine	UCU, UCC, UCA, UCG, AGU, AGC
Stop	UAA, UAG, UGA
Threonine	ACU, ACC, ACA, ACG
Tryptophan	UGG
Tyrosine	UAU, UAC
Valine	GUU, GUC, GUA, GUG

In an embodiment, a TREM comprises a ribonucleic acid (RNA) sequence encoded by a deoxyribonucleic acid (DNA) sequence disclosed in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM comprises an RNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM comprises an RNA sequence encoded by a DNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1.

In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by a DNA

sequence disclosed in Table 1, *e.g.*, at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by a DNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1.

In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence encoded by a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence encoded by a DNA sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1.

In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence encoded by a DNA sequence disclosed in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to an RNA

sequence encoded by a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence encoded by a DNA sequence with at least 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, 99% or 100% identity to a DNA sequence provided in Table 1, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 1.

In an embodiment, a TREM core fragment or a TREM fragment comprises a sequence of a length of between 10-90 ribonucleotides (rnt), between 10-80 rnt, between 10-70 rnt, between 10-60 rnt, between 10-50 rnt, between 10-40 rnt, between 10-30 rnt, between 10-20 rnt, between 20-90 rnt, between 20-80 rnt, 20-70 rnt, between 20-60 rnt, between 20-50 rnt, between 20-40 rnt, between 30-90 rnt, between 30-80 rnt, between 30-70 rnt, between 30-60 rnt, or between 30-50 rnt

Table 1: List of tRNA Sequences

SEQ ID NO	**tRNA name**	**tRNA sequence**
1	Ala_AGC_chr6:28763741-28763812 (-)	GGGGGTATAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGTCCTGGGTTCGATCCCC
2	Ala_AGC_chr6:26687485-26687557 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCACGCAAGAGGTAGTGGGATCGATGCC
3	Ala_AGC_chr6:26572092-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGATGCC
4	Ala_AGC_chr6:26682715-26682787 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTAGTGGGATCGATGCC
5	Ala_AGC_chr6:26705606-26705678 (+)	GGGGAATTAGCTCAAGCGGTAGAGCGCTTGCTTAGCATGCAAGAGGTAGTGGGATCGATGCC
6	Ala_AGC_chr6:26673590-26673662 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTAGTGGGATCAATGCC
7	Ala_AGC_chr14:89445442-89445514 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGTGGGATCGATGCC
8	Ala_AGC_chr6:58196623-58196695 (-)	GGGGAATTAGCCCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTAGTGGGATCGATGCC
9	Ala_AGC_chr6:28806221-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCCCGGGTTCAATCCCC
10	Ala_AGC_chr6:28574933-28575004 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGTACGAGGTCCCGGGTTCAATCCCC
11	Ala_AGC_chr6:28626014-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTAGCATGCATGAGGTCCCGGGTTCGATCCCC

12	Ala_AGC_chr6:28678366-28678437 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCCTGGGTTCAATCCCC
13	Ala_AGC_chr6:28779849-28779920 (-)	GGGGGTATAGCTCAGCGGTAGAGCGCGTGCTTAGCATGCACGAGGTCCTGGGTTCAATCCCC
14	Ala_AGC_chr6:28687481-28687552 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCCCGGGTTCAATCCCT
15	Ala_AGC_chr2:27274082-27274154 (+)	GGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGATGCC
16	Ala_AGC_chr6:26730737-26730809 (+)	GGGGAATTAGCTCAGGCGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGACGCC
17	Ala_CGC_chr6:26553731-26553802 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGTCCCGGGTTCGATCCCC
18	Ala_CGC_chr6:28641613-28641684 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGCCCCGGGTTCGATCCCC
19	Ala_CGC_chr2:157257281-157257352 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCGCGCTTCGCATGTGTGAGGTCCCGGGTTCAATCCCC
20	Ala_CGC_chr6:28697092-28697163 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTCGCATGTACGAGGCCCCGGGTTCGACCCCC
21	Ala_TGC_chr6:28757547-28757618 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGTCCCGGGTTCGATCCCC
22	Ala_TGC_chr6:28611222-28611293 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGTCCCGGGTTCGATCCCC
23	Ala_TGC_chr5:180633868-180633939 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCCCGGGTTCGATCCCC
24	Ala_TGC_chr12:125424512-125424583 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCACGTATGAGGCCCCGGGTTCAATCCCC
25	Ala_TGC_chr6:28785012-28785083 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCTCGGGTTCGATCCCC
26	Ala_TGC_chr6:28726141-28726212 (-)	GGGGGTGTAGCTCAGTGGTAGAGCACATGCTTTGCATGTGTGAGGCCCCGGGTTCGATCCCC
27	Ala_TGC_chr6:28770577-28770647 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCTCGGTTCGATCCCCG
28	Arg_ACG_chr6:26328368-26328440 (+)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATTCCAGGTTCGACTCC
29	Arg_ACG_chr3:45730491-45730563 (-)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATTCTAGGTTCGACTCC
30	Arg_CCG_chr6:28710729-28710801 (-)	GGCCGCGTGGCCTAATGGATAAGGCGTCTGATTCCGGATCAGAAGATTGAGGGTTCGAGTCC
31	Arg_CCG_chr17:660166013-66016085 (-)	GACCCAGTGGCCTAATGGATAAGGCATCAGCCTCCGGAGCTGGGGATTGTGGGTTCGAGTCC
32	Arg_CCT_chr17:730300001-73030073 (+)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTCC
33	Arg_CCT_chr17:730300526-73030598 (-)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTCC

34	Arg_CCT_chr16:3202901-3202973 (+)	GCCCCGGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTCC
35	Arg_CCT_chr7:139025446-139025518 (+)	GCCCCAGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTCC
36	Arg_CCT_chr16:3243918-3243990 (+)	GCCCCAGTGGCCTGATGGATAAGGTACTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTTC
37	Arg_TCG_chr15:898788304-89878376 (+)	GGCCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGCAGGTTCGAGTCC
38	Arg_TCG_chr6:26323046-26323118 (+)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAATCC
39	Arg_TCG_chr17:7303 1208-73031280 (+)	GACCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAGTCC
40	Arg_TCG_chr6:26299905-26299977 (+)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAATCC
41	Arg_TCG_chr6:28510891-28510963 (-)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAATCC
42	Arg_TCG_chr9:112960803-112960875 (+)	GGCCGTGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAAAAGATTGCAGGTTTGAGTTC
43	Arg_TCT_chr1:94313129-94313213 (+)	GGCTCCGTGGCGCAATGGATAGCGCATTGGACTTCTAGAGGCTGAAGGCATTCAAAGGTTCC
44	Arg_TCT_chr17:8024243-8024330 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGTGACGAATAGAGCAATTCAAAGGT
45	Arg_TCT_chr9:131102355-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCTGAGCCTAGTGTGGTCATTCAAA
46	Arg_TCT_chr11:59318767-59318852 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGATAGTTAGAGAAATTCAAAGGTTG
47	Arg_TCT_chr1:159111401-159111474 (-)	GTCTCTGTGGCGCAATGGACGAGCGCGCTGGACTTCTAATCCAGAGGTTCCGGGTTCGAGTC
48	Arg_TCT_chr6:27529963-27530049 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCCTAAATCAAGAGATTCAAAGGTT
49	Asn_GTT_chr1:161510031-161510104 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGTTGGTGGTTCGATCC
50	Asn_GTT_chr1:143879832-143879905 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTGGCTGTTAACTAAAAGGTTGGCGGTTCGAACC
51	Asn_GTT_chr1:144301611-144301684 (+)	GTCTCTGTGGTGCAATCGGTTAGCGCGTTCCGCTGTTAACCGAAAGCTTGGTGGTTCGAGCCC
52	Asn_GTT_chr1:149326272-149326345 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTGGCTGTTAACTAAAAAGTTGGTGGTTCGAACA
53	Asn_GTT_chr1:148248115-148248188 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
54	Asn_GTT_chr1:148598314-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCATTCGGCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
55	Asn_GTT_chr1:17216172-17216245 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGATTGGTGGTTCGAGCC

56	Asn_GTT_chr1:16847080-16847153 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTTAACTGAAAGGTTGGTGGTTCGAGCC
57	Asn_GTT_chr1:149230570-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCGCGTTCG GCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
58	Asn_GTT_chr1:148000805-148000878 (+)	GTCTCTGTGGCGTAGTCGGTTAGCGCGTTCG GCTGTTAACCGAAAAGTTGGTGGTTCGAGCC
59	Asn_GTT_chr1:149711798-149711871 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTG GCTGTTAACTAAAAGGTTGGTGGTTCGAACC
60	Asn_GTT_chr1:145979034-145979107 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTTAACTGAAAGGTTAGTGGTTCGAGCC
61	Asp_GTC_chr12:98897281-98897352 (+)	TCCTCGTTAGTATAGTGGTTAGTATCCCCGCC TGTCACGCGGGAGACCGGGGTTCAATTCCCC
62	Asp_GTC_chr1:161410615-161410686 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCC TGTCACGCGGGAGACCGGGGTTCGATTCCCC
63	Asp_GTC_chr6:27551236-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGTCCCCGTC TGTCACGCGGGAGACCGGGGTTCGATTCCCC
64	Cys_GCA_chr7:149007281-149007352 (+)	GGGGGCATAGCTCAGTGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCTGGTTCAAATCCA
65	Cys_GCA_chr7:149074601-149074672 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCTGGTTCAAATCCA
66	Cys_GCA_chr7:149112229-149112300 (-)	GGGGGTATAGCTTAGCGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCGGTTCAAATCCG
67	Cys_GCA_chr7:149344046-149344117 (-)	GGGGGTATAGCTTAGGGGTAGAGCATTTGAC TGCAGATCAAAAGGTCCCTGGTTCAAATCCA
68	Cys_GCA_chr7:149052766-149052837 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCAGTTCAAATCTG
69	Cys_GCA_chr17:37017937-37018008 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAAGTCCCCGGTTCAAATCCG
70	Cys_GCA_chr7:149281816-149281887 (+)	GGGGGTATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCTCTGGTTCAAATCCA
71	Cys_GCA_chr7:149243631-149243702 (+)	GGGGGTATAGCTCAGGGGTAGAGCACTTGAC TGCAGATCAAGAAGTCCTTGGTTCAAATCCA
72	Cys_GCA_chr7:149388272-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCGGTTCAAATCCG
73	Cys_GCA_chr7:149072850-149072921 (-)	GGGGGTATAGTTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCTGGTTCAAATCCA
74	Cys_GCA_chr7:149310156-149310227 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGAC TGCAAATCAAGAGGTCCCTGATTCAAATCCA
75	Cys_GCA_chr4:124430005-124430076 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCGGTTCAAATCCG
76	Cys_GCA_chr7:149295046-149295117 (+)	GGGCGTATAGCTCAGGGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCAGTTCAAATCTG
77	Cys_GCA_chr7:149361915-149361986 (+)	GGGGGTATAGCTCACAGGTAGAGCATTTGAC TGCAGATCAAGAGGTCCCCGGTTCAAATCTG

78	Cys_GCA_chr7:149253802-149253871 (+)	GGGCGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCAGTTCAAATCTG
79	Cys_GCA_chr7:149292305-149292376 (-)	GGGGGTATAGCTCACAGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCCG
80	Cys_GCA_chr7:149286164-149286235 (-)	GGGGGTATAGCTCAGGGGTAGAGCACTTGACTGCAGATCAAGAGGTCCCTGGTTCAAATCCA
81	Cys_GCA_chr17:37025545-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCTGGTTCAAATCCG
82	Cys_GCA_chr15:80036997-80037069 (+)	GGGGGTATAGCTCAGTGGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCC
83	Cys_GCA_chr3:131947944-131948015 (-)	GGGGGTGTAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCTGGTTCAAATCCA
84	Cys_GCA_chr1:93981834-93981906 (-)	GGGGGTATAGCTCAGGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCC
85	Cys_GCA_chr14:73429679-73429750 (+)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCCG
86	Cys_GCA_chr3:131950642-131950713 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCTGGTTCAAATCCA
87	Gln_CTG_chr6:18836402-18836473 (+)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAATCTC
88	Gln_CTG_chr6:27515531-27515602 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAGTCTC
89	Gln_CTG_chr1:145963304-145963375 (+)	GGTTCCATGGTGTAATGGTGAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCGAGTCTC
90	Gln_CTG_chr1:147737382-147737453 (-)	GGTTCCATGGTGTAATGGTAAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCGAGTCTC
91	Gln_CTG_chr6:27263212-27263283 (+)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCGGTAATCCGAGTTCAAATCTC
92	Gln_CTG_chr6:27759135-27759206 (-)	GGCCCCATGGTGTAATGGTCAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAATCTC
93	Gln_CTG_chr1:147800937-147801008 (+)	GGTTCCATGGTGTAATGGTAAGCACTCTGGACTCTGAATCCAGCCATCTGAGTTCGAGTCTCT
94	Gln_TTG_chr17:47269890-47269961 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCTC
95	Gln_TTG_chr6:28557156-28557227 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCAATCCGAGTTCGAATCTC
96	Gln_TTG_chr6:26311424-26311495 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCTC
97	Gln_TTG_chr6:145503859-145503930 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGGCTTTGAATCCAGCAATCCGAGTTCGAATCTTG
98	Glu_CTC_chr1:145399233-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCCGGGTTCGATTCCC
99	Glu_CTC_chr1:249168447-249168518 (+)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCCGGGTTCGATTCCC

100	Glu_TTC_chr2:131094701-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGTGGCCCGGGTTCGACTCCCG
101	Glu_TTC_chr13:45492062-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGCGGCCCGGGTTCGACTCCCG
102	Glu_TTC_chr1:17199078-17199149 (+)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCCGGGTTCGATTCCCG
103	Glu_TTC_chr1:16861774-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCCGGGTTCGATTCCCG
104	Gly_CCC_chr1:16872434-16872504 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTCCCACGCGGGAGACCCGGGTTCAATTCCCGG
105	Gly_CCC_chr2:70476123-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGATTCCCATTCTTGCGACCCGGGTTCGATTCCCGG
106	Gly_CCC_chr17:19764175-19764245 (+)	GCATTGGTGGTTCAATGGTAGAATTCTCGCCTCCCACGCAGGAGACCCAGGTTCGATTCCTGG
107	Gly_GCC_chr1:161413094-161413164 (+)	GCATGGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCG
108	Gly_GCC_chr1:161493637-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCGG
109	Gly_GCC_chr16:70812114-70812184 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTTGATTCCCGG
110	Gly_GCC_chr1:161450356-161450426 (+)	GCATAGGTGGTTCAGTGGTAGAATTCTTGCCTGCCACGCAGGAGGCCCAGGTTTGATTCCTG
111	Gly_GCC_chr16:70822597-70822667 (+)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCATGCGGGCGGCCGGGCTTCGATTCCTGG
112	Gly_TCC_chr19:4724082-4724153 (+)	GCGTTGGTGGTATAGTGGTTAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
113	Gly_TCC_chr1:145397864-145397935 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
114	Gly_TCC_chr17:8124866-8124937 (+)	GCGTTGGTGGTATAGTGGTAAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
115	Gly_TCC_chr1:161409961-161410032 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGTTGCCTTCCAAGCAGTTGACCCGGGCTCGATTCCC
116	His_GTG_chr1:145396881-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCTCGGTTCGAATCCGA
117	His_GTG_chr1:149155828-149155899 (-)	GCCATGATCGTATAGTGGTTAGTACTCTGCGCTGTGGCCGCAGCAACCTCGGTTCGAATCCG
118	Ile_AAT_chr6:58149254-58149327 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGCGCTAATAACGCCAAGGTCGCGGGTTCGATCC
119	Ile_AAT_chr6:27655967-27656040 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC
120	Ile_AAT_chr6:27242990-27243063 (-)	GGCTGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC
121	Ile_AAT_chr17:8130309-8130382 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGAACC

122	Ile_AAT_chr6:26554350-26554423 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC
123	Ile_AAT_chr6:26745255-26745328 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCTAAGGTCGCGGGTTCGATCC
124	Ile_AAT_chr6:26721221-26721294 (-)	GGCCGGTTAGCTCAGTTGGTCAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC
125	Ile_AAT_chr6:27636362-27636435 (+)	GGCCGGTTAGCTCAGTCGGCTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC
126	Ile_AAT_chr6:27241739-27241812 (+)	GGCTGGTTAGTTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGTGGGTTCGATCC
127	Ile_GAT_chrX:3756418-3756491 (-)	GGCCGGTTAGCTCAGTTGGTAAGAGCGTGGTGCTGATAACACCAAGGTCGCGGGCTCGACTC
128	Ile_TAT_chr19:39902808-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGACAGTGCGAGCGGAGCAATGCC
129	Ile_TAT_chr2:43037676-43037768 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAGCAGTACATGCAGAGCAATGCC
130	Ile_TAT_chr6:26988125-26988218 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGGCAGTATGTGTGCGAGTGATGC
131	Ile_TAT_chr6:27599200-27599293 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAACAGTATATGTGCGGGTGATGC
132	Ile_TAT_chr6:28505367-28505460 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATAAGACAGTGCACCTGTGAGCAATGC
133	Leu_AAG_chr5:180524474-180524555 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTCTTCGGAGGCGTGGG
134	Leu_AAG_chr5:180614701-180614782 (+)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG
135	Leu_AAG_chr6:28956779-28956860 (+)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG
136	Leu_AAG_chr6:28446400-28446481 (-)	GGTAGCGTGGCCGAGTGGTCTAAGACGCTGGATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG
137	Leu_CAA_chr6:28864000-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTAAGCTTCCTCCGCGGTGGGGAT
138	Leu_CAA_chr6:28908830-28908934 (+)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTGGCTTCCTCGTGTTGAGGATTC
139	Leu_CAA_chr6:27573417-27573524 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTACTGCTTCCTGTGTTCGGGTCT
140	Leu_CAA_chr6:27570348-27570454 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGTTGCTACTTCCCAGGTTTGGGGCTT
141	Leu_CAA_chr1:249168054-249168159 (+)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGGTAAGCACCTTGCCTGCGGGCTTT
142	Leu_CAA_chr11:9296790-9296863 (+)	GCCTCCTTAGTGCAGTAGGTAGCGCATCAGTCTCAAAATCTGAATGGTCCTGAGTTCAAGCC
143	Leu_CAA_chr1:161581736-161581819 (-)	GTCAGGATGGCCGAGCAGTCTTAAGGCGCTGCGTTCAAATCGCACCCTCCGCTGGAGGCGTG

144	Leu_CAG_chr1:161411323-161411405 (+)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG
145	Leu_CAG_chr16:57333863-57333945 (+)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG
146	Leu_TAA_chr6:144537684-144537766 (+)	ACCAGGATGGCCGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGACATATGTCCGCGTGG
147	Leu_TAA_chr6:27688898-27688980 (-)	ACCGGGATGGCCGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGGCTGGTGCCCGCGTGG
148	Leu_TAA_chr11:59319228-59319310 (+)	ACCAGAATGGCCGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGATTCATATCCGCGTGG
149	Leu_TAA_chr6:27198334-27198416 (-)	ACCGGGATGGCTGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGACAGGTGTCCGCGTGG
150	Leu_TAG_chr17:8023632-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCTCTTCGGAGGCGTGGG
151	Leu_TAG_chr14:21093529-21093610 (+)	GGTAGTGTGGCCGAGCGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCTCTTCGGGGGCGTGGG
152	Leu_TAG_chr16:22207032-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCATTTCGATGGCGTGGGT
153	Lys_CTT_chr14:58706613-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGA CTCTTAATCCCAGGGTCGTGGGTTCGAGCCC
154	Lys_CTT_chr19:36066750-36066822 (+)	GCCCAGCTAGCTCAGTCGGTAGAGCATAAGA CTCTTAATCTCAGGGTTGTGGATTCGTGCCCC
155	Lys_CTT_chr19:52425393-52425466 (-)	GCAGCTAGCTCAGTCGGTAGAGCATGAGACT CTTAATCTCAGGGTCATGGGTTCGTGCCCCAT
156	Lys_CTT_chr1:145395522-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGA CTCTTAATCTCAGGGTCGTGGGTTCGAGCCCC
157	Lys_CTT_chr16:3207406-3207478 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGA CCCTTAATCTCAGGGTCGTGGGTTCGAGCCC
158	Lys_CTT_chr16:3241501-3241573 (+)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGA CTCTTAATCTCAGGGTCGTGGGTTCGAGCCCC
159	Lys_CTT_chr16:3230555-3230627 (-)	GCCCGGCTAGCTCAGTCGATAGAGCATGAGA CTCTTAATCTCAGGGTCGTGGGTTCGAGCCG
160	Lys_CTT_chr1:55423542-55423614 (-)	GCCCAGCTAGCTCAGTCGGTAGAGCATGAGA CTCTTAATCTCAGGGTCATGGGTTTGAGCCCC
161	Lys_CTT_chr16:3214939-3215011 (+)	GCCTGGCTAGCTCAGTCGGCAAAGCATGAGA CTCTTAATCTCAGGGTCGTGGGCTCGAGCTCC
162	Lys_CTT_chr5:26198539-26198611 (-)	GCCCGACTACCTCAGTCGGTGGAGCATGGGA CTCTTCATCCCAGGGTTGTGGGTTCGAGCCCC
163	Lys_TTT_chr16:7351 2216-73512288 (-)	GCCTGGATAGCTCAGTTGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC
164	Lys_TTT_chr12:27843306-27843378 (+)	ACCCAGATAGCTCAGTCAGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAAGGTTCATGTCCC
165	Lys_TTT_chr11:122430655-122430727 (+)	GCCTGGATAGCTCAGTTGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC

166	Lys_TTT_chr1:20447 5655-204475727 (+)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC
167	Lys_TTT_chr6:27559 593-27559665 (-)	GCCTGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC
168	Lys_TTT_chr11:5932 3902-59323974 (+)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCGGGGTTCAAGTCCC
169	Lys_TTT_chr6:27302 769-27302841 (-)	GCCTGGGTAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC
170	Lys_TTT_chr6:28715 521-28715593 (+)	GCCTGGATAGCTCAGTTGGTAGAACATCAGA CTTTTAATCTGACGGTGCAGGGTTCAAGTCCC
171	Met_CAT_chr8:12416 9470-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCGCGTCAGT CTCATAATCTGAAGGTCGTGAGTTCGATCCTC
172	Met_CAT_chr16:7146 0396-71460468 (+)	GCCCTCTTAGCGCAGTGGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAGCCT
173	Met_CAT_chr6:28912 352-28912424 (+)	GCCTCCTTAGCGCAGTAGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAACCT
174	Met_CAT_chr6:26735 574-26735646 (-)	GCCCTCTTAGCGCAGCGGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAGCCT
175	Met_CAT_chr6:26701 712-26701784 (+)	GCCCTCTTAGCGCAGCTGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCAAGCCT
176	Met_CAT_chr16:8741 7628-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCGCGTCAGT CTCATAATCTGAAGGTCGTGAGTTCGAGCCT
177	Met_CAT_chr6:58168 492-58168564 (-)	GCCCTCTTAGTGCAGCTGGCAGCGCGTCAGT TTCATAATCTGAAAGTCCTGAGTTCAAGCCTC
178	Phe_GAA_chr6:28758 499-28758571 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCTAAAGGTCCCTGGTTCGATCCC
179	Phe_GAA_chr11:5933 3853-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCTAAAGGTCCCTGGTTCAATCCC
180	Phe_GAA_chr6:28775 610-28775682 (-)	GCCGAGATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCTAAAGGTCCCTGGTTCAATCCC
181	Phe_GAA_chr6:28791 093-28791166 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGA CCGAAGATCTTAAAGGTCCCTGGTTCAATCC
182	Phe_GAA_chr6:28731 374-28731447 (-)	GCTGAAATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCTTAAAGTTCCCTGGTTCAACCCT
183	Pro_AGG_chr16:3241 989-3242060 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT AGGATGCGAGAGGTCCCGGGTTCAAATCCCG
184	Pro_AGG_chr1:16768 4725-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT AGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
185	Pro_CGG_chr1:16768 3962-167684033 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT CGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
186	Pro_CGG_chr6:27059 521-27059592 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT CGGGTGTGAGAGGTCCCGGGTTCAAATCCCG
187	Pro_TGG_chr14:2110 1165-21101236 (+)	GGCTCGTTGGTCTAGTGGTATGATTCTCGCTT TGGGTGCGAGAGGTCCCGGGTTCAAATCCCG

188	Pro_TGG_chr11:75946869-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGGTTTGGGTCCGAGAGGTCCCGGGTTCAAATCCCG
189	Pro_TGG_chr5:180615854-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
190	SeC_TCA_chr19:45981859-45981945 (-)	GCCCGGATGATCCTCAGTGGTCTGGGGTGCAGGCTTCAAACCTGTAGCTGTCTAGCGACAGA
191	SeC_TCA_chr22:44546537-44546620 (+)	GCTCGGATGATCCTCAGTGGTCTGGGGTGCAGGCTTCAAACCTGTAGCTGTCTAGTGACAGA
192	Ser_AGA_chr6:27509554-27509635 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTTTCCCCGCGCAGG
193	Ser_AGA_chr6:26327817-26327898 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTCTCCCCGCGCAGG
194	Ser_AGA_chr6:27499987-27500068 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTTTCCCCACGCAGG
195	Ser_AGA_chr6:27521192-27521273 (-)	GTAGTCGTGGCCGAGTGGTTAAGGTGATGGACTAGAAACCCATTGGGGTCTCCCCGCGCAGG
196	Ser_CGA_chr17:8042199-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGGTCTCCCCGCGCAGG
197	Ser_CGA_chr6:27177628-27177709 (+)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGGTCTCCCCGCGCAGG
198	Ser_CGA_chr6:27640229-27640310 (-)	GCTGTGATGGCCGAGTGGTTAAGGTGTTGGACTCGAAATCCAATGGGGGTTCCCCGCGCAGG
199	Ser_CGA_chr12:56584148-56584229 (+)	GTCACGGTGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGGTTTCCCCGCACAGG
200	Ser_GCT_chr6:27065085-27065166 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTGG
201	Ser_GCT_chr6:27265775-27265856 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTGG
202	Ser_GCT_chr11:66115591-66115672 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTTTGCACGCGTGGG
203	Ser_GCT_chr6:28565117-28565198 (-)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTGG
204	Ser_GCT_chr6:28180815-28180896 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACACGTGG
205	Ser_GCT_chr6:26305718-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTG
206	Ser_TGA_chr10:69524261-69524342 (+)	GCAGCGATGGCCGAGTGGTTAAGGCGTTGGACTTGAAATCCAATGGGGTCTCCCCGCGCAGG
207	Ser_TGA_chr6:27513468-27513549 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGGTTTCCCCGCGCAGG
208	Ser_TGA_chr6:26312824-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGGTCTCCCCGCGCAGG
209	Ser_TGA_chr6:27473607-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGGTTTCCCCGCGCAGG

210	Thr_AGT_chr17:8090478-8090551 (+)	GGCGCCGTGGCTTAGTTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
211	Thr_AGT_chr6:26533145-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
212	Thr_AGT_chr6:28693795-28693868 (+)	GGCTCCGTAGCTTAGTTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGACTC
213	Thr_AGT_chr6:27694473-27694546 (+)	GGCTTCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
214	Thr_AGT_chr17:8042770-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
215	Thr_AGT_chr6:27130050-27130123 (+)	GGCCCTGTGGCTTAGCTGGTCAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
216	Thr_CGT_chr6:28456770-28456843 (-)	GGCTCTATGGCTTAGTTGGTTAAAGCGCCTGT CTCGTAAACAGGAGATCCTGGGTTCGACTCC
217	Thr_CGT_chr16:14379750-14379821 (+)	GGCGCGGTGGCCAAGTGGTAAGGCGTCGGTC TCGTAAACCGAAGATCACGGGTTCGAACCCC
218	Thr_CGT_chr6:28615984-28616057 (-)	GGCTCTGTGGCTTAGTTGGCTAAAGCGCCTG TCTCGTAAACAGGAGATCCTGGGTTCGAATC
219	Thr_CGT_chr17:29877093-29877164 (+)	GGCGCGGTGGCCAAGTGGTAAGGCGTCGGTC TCGTAAACCGAAGATCGCGGGTTCGAACCCC
220	Thr_CGT_chr6:27586135-27586208 (+)	GGCCCTGTAGCTCAGCGGTTGGAGCGCTGGT CTCGTAAACCTAGGGGTCGTGAGTTCAAATC
221	Thr_TGT_chr6:28442329-28442402 (-)	GGCTCTATGGCTTAGTTGGTTAAAGCGCCTGT CTTGTAAACAGGAGATCCTGGGTTCGAATCC
222	Thr_TGT_chr1:222638347-222638419 (+)	GGCTCCATAGCTCAGTGGTTAGAGCACTGGT CTTGTAAACCAGGGGTCGCGAGTTCGATCCT
223	Thr_TGT_chr14:21081949-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAGCGCTGGT CTTGTAAACCAGGGGTCGCGAGTTCAATTCT
224	Thr_TGT_chr14:21099319-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGT CTTGTAAACCAGGGGTCGCGAGTTCAAATCT
225	Thr_TGT_chr14:21149849-21149921 (+)	GGCCCTATAGCTCAGGGGTTAGAGCACTGGT CTTGTAAACCAGGGGTCGCGAGTTCAAATCT
226	Thr_TGT_chr5:180618687-180618758 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGT CTTGTAAACCAGGGTCGCGAGTTCAAATCTC
227	Trp_CCA_chr17:8124187-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAATCAC
228	Trp_CCA_chr17:19411494-19411565 (+)	GACCTCGTGGCGCAATGGTAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAGTCAC
229	Trp_CCA_chr6:26319330-26319401 (-)	GACCTCGTGGCGCAACGGTAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAATCAC
230	Trp_CCA_chr12:98898030-98898101 (+)	GACCTCGTGGCGCAACGGTAGCGCGTCTGAC TCCAGATCAGAAGGCTGCGTGTTCGAATCAC
231	Trp_CCA_chr7:99067307-99067378 (+)	GACCTCGTGGCGCAACGGCAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAATCAC

232	Tyr_ATA_chr2:21911 0549-219110641 (+)	CCTTCAATAGTTCAGCTGGTAGAGCAGAGGA CTATAGCTACTTCCTCAGTAGGAGACGTCCTT
233	Tyr_GTA_chr6:26569 086-26569176 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGA CTGTAGTTGGCTGTGTCCTTAGACATCCTTAG
234	Tyr_GTA_chr2:27273 650-27273738 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGA CTGTAGTGGATAGGGCGTGGCAATCCTTAGG
235	Tyr_GTA_chr6:26577 332-26577420 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGA CTGTAGGCTCATTAAGCAAGGTATCCTTAGG
236	Tyr_GTA_chr14:2112 5623-21125716 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGATTGTATAGACATTTGCGGACATCCT
237	Tyr_GTA_chr8:67025 602-67025694 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGCTACTTCCTCAGCAGGAGACATCCTT
238	Tyr_GTA_chr8:67026 223-67026311 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGGCGCGCGCCCGTGGCCATCCTTAGG
239	Tyr_GTA_chr14:2112 1258-21121351 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGCCTGTAGAAACATTTGTGGACATCC
240	Tyr_GTA_chr14:2113 1351-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGATTGTACAGACATTTGCGGACATCC
241	Tyr_GTA_chr14:2115 1432-21151520 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGTACTTAATGTGTGGTCATCCTTAGGT
242	Tyr_GTA_chr6:26595 102-26595190 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGGGGTTTGAATGTGGTCATCCTTAGGT
243	Tyr_GTA_chr14:2112 8117-21128210 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGACTGCGGAAACGTTTGTGGACATCC
244	Tyr_GTA_chr6:26575 798-26575887 (+)	CTTTCGATAGCTCAGTTGGTAGAGCGGAGGA CTGTAGGTTCATTAAACTAAGGCATCCTTAG
245	Tyr_GTA_chr8:66609 532-66609619 (-)	TCTTCAATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGGTGCACGCCCGTGGCCATTCTTAGG
246	Val_AAC_chr3:16949 0018-169490090 (+)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TAACACGCGAAAGGTCCCCGGTTCGAAACCG
247	Val_AAC_chr5:18061 5416-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCACGTTCGCC TAACACGCGAAAGGTCCCCGGTTCGAAACCG
248	Val_AAC_chr6:27618 707-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TAACACGCGAAAGGTCCCTGGATCAAAACCA
249	Val_AAC_chr6:27648 885-27648957 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TAACACGCGAAAGGTCCGCGGTTCGAAACCG
250	Val_AAC_chr6:27203 288-27203360 (+)	GTTTCCGTAGTGTAGTGGTTATCACGTTTGCC TAACACGCGAAAGGTCCCCGGTTCGAAACCG
251	Val_AAC_chr6:28703 206-28703277 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGTATGCT TAACATTCATGAGGCTCTGGGTTCGATCCCC
252	Val_CAC_chr1:16136 9490-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGAAAGGTCCCCGGTTCGAAACCG
253	Val_CAC_chr6:27248 049-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGAAAGGTCCCCGGTTCGAAACCG

254	Val_CAC_chr19:4724647-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCACATTCGCCTCACACGCGAAAGGTCCCCGGTTCGATCCCG
255	Val_CAC_chr1:149298555-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCCCCGGTTCGAAACTG
256	Val_CAC_chr1:149684088-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGTAAAGGTCCCCGGTTCGAAACC
257	Val_CAC_chr6:27173867-27173939 (-)	GTTTCCGTAGTGGAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCCCCGGTTTGAAACCA
258	Val_TAC_chr11:59318102-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCACGTCTGCTTTACACGCAGAAGGTCCTGGGTTCGAGCCCC
259	Val_TAC_chr11:59318460-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCACGTCTGCTTTACACGCAGAAGGTCCTGGGTTCGAGCCCC
260	Val_TAC_chr10:5895674-5895746 (-)	GGTTCCATAGTGTAGTGGTTATCACATCTGCTTTACACGCAGAAGGTCCTGGGTTCAAGCCCC
261	Val_TAC_chr6:27258405-27258477 (+)	GTTTCCGTGGTGTAGTGGTTATCACATTCGCCTTACACGCGAAAGGTCCTCGGGTCGAAACCG
262	iMet_CAT_chr1:153643726-153643797 (+)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCGAAACC
263	iMet_CAT_chr6:27745664-27745735 (+)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCTAAACC
264	Glu_TTC_chr1:16861773-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCCGGGTTCGATTCCCG
265	Gly_CCC_chr1:17004765-17004836 (-)	GCGTTGGTGGTTTAGTGGTAGAATTCTCGCCTCCCATGCGGGAGACCCGGGTTCAATTCCCGG
266	Gly_CCC_chr1:17053779-17053850 (+)	GGCCTTGGTGGTGCAGTGGTAGAATTCTCGCCTCCCACGTGGGAGACCCGGGTTCAATTCCC
267	Glu_TTC_chr1:17199077-17199149 (+)	GTCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCCGGGTTCGATTCCC
268	Asn_GTT_chr1:17216171-17216245 (+)	TGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGATTGGTGGTTCGAGCC
269	Arg_TCT_chr1:94313128-94313213 (+)	TGGCTCCGTGGCGCAATGGATAGCGCATTGGACTTCTAGAGGCTGAAGGCATTCAAAGGTTC
270	Lys_CTT_chr1:145395521-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTCGTGGGTTCGAGCCCC
271	His_GTG_chr1:145396880-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCTCGGTTCGAATCCGA
272	Gly_TCC_chr1:145397863-145397935 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
273	Glu_CTC_chr1:145399232-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCCGGGTTCGATTCCC
274	Gln_CTG_chr1:145963303-145963375 (+)	AGGTTCCATGGTGTAATGGTGAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCGAGTCT
275	Asn_GTT_chr1:148000804-148000878 (+)	TGTCTCTGTGGCGTAGTCGGTTAGCGCGTTCGGCTGTTAACCGAAAAGTTGGTGGTTCGAGCC

276	Asn_GTT_chr1:148248114-148248188 (+)	TGTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
277	Asn_GTT_chr1:148598313-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCATTCG GCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
278	Asn_GTT_chr1:149230569-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCGCGTTCG GCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
279	Val_CAC_chr1:149294665-149294736 (-)	GCACTGGTGGTTCAGTGGTAGAATTCTCGCC TCACACGCGGGACACCCGGGTTCAATTCCCG
280	Val_CAC_chr1:149298554-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGAAAGGTCCCCGGTTCGAAACTG
281	Gly_CCC_chr1:149680209-149680280 (-)	GCACTGGTGGTTCAGTGGTAGAATTCTCGCC TCCCACGCGGGAGACCCGGGTTTAATTCCCG
282	Val_CAC_chr1:149684087-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGTAAAGGTCCCCGGTTCGAAACC
283	Met_CAT_chr1:153643725-153643797 (+)	TAGCAGAGTGGCGCAGCGGAAGCGTGCTGG GCCCATAACCCAGAGGTCGATGGATCGAAAC
284	Val_CAC_chr1:161369489-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGAAAGGTCCCCGGTTCGAAACCG
285	Asp_GTC_chr1:161410614-161410686 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCC TGTCACGCGGGAGACCGGGGTTCGATTCCCC
286	Gly_GCC_chr1:161413093-161413164 (+)	TGCATGGGTGGTTCAGTGGTAGAATTCTCGC CTGCCACGCGGGAGGCCCGGGTTCGATTCCC
287	Glu_CTC_chr1:161417017-161417089 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCG CTCTCACCGCCGCGGCCCGGGTTCGATTCCC
288	Asp_GTC_chr1:161492934-161493006 (+)	ATCCTTGTTACTATAGTGGTGAGTATCTCTGC CTGTCATGCGTGAGAGAGGGGGTCGATTCCC
289	Gly_GCC_chr1:161493636-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCT GCCACGCGGGAGGCCCGGGTTCGATTCCCGG
290	Leu_CAG_chr1:161500131-161500214 (-)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG
291	Gly_TCC_chr1:161500902-161500974 (+)	CGCGTTGGTGGTATAGTGGTGAGCATAGCTG CCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
292	Asn_GTT_chr1:161510030-161510104 (+)	CGTCTCTGTGGCGCAATCGGTTAGCGCGTTC GGCTGTTAACCGAAAGGTTGGTGGTTCGATC
293	Glu_TTC_chr1:161582507-161582579 (+)	CGCGTTGGTGGTGTAGTGGTGAGCACAGCTG CCTTTCAAGCAGTTAACGCGGGTTCGATTCCC
294	Pro_CGG_chr1:167683961-167684033 (+)	CGGCTCGTTGGTCTAGGGGTATGATTCTCGCT TCGGGTGCGAGAGGTCCCGGGTTCAAATCCC
295	Pro_AGG_chr1:167684724-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT AGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
296	Lys_TTT_chr1:204475654-204475727 (+)	CGCCCGGATAGCTCAGTCGGTAGAGCATCAG ACTTTTAATCTGAGGGTCCAGGGTTCAAGTC
297	Lys_TTT_chr1:204476157-204476230 (-)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC

298	Leu_CAA_chr1:249168053-249168159 (+)	TGTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGGTAAGCACCTTGCCTGCGGGCTT
299	Glu_CTC_chr1:249168446-249168518 (+)	TTCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCCGGGTTCGATTCCC
300	Tyr_GTA_chr2:27273649-27273738 (+)	GCCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTGGATAGGGCGTGGCAATCCTTAG
301	Ala_AGC_chr2:27274081-27274154 (+)	CGGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGATGC
302	Ile_TAT_chr2:43037675-43037768 (+)	AGCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAGCAGTACATGCAGAGCAATGC
303	Gly_CCC_chr2:70476122-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGATTCCCATTCTTGCGACCCGGGTTCGATTCCCGG
304	Glu_TTC_chr2:131094700-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGTGGCCCGGGTTCGACTCCCG
305	Ala_CGC_chr2:157257280-157257352 (+)	GGGGGATGTAGCTCAGTGGTAGAGCGCGCGCTTCGCATGTGTGAGGTCCCGGGTTCAATCCCC
306	Gly_GCC_chr2:157257658-157257729 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCGG
307	Arg_ACG_chr3:45730490-45730563 (-)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATTCTAGGTTCGACTCC
308	Val_AAC_chr3:169490017-169490090 (+)	GGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCCCCGGTTCGAAACC
309	Val_AAC_chr5:180596609-180596682 (+)	AGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCCCCGGTTCGAAACC
310	Leu_AAG_chr5:180614700-180614782 (+)	AGGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTCTTCGGGGGCGTGG
311	Val_AAC_chr5:180615415-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCACGTTCGCCTAACACGCGAAAGGTCCCCGGTTCGAAACCG
312	Pro_TGG_chr5:180615853-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
313	Thr_TGT_chr5:180618686-180618758 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGTCGCGAGTTCAAATCTC
314	Ala_TGC_chr5:180633867-180633939 (+)	TGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCCCGGGTTCGATCCCC
315	Lys_CTT_chr5:180634754-180634827 (+)	CGCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTCGTGGGTTCGAGCC
316	Val_AAC_chr5:180645269-180645342 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCCCCGGTTCGAAACCG
317	Lys_CTT_chr5:180648978-180649051 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTCGTGGGTTCGAGCCCC
318	Val_CAC_chr5:180649394-180649467 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCCCCGGTTCGAAACCG
319	Met_CAT_chr6:26286753-26286825 (+)	CAGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCGAAAC

320	Ser_GCT_chr6:26305717-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTG
321	Gln_TTG_chr6:26311423-26311495 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCTC
322	Gln_TTG_chr6:26311974-26312046 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCTC
323	Ser_TGA_chr6:26312823-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGGTCTCCCCGCGCAGG
324	Met_CAT_chr6:26313351-26313423 (-)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCGAAACC
325	Arg_TCG_chr6:26323045-26323118 (+)	GGACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAATC
326	Ser_AGA_chr6:26327816-26327898 (+)	TGTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTCTCCCCGCGCAG
327	Met_CAT_chr6:26330528-26330600 (-)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCGAAACC
328	Leu_CAG_chr6:26521435-26521518 (+)	CGTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCTCCCCTGGAGGCGTG
329	Thr_AGT_chr6:26533144-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGATCCTGGGTTCGAATC
330	Arg_ACG_chr6:26537725-26537798 (+)	AGGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATTCCAGGTTCGACTC
331	Val_CAC_chr6:26538281-26538354 (+)	GGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCCCCGGTTCGAAACC
332	Ala_CGC_chr6:26553730-26553802 (+)	AGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGTCCCGGGTTCGATCCCC
333	Ile_AAT_chr6:26554349-26554423 (+)	TGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATC
334	Pro_AGG_chr6:26555497-26555569 (+)	CGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTCCCGGGTTCAAATCCC
335	Lys_CTT_chr6:26556773-26556846 (+)	AGCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTCGTGGGTTCGAGCC
336	Tyr_GTA_chr6:26569085-26569176 (+)	TCCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTTGGCTGTGTCCTTAGACATCCTTA
337	Ala_AGC_chr6:26572091-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGATGCC
338	Met_CAT_chr6:26766443-26766516 (+)	CGCCCTCTTAGCGCAGCGGGCAGCGCGTCAGTCTCATAATCTGAAGGTCCTGAGTTCGAGCCT
339	Ile_TAT_chr6:26988124-26988218 (+)	TGCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGGCAGTATGTGTGCGAGTGATG
340	His_GTG_chr6:27125905-27125977 (+)	TGCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCTCGGTTCGAATCCG
341	Ile_AAT_chr6:27144993-27145067 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATCC

342	Val_AAC_chr6:27203287-27203360 (+)	AGTTTCCGTAGTGTAGTGGTTATCACGTTTGCCTAACACGCGAAAGGTCCCCGGTTCGAAACC
343	Val_CAC_chr6:27248048-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCCCCGGTTCGAAACCG
344	Asp_GTC_chr6:27447452-27447524 (+)	TTCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACCGGGGTTCGATTCCC
345	Ser_TGA_chr6:27473606-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGGTTTCCCCGCGCAGG
346	Gln_CTG_chr6:27487307-27487379 (+)	AGGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAATCT
347	Asp_GTC_chr6:27551235-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGTCCCCGTCTGTCACGCGGGAGACCGGGGTTCGATTCCCC
348	Val_AAC_chr6:27618706-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCCCTGGATCAAAACCA
349	Ile_AAT_chr6:27655966-27656040 (+)	CGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATC
350	Gln_CTG_chr6:27759134-27759206 (-)	GGCCCCATGGTGTAATGGTCAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAATCTC
351	Gln_TTG_chr6:27763639-27763711 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCTC
352	Ala_AGC_chr6:28574932-28575004 (+)	TGGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGTACGAGGTCCCGGGTTCAATCCC
353	Ala_AGC_chr6:28626013-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTAGCATGCATGAGGTCCCGGGTTCGATCCCC
354	Ala_CGC_chr6:28697091-28697163 (+)	AGGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTCGCATGTACGAGGCCCCGGGTTCGACCCC
355	Ala_AGC_chr6:28806220-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCCCGGGTTCAATCCCC
356	Ala_AGC_chr6:28831461-28831533 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCCCGGGTTCAATCCCC
357	Leu_CAA_chr6:28863999-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTAAGCTTCCTCCGCGGTGGGGAT
358	Leu_CAA_chr6:28908829-28908934 (+)	TGTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTGGCTTCCTCGTGTTGAGGATT
359	Gln_CTG_chr6:28909377-28909449 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCCGAGTTCAAATCTC
360	Leu_AAG_chr6:28911398-28911480 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG
361	Met_CAT_chr6:28912351-28912424 (+)	TGCCTCCTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAATCTGAAGGTCCTGAGTTCGAACCT
362	Lys_TTT_chr6:28918805-28918878 (+)	AGCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTCCAGGGTTCAAGTC
363	Met_CAT_chr6:28921041-28921114 (-)	GCCTCCTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAATCTGAAGGTCCTGAGTTCGAACCT

364	Glu_CTC_chr6:28949975-28950047 (+)	TTCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCCGGGTTCGATTCCC
365	Leu_TAA_chr6:144537683-144537766 (+)	CACCAGGATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGACATATGTCCGCGTG
366	Pro_AGG_chr7:128423503-128423575 (+)	TGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTCCCGGGTTCAAATCCC
367	Arg_CCT_chr7:139025445-139025518 (+)	AGCCCCAGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTC
368	Cys_GCA_chr7:149388271-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCCG
369	Tyr_GTA_chr8:67025601-67025694 (+)	CCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGCTACTTCCTCAGCAGGAGACATCC
370	Tyr_GTA_chr8:67026222-67026311 (+)	CCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGGCGCGCGCCCGTGGCCATCCTTAG
371	Ala_AGC_chr8:67026423-67026496 (+)	TGGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTAGCGGGATCGATGC
372	Ser_AGA_chr8:96281884-96281966 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTCTCCCCGCGCAGG
373	Met_CAT_chr8:124169469-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCGCGTCAGTCTCATAATCTGAAGGTCGTGAGTTCGATCCTC
374	Arg_TCT_chr9:131102354-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCTGAGCCTAGTGTGGTCATTCAAA
375	Asn_GTT_chr10:22518437-22518511 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
376	Ser_TGA_chr10:6952 4260-69524342 (+)	GGCAGCGATGGCCGAGTGGTTAAGGCGTTGGACTTGAAATCCAATGGGGTCTCCCCGCGCAG
377	Val_TAC_chr11:59318101-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCACGTCTGCTTTACACGCAGAAGGTCCTGGGTTCGAGCCCC
378	Val_TAC_chr11:59318459-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCACGTCTGCTTTACACGCAGAAGGTCCTGGGTTCGAGCCCC
379	Arg_TCT_chr11:59318766-59318852 (+)	TGGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGATAGTTAGAGAAATTCAAAGGTT
380	Leu_TAA_chr11:59319227-59319310 (+)	TACCAGAATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGATTCATATCCGCGTG
381	Lys_TTT_chr11:59323901-59323974 (+)	GGCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTCCGGGGTTCAAGTC
382	Phe_GAA_chr11:59324969-59325042 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTCCCTGGTTCGATCCC
383	Lys_TTT_chr11:59327807-59327880 (-)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC
384	Phe_GAA_chr11:59333852-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTCCCTGGTTCAATCCC
385	Ser_GCT_chr11:6611 5590-66115672 (+)	GGACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTTTGCACGCGTGG

386	Pro_TGG_chr11:75946868-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGGTTTGGGTCCGAGAGGTCCCGGGTTCAAATCCCG
387	Ser_CGA_chr12:56584147-56584229 (+)	AGTCACGGTGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGGTTTCCCCGCACAG
388	Asp_GTC_chr12:98897280-98897352 (+)	CTCCTCGTTAGTATAGTGGTTAGTATCCCCGCCTGTCACGCGGGAGACCGGGGTTCAATTCCC
389	Trp_CCA_chr12:98898029-98898101 (+)	GGACCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGCTGCGTGTTCGAATCA
390	Ala_TGC_chr12:125406300-125406372 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCCCGGGTTCGATCCCC
391	Phe_GAA_chr12:125412388-125412461 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTCCCTGGTTCGATCCC
392	Ala_TGC_chr12:125424511-125424583 (+)	AGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCACGTATGAGGCCCCGGGTTCAATCCC
393	Asn_GTT_chr13:31248100-31248174 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGTTGGTGGTTCGAGCC
394	Glu_TTC_chr13:45492061-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGCGGCCCGGGTTCGACTCCCG
395	Thr_TGT_chr14:21081948-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAGCGCTGGTCTTGTAAACCAGGGGTCGCGAGTTCAATTCT
396	Leu_TAG_chr14:21093528-21093610 (+)	TGGTAGTGTGGCCGAGCGGTCTAAGGCGCTGGATTTAGGCTCCAGTCTCTTCGGGGGCGTGG
397	Thr_TGT_chr14:21099318-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGTCGCGAGTTCAAATCT
398	Pro_TGG_chr14:21101164-21101236 (+)	TGGCTCGTTGGTCTAGTGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCCGGGTTCAAATCCC
399	Tyr_GTA_chr14:21131350-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGATTGTACAGACATTTGCGGACATCC
400	Thr_TGT_chr14:21149848-21149921 (+)	AGGCCCTATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGTCGCGAGTTCAAATC
401	Tyr_GTA_chr14:21151431-21151520 (+)	TCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGTACTTAATGTGTGGTCATCCTTAGG
402	Pro_TGG_chr14:21152174-21152246 (+)	TGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCCGGGTTCAAATCCC
403	Lys_CTT_chr14:58706612-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGACTCTTAATCCCAGGGTCGTGGGTTCGAGCCC
404	Ile_AAT_chr14:102783428-102783502 (+)	CGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGTCGCGGGTTCGATC
405	Glu_TTC_chr15:26327380-26327452 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGCGGCCCGGGTTCGACTCCCG
406	Ser_GCT_chr15:40886022-40886104 (-)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGCTCTGCACGCGTGG
407	His_GTG_chr15:45490803-45490875 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCTCGGTTCGAATCCGA

408	His_GTG_chr15:45493348-45493420 (+)	CGCCGTGATCGTATAGTGGTTAGTACTCTGC GTTGTGGCCGCAGCAACCTCGGTTCGAATCC
409	Gln_CTG_chr15:66161399-66161471 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGA CTCTGAATCCAGCGATCCGAGTTCAAATCTC
410	Lys_CTT_chr15:79152903-79152976 (+)	TGCCCGGCTAGCTCAGTCGGTAGAGCATGGG ACTCTTAATCCCAGGGTCGTGGGTTCGAGCC
411	Arg_TCG_chr15:89878303-89878376 (+)	GGGCCGCGTGGCCTAATGGATAAGGCGTCTG ACTTCGGATCAGAAGATTGCAGGTTCGAGTC
412	Gly_CCC_chr16:686735-686806 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGAT TCCCATTCTTGCGACCCGGGTTCGATTCCCGG
413	Arg_CCG_chr16:3200674-3200747 (+)	GGGCCGCGTGGCCTAATGGATAAGGCGTCTG ATTCCGGATCAGAAGATTGAGGGTTCGAGTC
414	Arg_CCT_chr16:3202900-3202973 (+)	CGCCCCGGTGGCCTAATGGATAAGGCATTGG CCTCCTAAGCCAGGGATTGTGGGTTCGAGTC
415	Lys_CTT_chr16:3207405-3207478 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGA CCCTTAATCTCAGGGTCGTGGGTTCGAGCCC
416	Thr_CGT_chr16:14379749-14379821 (+)	AGGCGCGGTGGCCAAGTGGTAAGGCGTCGGT CTCGTAAACCGAAGATCACGGGTTCGAACCC
417	Leu_TAG_chr16:22207031-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCATTTCGATGGCGTGGGT
418	Leu_AAG_chr16:22308460-22308542 (+)	GGGTAGCGTGGCCGAGCGGTCTAAGGCGCTG GATTAAGGCTCCAGTCTCTTCGGGGGCGTGG
419	Leu_CAG_chr16:57333862-57333945 (+)	AGTCAGGATGGCCGAGCGGTCTAAGGCGCTG CGTTCAGGTCGCAGTCTCCCCTGGAGGCGTG
420	Leu_CAG_chr16:57334391-57334474 (-)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG
421	Met_CAT_chr16:87417627-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCGCGTCAGT CTCATAATCTGAAGGTCGTGAGTTCGAGCCT
422	Leu_TAG_chr17:8023631-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCTCTTCGGAGGCGTGGG
423	Arg_TCT_chr17:8024242-8024330 (+)	TGGCTCTGTGGCGCAATGGATAGCGCATTGG ACTTCTAGTGACGAATAGAGCAATTCAAAGG
424	Gly_GCC_chr17:8029063-8029134 (+)	CGCATTGGTGGTTCAGTGGTAGAATTCTCGC CTGCCACGCGGGAGGCCCGGGTTCGATTCCC
425	Ser_CGA_chr17:8042198-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGA CTCGAAATCCAATGGGGTCTCCCCGCGCAGG
426	Thr_AGT_chr17:8042769-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC
427	Trp_CCA_chr17:8089675-8089747 (+)	CGACCTCGTGGCGCAACGGTAGCGCGTCTGA CTCCAGATCAGAAGGTTGCGTGTTCAAATCA
428	Ser_GCT_chr17:8090183-8090265 (+)	AGACGAGGTGGCCGAGTGGTTAAGGCGATG GACTGCTAATCCATTGTGCTCTGCACGCGTG
429	Thr_AGT_chr17:8090477-8090551 (+)	CGGCGCCGTGGCTTAGTTGGTTAAAGCGCCT GTCTAGTAAACAGGAGATCCTGGGTTCGAAT

430	Trp_CCA_chr17:8124186-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGTTGCGTGTTCAAATCAC
431	Gly_TCC_chr17:8124865-8124937 (+)	AGCGTTGGTGGTATAGTGGTAAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
432	Asp_GTC_chr17:8125555-8125627 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACCGGGGTTCGATTCCCC
433	Pro_CGG_chr17:8126150-8126222 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTCGGGTGCGAGAGGTCCCGGGTTCAAATCCCG
434	Thr_AGT_chr17:8129552-8129626 (-)	GGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGATCCTGGGTTCGAATC
435	Ser_AGA_chr17:8129927-8130009 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTCTCCCCGCGCAGG
436	Trp_CCA_chr17:19411493-19411565 (+)	TGACCTCGTGGCGCAATGGTAGCGCGTCTGACTCCAGATCAGAAGGTTGCGTGTTCAAGTCA
437	Thr_CGT_chr17:29877092-29877164 (+)	AGGCGCGGTGGCCAAGTGGTAAGGCGTCGGTCTCGTAAACCGAAGATCGCGGGTTCGAACCC
438	Cys_GCA_chr17:37023897-37023969 (+)	AGGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCC
439	Cys_GCA_chr17:37025544-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCTGGTTCAAATCCG
440	Cys_GCA_chr17:37309986-37310058 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCCCCGGTTCAAATCCG
441	Gln_TTG_chr17:47269889-47269961 (+)	AGGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCCGAGTTCAAATCT
442	Arg_CCG_chr17:66016012-66016085 (-)	GACCCAGTGGCCTAATGGATAAGGCATCAGCCTCCGGAGCTGGGGATTGTGGGTTCGAGTCC
443	Arg_CCT_chr17:73030000-73030073 (+)	AGCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTC
444	Arg_CCT_chr17:73030525-73030598 (-)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATTGTGGGTTCGAGTCC
445	Arg_TCG_chr17:73031207-73031280 (+)	AGACCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATTGAGGGTTCGAGTC
446	Asn_GTT_chr19:1383561-1383635 (+)	CGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGTTGGTGGTTCGAGC
447	Gly_TCC_chr19:4724081-4724153 (+)	GGCGTTGGTGGTATAGTGGTTAGCATAGCTGCCTTCCAAGCAGTTGACCCGGGTTCGATTCCC
448	Val_CAC_chr19:4724646-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCACATTCGCCTCACACGCGAAAGGTCCCCGGTTCGATCCCG
449	Thr_AGT_chr19:3366 7962-33668036 (+)	TGGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGATCCTGGGTTCGAAT
450	Ile_TAT_chr19:39902807-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGACAGTGCGAGCGGAGCAATGCC
451	Gly_GCC_chr21:18827106-18827177 (-)	GCATGGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCG

Non-naturally occurring modification

A TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification, e.g., a modification described in any one of Tables 5-9. A non-naturally occurring modification can be made according to methods known in the art. Exemplary methods of making non-naturally occurring modifications are provided in Examples 4-7.

In an embodiment, a non-naturally occurring modification is a modification that a cell, e.g., a human cell, does not make on an endogenous tRNA.

In an embodiment, a non-naturally occurring modification is a modification that a cell, e.g., a human cell, can make on an endogenous tRNA, but wherein such modification is in a location in which it does not occur on a native tRNA. In an embodiment, the non-naturally occurring modification is in a domain, linker or arm which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is at a position within a domain, linker or arm, which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is on a nucleotide which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is on a nucleotide at a position within a domain, linker or arm, which does not have such modification in nature.

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 5, or a combination thereof.

Table 5: Exemplary non-naturally occurring modifications

Modification
7-deaza-adenosine
Nl-methyl-adenosine
N6, N6 (dimethyl)adenine
N6-cis-hydroxy-isopentenyl-adenosine
thio-adenosine
2-(amino)adenine
2-(aminopropyl)adenine
2-(methylthio) N6 (isopentenyl)adenine
2-(alkyl)adenine
2-(aminoalkyl)adenine
2-(aminopropyl)adenine
2-(halo)adenine
2-(propyl)adenine
2'-azido-2'-deoxy-adenosine
2'-Deoxy-2'-alpha-aminoadenosine
2'-Deoxy-2'-alpha-azidoadenosine
6-(alkyl)adenine
6-(methyl)adenine
6-(alkyl)adenine
6-(methyl)adenine
7-(deaza)adenine
8-(alkenyl)adenine
8-(alkynyl)adenine
8-(amino)adenine
8-(thioalkyl)adenine
8-(alkenyl)adenine

Modification
8-(alkyl)adenine
8-(alkynyl)adenine
8-(amino)adenine
8-(halo)adenine
8-(hydroxyl)adenine
8-(thioalkyl)adenine
8-(thiol)adenine
8-azido-adenosine
azaadenine
deazaadenine
N6-(methyl)adenine
N6-(isopentyl)adenine
7-deaza-8-aza-adenosine
7-methyladenine
1-deazaadenosine
2'-Fluoro-N6-Bz-deoxyadenosine
2' -OMe-2-Amino-adenosine
2'O-methyl-N6-Bz-deoxyadenosine
2'-alpha-ethynyladenosine
2-aminoadenine
2-Aminoadenosine
2-Amino-adenosine
2' -alpha-Trifluoromethyladenosine
2-Azidoadenosine
2' -beta-Ethynyladenosine
2-Bromoadenosine

Modification
2’-beta-Trifluoromethyladenosine
2-Chloroadenosine
2’ -Deoxy-2’,2’-difluoroadenosine
2’ -Deoxy-2’-alpha-mercaptoadenosine
2’ -Deoxy-2’-alpha-thiomethoxyadenosine
2’ -Deoxy-2’-beta-aminoadenosine
2’ -Deoxy-2’-beta-azidoadenosine
2’ -Deoxy-2’-beta-bromoadenosine
2’ -Deoxy-2’-beta-chloroadenosine
2’ -Deoxy-2’-beta-fluoroadenosine
2’ -Deoxy-2’-beta-iodoadenosine
2’ -Deoxy-2’-beta-mercaptoadenosine
2’ -Deoxy-2’-beta-thiomethoxyadenosine
2-Fluoroadenosine
2-Iodoadenosine
2-Mercaptoadenosine
2-methoxy-adenine
2-methylthio-adenine
2-Trifluoromethyladenosine
3-Deaza-3-bromoadenosine
3-Deaza-3-chloroadenosine
3-Deaza-3-fluoroadenosine
3-Deaza-3-iodoadenosine
3-Deazaadenosine
4’ -Azidoadenosine
4’-Carbocyclic adenosine
4’ -Ethynyladenosine
5’-Homo-adenosine
8-Aza-adenosine
8-bromo-adenosine

Modification
8-Trifluoromethyladenosine
9-Deazaadenosine
2-aminopurine
7-deaza-2,6-diaminopurine
7-deaza-8-aza-2,6-diaminopurine
7-deaza-8-aza-2-aminopurine
2,6-diaminopurine
7-deaza-8-aza-adenine, 7-deaza-2-aminopurine
4-methylcytidine
5-aza-cytidine
Pseudo-iso-cytidine
pyrrolo-cytidine
alpha-thio-cytidine
2-(thio)cytosine
2’ -Amino-2’ -deoxy-cytosine
2’ -Azido-2’-deoxy-cytosine
2’ -Deoxy-2’-alpha-aminocytidine
2’ -Deoxy-2’-alpha-azidocytidine
3 (deaza) 5 (aza)cytosine
3 (methyl)cytosine
3-(alkyl)cytosine
3-(deaza) 5 (aza)cytosine
3-(methyl)cytidine
4,2’-O-dimethylcytidine
5 (halo)cytosine
5 (methyl)cytosine
5 (propynyl)cytosine
5 (trifluoromethyl)cytosine
5-(alkyl)cytosine
5-(alkynyl)cytosine

Modification
5-(halo)cytosine
5-(propynyl)cytosine
5-(trifluoromethyl)cytosine
5-bromo-cytidine
5-iodo-cytidine
5-propynyl cytosine
6-(azo)cytosine
6-aza-cytidine
aza cytosine
deaza cytosine
N4 (acetyl)cytosine
l-methyl-1-deaza-pseudoisocytidine
1-methyl-pseudoisocytidine
2-methoxy-5-methyl-cytidine
2-methoxy-cytidine
2-thio-5-methyl-cytidine
4-methoxy-1-methyl-pseudoisocytidine
4-methoxy-pseudoisocytidine
4-thio- l-methyl-1-deaza-pseudoisocytidine
4-thio-1-methyl-pseudoisocytidine
4-thio-pseudoisocytidine
5-aza-zebularine
5-methyl-zebularine
pyrrolo-pseudoisocytidine
zebularine
(E)-5-(2-Bromo-vinyl)cytidine
2,2'-anhydro-cytidine
2'-Fluor-N4-Bz-cytidine
2'-Fluoro-N4-Acetyl-cytidine
2'-O-Methyl-N4-Acetyl-cytidine

Modification
2'-O-methyl-N4-Bz-cytidine
2' -a-Ethynylcytidine
2' -a-Trifluoromethylcytidine
2' -b-Ethynylcytidine
2'-b-Trifluoromethylcytidine
2' -Deoxy-2',2'-difluorocytidine
2' -Deoxy-2'-alpha-mercaptocytidine
2' -Deoxy-2'-alpha-thiomethoxycytidine
2' -Deoxy-2'-betab-aminocytidine
2' -Deoxy-2'-beta-azidocytidine
2' -Deoxy-2'-beta-bromocytidine
2' -Deoxy-2'-beta-chlorocytidine
2' -Deoxy-2'-beta-fluorocytidine
2' -Deoxy-2'-beta-iodocytidine
2' -Deoxy-2'-beta-mercaptocytidine
2' -Deoxy-2'-beta-thiomethoxycytidine TP
2' -O-Methyl-5-(1-propynyl)cytidine
3'-Ethynylcytidine
4'-Azidocytidine
4'-Carbocyclic cytidine
4' -Ethynylcytidine
5-(1-Propynyl)ara-cytidine
5-(2-Chloro-phenyl)-2-thiocytidine
5-(4-Amino-phenyl)-2-thiocytidine
5-Aminoallyl-cytosine
5-Cyanocytidine
5-Ethynylara-cytidine
5-Ethynylcytidine
5'-Homo-cytidine
5-Methoxycytidine

Modification
5-Trifluoromethyl-Cytidine
N4-Amino-cytidine
N4-Benzoyl-cytidine
pseudoisocytidine
6-thio-guanosine
7-deaza-guanosine
8-oxo-guanosine
Nl-methyl-guanosine
alpha-thio-guanosine
2-(propyl)guanine
2-(alky1)guanine
2'-Amino-2' -deoxy-guanosine
2'-Azido-2'-deoxy-guanosine
2'-Deoxy-2'-alpha-aminoguanosine
2'-Deoxy-2'-alpha-azidoguanosine
6-(methyl)guanine
6-(alky1)guanine
6-(methyl)guanine
6-methyl-guanosine
7-(alkyl)guanine
7-(deaza)guanine
7-(methyl)guanine
7-(alkyl)guanine
7-(deaza)guanine
7-(methyl)guanine
8-(alkyl)guanine
8-(alkynyl)guanine
8-(halo)guanine
8-(thioalkyl)guanine
8-(alkenyl)guanine
8-(alkyl)guanine

Modification
8-(alkynyl)guanine
8-(amino)guanine
8-(halo)guanine
8-(hydroxyl)guanine
8-(thioalkyl)guanine
8-(thiol)guanine
azaguanine
deaza guanine
N (methyl)guanine
N-(methyl)guanine
l-methyl-6-thio-guanosine
6-methoxy-guanosine
6-thio-7-deaza-8-aza-guanosine
6-thio-7-deaza-guanosine
6-thio-7-methyl-guanosine
7-deaza-8-aza-guanosine
7-methyl-8-oxo-guanosine
N2,N2-dimethyl-6-thio-guanosine
N2-methyl-6-thio-guanosine
1-Me-guanosine
2'Fluoro-N2-isobutyl-guanosine
2'O-methyl-N2-isobutyl-guanosine
2' -alpha-Ethynylguanosine
2' -alpha-Trifluoromethylguanosine
2' -beta-Ethynylguanosine
2'-beta-Trifluoromethylguanosine
2' -Deoxy-2',2'-difluoroguanosine
2' -Deoxy-2'-alpha-mercaptoguanosine
2' -Deoxy-2'-alpha-thiomethoxyguanosine
2' -Deoxy-2'-beta-aminoguanosine

Modification
2’ -Deoxy-2’-beta-azidoguanosine
2’ -Deoxy-2’-beta-bromoguanosine
2’ -Deoxy-2’-beta-chloroguanosine
2’ -Deoxy-2’-beta-fluoroguanosine
2’ -Deoxy-2’-beta-iodoguanosine
2’ -Deoxy-2’-beta-mercaptoguanosine
2’-Deoxy-2’-beta-thiomethoxyguanosine
4’-Azidoguanosine
4’-Carbocyclic guanosine
4’ -Ethynylguanosine
5’-Homo-guanosine
8-bromo-guanosine
9-Deazaguanosine
N2-isobutyl-guanosine
7-methylinosine
allyamino- thymidine
aza thymidine
deaza thymidine
deoxy-thymidine
5-propynyl uracil
alpha-thio-uridine
1-(aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-pseudouracil
1-(aminocarbonylethylenyl)-2(thio)-pseudouracil
1-(aminocarbonylethylenyl)-2,4-(dithio)pseudouracil
1-(aminocarbonylethylenyl)-4 (thio)pseudouracil

Modification
1-(aminocarbonylethylenyl)-pseudouracil
1-substituted 2-(thio)-pseudouracil
1-substituted 2,4-(dithio)pseudouracil
1-substituted 4 (thio)pseudouracil
1-substituted pseudouracil
1-(aminoalkylamino-carbonylethylenyl)-2- (thio)-pseudouracil
l-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine
l-Methyl-3-(3-amino-3-carboxyproovl)pseudo-Uradine
1-Methyl-pseudo-UTP
2 (thio)pseudouracil
2’ deoxy uridine
2’ fluorouridine
2-(thio)uracil
2,4-(dithio)psuedouracil
2’-methyl, 2’-amino, 2’azido, 2’fluro-guanosine
2’-Amino-2’-deoxy-uridine
2’-Azido-2’-deoxy-uridine
2’ -Azido-deoxyuridine
2’-O-methylpseudouridine
2’ deoxyuridine
2’ fluorouridine
2’ -Deoxy-2’-alpha-aminouridine TP
2’ -Deoxy-2’-alpha-azidouridine TP
2-methylpseudouridine
3-(3 amino-3-carboxypropyl)uracil
4-(thio)pseudouracil
4-(thio)pseudouracil
4-(thio)uracil
4-thiouracil

Modification
5-(l ,3-diazole-1-alkyl)uracil
5-(2-aminopropyl)uracil
5-(aminoalkyl)uracil
5-(dimethylaminoalkyl)uracil
5-(guanidiniumalkyl)uracil
5-(methoxycarbonylmethyl)-2-(thio)uracil
5-(methoxycarbonyl-methyl)uracil
5-(methyl)-2-(thio)uracil
5-(methyl)-2,4-(dithio)uracil
5 (methyl) 4 (thio)uracil
5 (methylaminomethyl)-2 (thio)uracil
5 (methylaminomethyl)-2,4 (dithio)uracil
5 (methylaminomethyl)-4 (thio)uracil
5 (propynyl)uracil
5 (trifluoromethyl)uracil
5-(2-aminopropyl)uracil
5-(alky1)-2-(thio)pseudouracil
5-(alkyl)-2,4 (dithio)pseudouracil
5-(alky1)-4 (thio)pseudouracil
5-(alkyl)pseudouracil
5-(alkyl)uracil
5-(alkynyl)uracil
5-(allylamino)uracil
5-(cyanoalkyl)uracil
5-(dialkylaminoalkyl)uracil
5-(dimethylaminoalkyl)uracil
5-(guanidiniumalkyl)uracil
5-(halo)uracil
5-(1,3-diazole-l-alkyl)uracil
5-(methoxy)uracil

Modification
5-(methoxycarbonylmethyl)-2-(thio)uracil
5-(methoxycarbonyl-methyl)uracil
5-(methyl) 2(thio)uracil
5-(methyl) 2,4 (dithio)uracil
5-(methyl) 4 (thio)uracil
5-(methyl)-2-(thio)pseudouracil
5-(methyl)-2,4 (dithio)pseudouracil
5-(methyl)-4 (thio)pseudouracil
5-(methyl)pseudouracil
5-(methylaminomethyl)-2 (thio)uracil
5-(methylaminomethyl)-2,4(dithio)uracil
5-(methylaminomethyl)-4-(thio)uracil
5-(propyny1)uracil
5-(trifluoromethyl)uracil
5-aminoallyl-uridine
5-bromo-uridine
5-iodo-uridine
5-uracil
6 (azo)uracil
6-(azo)uracil
6-aza-uridine
allyamino-uracil
aza uracil
deaza uracil
N3 (methyl)uracil
Pseudo-uridine-1-2-ethanoic acid
pseudouracil
4-Thio-pseudouridine
1-carboxymethyl-pseudouridine
l-methyl-1-deaza-pseudouridine

Modification
1-propynyl-uridine
l-taurinomethyl-1-methyl-uridine
l-taurinomethyl-4-thio-uridine
1-taurinomethyl-pseudouridine
2-methoxy-4-thio-pseudouridine
2-thio- l-methyl-1-deaza-pseudouridine
2-thio-1-methyl-pseudouridine
2-thio-5-aza-uridine
2-thio-dihydropseudouridine
2-thio-dihydrouridine
2-thio-pseudouridine
4-methoxy-2-thio-pseudouridine
4-methoxy-pseudouridine
4-thio-1-methyl-pseudouridine
4-thio-pseudouridine
5-aza-uridine
dihydropseudouridine
(±)1-(2-Hydroxypropyl)pseudouridine
(2R)- l -(2-Hydroxypropyl)pseudouridine
(2S)- l -(2-Hydroxypropyl)pseudouridine
(E)-5-(2-Bromo-vinyl)ara-uridine
(E)-5-(2-Bromo-vinyl)uridine
(Z)-5-(2-Bromo-vinyl)ara-uridine
(Z)-5-(2-Bromo-vinyl)uridine
1-(2,2,2-Trifluoroethyl)-pseudouridine
1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine
1-(2,2-Diethoxyethy l)pseudouridine
1-(2,4,6-Trimethylbenzyl)pseudouridine
1-(2,4,6-Trimethyl-benzyl)pseudo-uridine
1-(2,4,6-Trimethyl-phenyl)pseudo-uridine

Modification
1-(2-Amino-2-carboxyethyl)pseudo-uridine
1-(2-Amino-ethyl)pseudouridine
1-(2-Hydroxyethyl)pseudouridine
1-(2-Methoxyethyl)pseudouridine
1-(3,4-Bis-trifluoromethoxvbenzvl)pseudouridine
1-(3,4-Dimethoxybenzyl)pseudouridine
1-(3-Amino-3-carboxypropyl)pseudo-uridine
1-(3-Amino-propyl)pseudouridine
1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP
1-(4-Amino-4-carboxybutyl)pseudouridine
1-(4-Amino-benzyl)pseudouridine
1-(4-Amino-buty l)pseudouridine
1-(4-Amino-phenyl)pseudouridine
1-(4-Azidobenzyl)pseudouridine
1-(4-Bromobenzyl)pseudouridine
1-(4-Chlorobenzyl)pseudouridine
1-(4-Fluorobenzyl)pseudouridin
1-(4-Iodobenzyl)pseudouridine
1-(4-Methanesulfonvlbenzvl)pseudouridine
1-(4-Methoxybenzy l)pseudouridine
1-(4-Methoxy-benzyl)pseudouridine
1-(4-Methoxy-phenyl)pseudouridine
1-(4-Methylbenzyl)pseudouridine
1-(4-Methyl-benzyl)pseudouridine
1-(4-Nitrobenzyl)pseudouridine
1-(4-Nitro-benzy!)pseudouridine
1(4-Nitro-phenyl)pseudouridine
1-(4-Thiomethoxybenzyl)pseudouridine
1-(4-

Modification
Trifluoromethoxybenzvl)pseudouridine
1-(4-Trifluoromethylbenzyl)pseudouridine
1-(5-Amino-pentyl)pseudouridine
1-(6-Amino-hexyl)pseudouridine
1,6-Dimethyl-pseudouridine
l-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine
1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionvl } pseudouridine
1-Acetylpseudouridine
l-Alkyl-6-(1-propynyl)-pseudo-uridine
l-Alkyl-6-(2-propynyl)-pseudo-uridine
l-Alkyl-6-allyl-pseudo-uridine
l-Alkyl-6-ethynyl-pseudo-uridine
l -Alkyl-6-homoallyl-pseudo-uridine
l-Alkyl-6-vinyl-pseudo-uridine
1-Allylpseudouridine
1-Aminomethyl-pseudo-uridine
1-Benzoylpseudouridine
1-Benzyloxymethylpseudouridine
1-Benzyl-pseudo-uridine
l-Biotinyl-PEG2-pseudouridine
1-Biotinylpseudouridine
1-Butyl-pseudo-uridine
1-Cyanomethylpseudouridine
1-Cyclobutylmethyl-pseudo-uridine
1-Cyclobutyl-pseudo-uridine
1-Cycloheptylmethyl-pseudo-uridine
1-Cycloheptyl-pseudo-uridine
1-Cyclohexylmethyl-pseudo-uridine
1-Cyclohexyl-pseudo-uridine
1-Cyclooctylmethyl-pseudo-uridine

Modification
1-Cyclooctyl-pseudo-uridine
1-Cyclopentylmethyl-pseudo-uridine
1-Cyclopentyl-pseudo-uridine
1-Cyclopropylmethyl-pseudo-uridine
1-Cyclopropyl-pseudo-uridine
1-Ethyl-pseudo-uridine
1-Hexyl-pseudo-uridine
1-Homoallylpseudouridine
1-Hydroxymethylpseudouridine
1-iso-propyl-pseudo-uridine
1-Me-2-thio-pseudo-uridine
1-Me-4-thio-pseudo-uridine
1-Me-alpha-thio-pseudo-uridine
1-Methanesulfonylmethylpseudouridine
1-Methoxymethylpseudouridine uridine
l -Methyl-6-(2,2,2-Trifluoroethyl)pseudo-uridine
l-Methyl-6-(4-morpholino)-pseudo-uridine
l -Methyl-6-(4-thiomorpholino)-pseudo-uridine
l-Methyl-6-(substituted phenyl)pseudo-uridine
1-Methyl-6-amino-pseudo-uridine
l -Methyl-6-azido-pseudo-uridine
1-Methyl-6-bromo-pseudo-uridine
l-Methyl-6-butyl-pseudo-uridine
l -Methyl-6-chloro-pseudo-uridine
1-Methyl-6-cyano-pseudo-uridine
l -Methyl-6-dimethylamino-pseudo-uridine
l -Methyl-6-ethoxy-pseudo-uridine
l -Methyl-6-ethylcarboxylate-pseudo-uridine
l-Methyl-6-ethyl-pseudo-uridine

Modification
l -Methyl-6-fluoro-pseudo-uridine
l-Methyl-6-formyl-pseudo-uridine
1-Methyl-6-hydroxyamino-pseudo-uridine
l -Methyl-6-hydroxy-pseudo-uridine
l -Methyl-6-iodo-pseudo-uridine
l-Methyl-6-iso-propyl-pseudo-uridine
l-Methyl-6-methoxy-pseudo-uridine
l -Methyl-6-methylamino-pseudo-uridine
l-Methyl-6-phenyl-pseudo-uridine
l-Methyl-6-propyl-pseudo-uridine
l-Methyl-6-tert-butyl-pseudo-uridine
1-Methyl-6-trifluoromethoxy-pseudo-uridine
l-Methyl-6-trifluoromethyl-pseudo-uridine
1-Morpholinomethylpseudouridine
1-Pentyl-pseudo-uridineuridine
1-Phenyl-pseudo-uridine
1-Pivaloylpseudouridine
1-Propargylpseudouridine
1-Propyl-pseudo-uridine
1-propynyl-pseudouridine
1-p-tolyl-pseudo-uridine
1-tert-Butyl-pseudo-uridine
1-Thiomethoxymethylpseudouridine
1-Thiomorpholinomethylpseudouridine
1-Trifluoroacetylpseudouridine
1-Trifluoromethyl-pseudouridine
1-Vinylpseudouridine
2,2'-anhydro-uridine
2' -bromo-deoxyuridine
2' -F-5-Methyl-2'-deoxy-uridine

Modification
2' -OMe-5-Me-uridine
2' -OMe-pseudouridine
2' -alpha-Ethynyluridine
2' -alpha-Trifluoromethyluridine
2' -beta-Ethynyluridine
2' -beta-Trifluoromethyluridiner
2' -Deoxy-2',2'-difluorouridine
2' -Deoxy-2'-a-mercaptouridin
2' -Deoxy-2'-alpha-thiomethoxyuridine
2' -Deoxy-2'-beta-aminouridine
2' -Deoxy-2'-beta-azidouridine
2' -Deoxy-2'-beta-bromouridine
2' -Deoxy-2'-beta-chlorouridine
2' -Deoxy-2'-beta-fluorouridine
2' -Deoxy-2'-beta-iodouridine
2' -Deoxy-2'-beta-mercaptouridine
2' -Deoxy-2'-beta-thiomethoxyuridine
2-methoxy-4-thio-uridine
2-methoxyuridine
2' -O-Methyl-5-(1-propynyl)uridine
3-Alkyl-pseudo-uridine
4' -Azidouridine
4'-Carbocyclic uridine
4' -Ethynyluridine
5-(1-Propynyl)ara-uridine
5-(2-Furanyl)uridine
5-Cyanouridine
5-Dimethylaminouridine
5'-Homo-uridine
5-iodo-2'-fluoro-deoxyuridine
5-Phenylethynyluridine

Modification
5-Trideuteromethyl-6-deuterouridine
5-Trifluoromethyl-Uridine
5-Vinylarauridine
6-(2,2,2-Trifluoroethyl)-pseudo-uridine
6-(4-Morpholino)-pseudo-uridine
6-(4-Thiomorpholino)-pseudo-uridine
6-(Substituted-Phenyl)-pseudo-uridine
6-Amino-pseudo-uridine
6-Azido-pseudo-uridine
6-Bromo-pseudo-uridine
6-Butyl-pseudo-uridine
6-Chloro-pseudo-uridine
6-Cyano-pseudo-uridine
6-Dimethylamino-pseudo-uridine
6-Ethoxy-pseudo-uridine
6-Ethylcarboxylate-pseudo-uridine
6-Ethyl-pseudo-uridine
6-Fluoro-pseudo-uridine
6-Formyl-pseudo-uridine
6-Hydroxyamino-pseudo-uridine
6-Hydroxy-pseudo-uridine
6-Iodo-pseudo-uridine
6-iso-Propyl-pseudo-uridine
6-Methoxy-pseudo-uridine
6-Methylamino-pseudo-uridine
6-Methyl-pseudo-uridine
6-Phenyl-pseudo-uridine

Modification
6-Phenyl-pseudo-uridine
6-Propyl-pseudo-uridine
6-tert-Butyl-pseudo- uridine
6-Trifluoromethoxy-pseudo-uridine
6-Trifluoromethyl-pseudo-uridine
alpha-thio-pseudo-uridine
Pseudouridine 1-(4-methylbenzenesulfonic acid)
Pseudouridine 1-(4-methylbenzoic acid) TP
Pseudouridine l-[3-(2-ethoxy)]propionic acid
Pseudouridine l-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine l-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine l-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxv}]propionic acid
Pseudouridine l-[3-{2-(2-ethoxy)-ethoxv}] propionic acid
Pseudouridine 1-methylphosphonic acid
Pseudouridine TP 1-methylphosphonic acid diethyl ester
Pseudo-uridine-N1-3-propionic acid
Pseudo-uridine-N1-4-butanoic acid
Pseudo-uridine-N 1-5-pentanoic acid
Pseudo-uridine-N1-6-hexanoic acid
Pseudo-uridine-Nl-7-heptanoic acid
Pseudo-uridine-N1-methy1-p-benzoic acid
Pseudo-uridine-N1-p-benzoic acid

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a modification provided in Table 6, or a combination thereof. The modifications provided in Table 6 occur naturally in RNAs, and are used herein on a synthetic TREM, a TREM core fragment or a TREM fragment at a position that does not occur in nature.

Table 6: Additional exemplary modifications

Modification
2-methylthio-N6-(cis-hydroxvisopentenvl)adenosine
2-methylthio-N6-methyladenosine
2-methylthio-N6-threonyl carbamoyladenosine
N6-glycinylcarbamoyladenosine
N6-isopentenyladenosine
N6-methyladenosine
N6-threonylcarbamoyladenosine
1,2'-O-dimethyladenosine
1-methyladenosine
2'-O-methyladenosine
2'-O-ribosyladenosine (phosphate)
2-methyladenosine
2-methylthio-N6 isopentenyladenosine
2-methylthio-N6-hydroxynorvalyl carbamoyladenosine
2' -O-methyladenosine
2' -O-ribosyladenosine (phosphate)
isopenteny ladenosine
N6-(cis-hydroxyisopentenyl)adenosine
N6,2'-O-dimethyladenosine
N6,2'-O-dimethyladenosine
N6,N6,2'-O-trimethyladenosine
N6,N6-dimethyladenosine
N6-acetyladenosine
N6-hydroxynorvalylcarbamoyladenosine
N6-methyl-N6-threonylcarbamoyladenosine
2-methyladenosine
2-methylthio-N^6-isopentenyladenosine

Modification
2-thiocytidine
3-methylcytidine
5-formylcytidine
5-hydroxymethylcytidine
5-methylcytidine
N4-acetylcytidine
2'-O-methylcytidine
2' -O-methylcytidine
5,2'-O-dimethylcytidine
5-formyl-2'-O-methylcytidine
lysidine
N4,2'-O-dimethy lcytidine
N4-acetyl-2'-O-methylcytidine
N4-methylcytidine
N4,N4-Dimethyl-2'-OMe-Cytidine
7-methylguanosine
N2,2'-O-dimethylguanosine
N2-methylguanosine
wyosme
1,2'-O-dimethylguanosine
1-methylguanosine
2'-O-methylguanosine
2'-O-ribosylguanosine (phosphate)
2' -O-methylguanosine
2'-O-ribosylguanosine (phosphate)

Modification
7-aminomethyl-7-deazaguanosine
7-cyano-7-deazaguanosine
archaeosine
methylwyosine
N2,7-dimethylguanosine
N2,N2,2'-O-trimethylguanosine
N2,N2,7-trimethylguanosine
N2,N2-dimethylguanosine
N2, 7,2 '-O-trimethylguanosine
1-methylinosine
mosme
1,2'-O-dimethylinosine
2'-O-methylinosine
2' -O-methylinosine
epoxyqueuosine
galactosyl-queuosine
mannosyl-queuosine
2' -O-methyluridine
2-thiouridine
3-methyluridine
5-carboxymethyluridine
5-hydroxyuridine
5-methyluridine
5-taurinomethyl-2-thiouridine
5-taurinomethyluridine
dihydrouridine
pseudouridine
(3-(3-amino-3-carboxypropyl)uridine
l-methyl-3-(3-amino-5-carboxypropyl)pseudouridine
1-methylpseduouridine

Modification
1-methyl-pseudouridine
2'-O-methyluridine
2'-O-methylpseudouridine
2' -O-methyluridine
2-thio-2'-O-methyluridine
3-(3-amino-3-carboxypropyl)uridine
3,2'-0-dimethyluridine
3-Methyl-pseudo-Uridine
4-thiouridine
5-(carboxyhydroxymethyl)uridine
5-(carboxyhydroxymethyl)uridine methyl ester
5,2'-O-dimethyluridine
5,6-dihydro-uridine
5-aminomethy1-2-thiouridine
5-carbamoylmethyl-2'-0-methyluridine
5-carbamoylmethyluridine
5-carboxyhydroxymethyluridine
5-carboxyhydroxymethyluridine methyl ester
5-carboxymethylaminomethyl-2'-O-methyluridine
5-carboxymethylaminomethyl-2-thiouridine
5-carboxymethylaminomethyl-2-thiouridine
5-carboxymethylaminomethyluridine
5-carboxymethylaminomethyluridine
5-Carbamoylmethyluridine
5-methoxycarbonylmethyl-2'-O-methyluridine
5-methoxycarbonylmethy1-2-thiouridine
5-methoxycarbonylmethyluridine
5-methoxyuridine

Modification
5-methyl-2-thiouridine
5-methylaminomethyl-2-selenouridine
5-methylaminomethyl-2-thiouridine
5-methylaminomethyluridine
5-Methyldihydrouridine
5-Oxyacetic acid- Uridine
5-Oxyacetic acid-methyl ester-Uridin Nl-methyl-pseudo-uridine
uridine 5-oxyacetic acid
uridine 5-oxyacetic acid methyl ester
3-(3-Amino-3-carboxypropyl)-Uridine

Modification
5-(iso-Pentenylaminomethyl)- 2-thiouridine
5-(iso-Pentenylaminomethyl)-2 '-O-methyluridine
5-(iso-Pentenylaminomethyl)uridine
wybutosine
hydroxywybutosine
isowyosme
peroxywybutosine
undermodified hydroxywybutosine
4-demethylwyosine
altriol

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 7, or a combination thereof.

Table 7: Additional exemplary non-naturally occurring modifications

Modification
2,6-(diamino)purine
1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
1,3-(diaza)-2-(oxo)-phenthiazin-1-yl
1,3-(diaza)-2-(oxo)-phenoxazin-1-yl
1,3,5-(triaza)-2,6-(dioxa)-naphthalene
2 (amino)purine
2,4,5-(trimethyl)phenyl
2' methyl, 2'amino, 2'azido, 2'fluro-cytidine
2' methyl, 2'amino, 2'azido, 2'fluro-adenine
2'methyl, 2'amino, 2'azido, 2'fluro-uridine
2' -amino-2' -deoxyribose
2-amino-6-Chloro-purine
2-aza-inosinyl
2' -azido-2'-deoxyribose
2'fluoro-2 '-deoxyribose

Modification
2' -fluoro-modified bases
2' -O-methyl-ribose
2-oxo-7-aminopyridopyrimidin-3-yl
2-oxo-pyridopyrimidine-3-yl
2-pyridinone
3 nitropyrrole
3-(methyl)-7-(propynyl)isocarbostyrilyl
3-(methyl)isocarbostyrilyl
4-(fluoro)-6-(methyl)benzimidazole
4-(methyl)benzimidazole
4-(methyl)indolyl
4,6-(dimethyl)indolyl
5 nitroindole
5 substituted pyrimidines
5-(methyl)isocarbostyrilyl
5-nitroindole
6-(aza)pyrimidine

Modification
6-(azo)thymine
6-(methyl)-7-(aza)indolyl
6-chloro-purine
6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenthiazin-1-yl
7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin- 1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-l- yl
7-(aza)indolyl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenoxazinl-yl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenoxazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)- phenoxazin-1-yl
7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)- phenoxazin-1-yl
7-(propynyl)isocarbostyrilyl
7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl
7-deaza-inosinyl
7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl
9-(methyl)-imidizopyridinyl
aminoindolyl
anthracenyl
bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo- nvrimidin-2-on-3-yl

Modification
bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
difluorotolyl
hypoxanthine
imidizopyridinyl
inosinyl
isocarbostyrilyl
isoguanosine
N2-substituted purines
N6-methyl-2-amino-purine
N6-substituted purines
N-alkylated derivative
napthalenyl
nitrobenzimidazolyl
nitroimidazolyl
nitroindazolyl
nitropyrazolyl
nubularine
O6-substituted purines
O-alkylated derivative
ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2- on-3-yl
ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
Oxoformycin TP
para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2- on-3-yl
para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
pentacenyl
phenanthracenyl
phenyl
propynyl-7-(aza)indolyl
pyrenyl
pyridopyrimidin-3-yl
pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3- yl
pyrrolo-pyrimidin-2-on-3-yl
pyrrolopyrimidinyl
pyrrolopyrizinyl

Modification
stilbenzyl
substituted 1,2,4-triazoles
tetracenyl
tubercidine
xanthine
Xanthosine
2-thio-zebularine
5-aza-2-thio-zebularine
7-deaza-2-amino-purine
pyridin-4-one ribonucleoside
2-Amino-riboside

Modification
Formycin A
Formycin B
Pyrrolosine
2’ -OH-ara-adenosine
2’ -OH-ara-cytidine
2’ -OH-ara-uridine
2’ -OH-ara-guanosine
5-(2-carbomethoxyvinyl)uridine
N6-(19-Amino-pentaoxanonadecyl)adenosine

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 8, or a combination thereof.

Table 8: Exemplary backbone modifications

Modification
3’-alkylene phosphonates
3’-amino phosphoramidate
alkene containing backbones
aminoalkylphosphoramidates
aminoalkylphosphotriesters
boranophosphates
-CH2-0-N(CH3)-CH2-
-CH2-N(CH3)-N(CH3)-CH2-
-CH2-NH-CH2-
chiral phosphonates
chiral phosphorothioates
formacetyl and thioformacetyl backbones
methylene (methylimino)
methylene formacetyl and thioformacetyl backbones
methyleneimino and methylenehydrazino backbones
morpholino linkages
-N(CH3)-CH2-CH2-

Modification
oligonucleosides with heteroatom intenucleoside linkage
phosphinates
phosphoramidates
phosphorodithioates
phosphorothioate intenucleoside linkages
phosphorothioates
phosphotriesters
PNA
siloxane backbones
sulfamate backbones
sulfide sulfoxide and sulfone backbones
sulfonate and sulfonamide backbones
thionoalkylphosphonates
thionoalkylphosphotriesters
thionophosphoramidates
methylphosphonates
phosphonoacetates
Phosphorothioate

Modification
Constrained nucleic acid (CNA)
2'-O-methyl
2'-O-methoxyethyl (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'-phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl
(*E*)-vinylphosphonate
Methyl phosphonate
(*S*) 5'-C-methyl with phosphate
(R) 5'-C-methyl with phosphate
DNA
(R) 5'-C-methyl
GNA (glycol nucleic acid)
alkyl phosphonates
Phosphorothioate

Modification
Constrained nucleic acid (CNA)
2'-O-methyl
2'-O-methoxyethyl (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'-phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl
(*E*)-vinylphosphonate
Methyl phosphonate
(*S*) 5'-C-methyl with phosphate
(R) 5'-C-methyl with phosphate
DNA
(R) 5'-C-methyl
GNA (glycol nucleic acid)
alkyl phosphonates

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 9, or a combination thereof.

Table 9: Exemplary non-naturally occurring backbone modificiations

Name of synthetic backbone modifications
Phosphorothioate
Constrained nucleic acid (CNA)
2' O'methylation
2'-O-methoxyethylribose (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl

(*E*)-vinylphosphonate
Methyl phosphonate
(*S*) 5'-C-methyl with phosphate

Design Guidance

The present disclosure further describes representative design principles for installing a non-naturally occurring modification on a TREM, TREM core fragment, or TREM fragment. Without being bound by theory, these design principles may provide guidance for modulating a parameter of a TREM, TREM core fragment, or TREM fragment described herein. These design principles are also referred to herein as "Design Guidances". For example, a TREM comprising a non-naturally occurring modification pattern according to a Design Guidance may exhibit improved stability, e.g., in vitro or in a cell. Representative Design Guidances are described in greater detail below.

Design Guidance 1

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification.

(a) In an embodiment, the nucleotide having a non-naturally occurring modification is any one of nucleotide positions 1-6 or 66-76., e.g., (i) wherein the nucleotide position corresponds to 1-6 or 66-76 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 1-6 or 66-76 according to the CtNS.

(b) In an embodiment, one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a 2'-O-methoxy (2'O-Me) modification. In an embodiment, the nucleotide having the 2'OMe modification is any one of nucleotide positions 1-6, 65-70, and 74-76, e.g., (i) wherein the nucleotide position corresponds to 1-6, 65-70, and 74-76 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 1-6, 65-70, and 74-76 according to the CtNS.

(c) In an embodiment, one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a phosphorothiorate (PS) modification. In an embodiment, the PS modiciation is present on any one of nucleotide positions 1-6 or 65-76, e.g., (i) wherein the

nucleotide position corresponds to 1-6 or 65-76 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 1-6 or 65-76 according to the CtNS.

(d) In an embodiment, one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a 2'-O-methoxy (2'O-Me) modification and a nucleotide having a phosphorothiorate (PS) modification. In an embodiment, both the 2'-OMe and the PS modiciation are independently present on any one of nucleotide positions 1-6 or 65-76, e.g., (i) wherein the nucleotide position corresponds to 1-6 or 65-76 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 1-6 or 65-76 according to the CtNS.

(e) In an embodiment, one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a 2'-O-methoxy (2'O-Me) modification and a nucleotide having a phosphorothiorate (PS) modification, provided that none of nucleotides corresponding to positions 71-73 (e.g., corresponding to SEQ ID NO: 622 or the CtNS) comprise a 2'-O-methoxy (2'O-Me) modification.

(f) In an embodiment, one of [L1], [ASt Domain1], [L4], and [ASt Domain2] comprises a nucleotide having a phosphorothiorate (PS) modification on one of positions 1-3 or 74-76 (e.g., corresponding to SEQ ID NO: 622 or the the CtNS).

Design Guidance 2

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and one of [DH Domain]-[L3] comprises a nucleotide having a non-naturally occurring modification.

(a) In an embodiment, the nucleotide having a non-naturally occurring modification is any one of nucleotide positions 10-13 or 22-25., e.g., (i) wherein the nucleotide position corresponds to 10-13 or 22-25 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 10-13 or 22-25 according to the CtNS.

(b) In an embodiment, one of [DH Domain]-[L3] comprises a nucleotide having a 2'-O-methoxy (2'O-Me) modification. In an embodiment, the nucleotide having the 2'OMe modification is any one of nucleotide positions 10-13 or 22-25., e.g., (i) wherein the nucleotide position corresponds to 10-13 or 22-25 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 10-13 or 22-25 according to the CtNS.

(c) In an embodiment, one of [DH Domain]-[L3] comprises a nucleotide that does not have a phosphorothioate (PS) modification. In an embodiment, the nucleotide that does not comprise the PS modification is any one of nucleotide positions 10-13 or 22-25., e.g., (i) wherein the nucleotide position corresponds to 10-13 or 22-25 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 10-13 or 22-25 according to the CtNS.

Design Guidance 3

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and the [ACH Domain] does not comprise a 2'-nucleotide sugar modification (e.g., 2'-ribose modification).

(a) In an embodiment, the [ACH Domain] comprises a nucleotide having an internucleotide modification. In an embodiment, the nucleotide having the internucleotide modification is present on any one of nucleotide positions 32-28, e.g., (i) wherein the nucleotide position corresponds to any one of 32-38 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of 32-38 according to the CtNS.

(b) In an embodiment, the [ACH Domain] comprises a nucleotide having a phosphorothioate (PS) modification. In an embodiment, the nucleotide having the PS modification is present on any one of nucleotide positions 32-28, e.g., (i) wherein the nucleotide position corresponds to any one of 32-38 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of 32-38 according to the CtNS.

(c) In an embodiment, the [ACH Domain] comprises a nucleotide that does not have a 2'-nucleotide sugar modification. In an embodiment, the [ACH Domain] comprises a nucleotide that does not have a 2'-O-methoxy (2'O-Me) modification.

(d) In an embodiment, the [ACH Domain] comprises a nucleotide having an internucleotide modification (e.g., a PS modification) and a nucleotide that does not have a 2'-nucleotide sugar modification (e.g., a 2'O-Me modification).

(e) In an embodiment, the [ACH Domain] comprises a nucleotide having a 2'-fluoro (2'F) modification. In an embodiment, the nucleotide having the 2'F modification is nucleotide position 33, e.g., (i) wherein the nucleotide position corresponds to 33 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 33 according to the CtNS.

(f) In an embodiment, the [ACH Domain] comprises a nucleotide having an (i) internucleotide modification (e.g., a PS modification); (ii) a nucleotide having a 2'F modification; and (iii) a nucleotide that does not have a 2'OMe modification. In an embodiment, the nucleotide having the 2'F modification is nucleotide position 33, e.g., (i) wherein the nucleotide position corresponds to 33 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 33 according to the CtNS.

(g) In an embodiment, the [ACH Domain] comprises a nucleotide having a phosphorothioate (PS) modification on the anticodon, e.g., at any one of positions 34-36, (i) wherein the nucleotide position corresponds to any one of 34-36 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of 34-36 according to the CtNS.

Design Guidance 4

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and the [VL Domain] comprises a nucleotide having a non-naturally occurring modification.

(a) In an embodiment, the [VL Domain] comprises a nucleotide having a 2'-nucleotide sugar modification., e.g., (i) wherein the nucleotide having the 2'-nucleotide sugar modification corresponds to any one of 44-48 of SEQ ID NO: 622 or (ii) wherein the nucleotide having the 2'-nucleotide sugar modification corresponds to any one of V1-V27 and 46-48 according to the CtNS.

(b) In an embodiment, the [VL Domain] comprises a nucleotide having a 2'-OMe modification. In an embodiment, the 2'OMe modification is present on any one of nucleotide positions within the [VL Domain]., e.g., (i) wherein the nucleotide position corresponds to any one of 44-48 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of V1-V27 and 46-48 according to the CtNS.

(b) In an embodiment, the [VL Domain] comprises a nucleotide having a 2'-F modification. In an embodiment, the F modification is present on any one of nucleotide positions within the [VL Domain]., e.g., (i) wherein the nucleotide position corresponds to any one of 44-48 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of V1-V27 and 46-48 according to the CtNS.

(d) In an embodiment, the [VL Domain] comprises a nucleotide that does not have an internucleotide modification. In an embodiment, the [VL Domain] comprises a nucleotide that does not have a PS modification, e.g., (i) wherein the nucleotide position corresponds to any one of 44-48 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to any one of V1-V27 and 46-48 according to the CtNS.

(e) In an embodiment, the [VL Domain] comprises (i) a nucleotide having a 2'-OMe modification; (ii) a nucleotide having a 2'-F modification; and (iii) a nucleotide that does not have an internucleotide modification (e.g., a PS modification). In an embodiment, the nucleotide having the 2'OMe modification, the nucleotide having the 2'F modification, and the nucleotide not having the internucleotide modification (e.g., the PS modification) are present on any one of nucleotide positions within the [VL Domain]., e.g., (i) wherein the nucleotide positions correspond to any one of 44-48 of SEQ ID NO: 622 or (ii) wherein the nucleotide positions correspond to any one of V1-V27 and 46-48 according to the CtNS.

Design Guidance 5

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and one of [TH Domain] comprises a nucleotide having a non-naturally occurring modification. In an embodiment, the nucleotide having a non-naturally occurring modification is present on any one of nucleotide positions 49-65., e.g., (i) wherein the nucleotide position corresponds to 49-65 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 49-65 according to the CtNS. In an embodiment, the [TH Domain] comprises a nucleotide having a 2'-nucleotide sugar modification. In an embodiment, the nucleotide having the 2'-nucleotide sugar modification is any one of nucleotide positions 49-65, e.g., (i) wherein the nucleotide position corresponds to 49-65 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 49-65 according to the CtNS.

(a) In an embodiment, the nucleotide having a non-naturally occurring modification is any one of nucleotide positions 49-53 and 61-65, e.g., (i) wherein the nucleotide position corresponds to 49-53 and 61-65of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 49-53 and 61-65 according to the CtNS.

(b) In an embodiment, the [TH Domain] comprises a nucleotide having a 2'-OMe modification. In an embodiment, the nucleotide having the 2'-OMe modification is any one of nucleotide positions 49-53, 61-62, and 64-65, e.g., (i) wherein the nucleotide position corresponds to 49-53, 61-62, and 64-65 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 49-53, 61-62, and 64-65 according to the CtNS.

(c) In an embodiment, the [TH Domain] comprises a nucleotide having a 2'-F modification. In an embodiment, the nucleotide having the 2'-F modification is nucleotide position 63, e.g., (i) wherein the nucleotide position corresponds to 63 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 63 according to the CtNS.

(d) In an embodiment, the [TH Domain] comprises a nucleotide that does not have an internucleotide modification (e.g., a PS modidfication). In an embodiment, the nucleotide not having an internucleotide modification (e.g., a PS modidfication) is any one of nucleotide positions 49-53 and 61-65, e.g., (i) wherein the nucleotide position corresponds to 49-53 and 61-65of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 49-53 and 61-65 according to the CtNS.

Design Guidance 6

In an embodiment, a TREM comprises a sequence of Formula (I): [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], wherein independently, [L1] and [VL Domain], are optional; and each of [DH Domain] and the [TH Domain] comprises a nucleotide having a non-naturally occurring modification.

(a) In an embodiment, the [DH Domain] comprises a nucleotide having a non-naturally occurring modification at any one of nucleotide positions 14-21 (e.g., 14-20, e.g., 16-18), e.g., (i) wherein the nucleotide position corresponds to 14-21 (e.g., 14-20, e.g., 16-18) of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 14-21 (e.g., 14-20, e.g., 16-18) according to the CtNS. In an embodiment, the non-naturally occurring modification is a 2'-nucleotide sugar modification (e.g., 2'-OMe).

(b) In an embodiment, the [TH Domain] comprises a nucleotide having a non-naturally occurring modification at any one of nucleotide positions 54-60, e.g., (i) wherein the nucleotide position corresponds to 54-60 of SEQ ID NO: 622 or (ii) wherein the nucleotide position

corresponds to 54-60 according to the CtNS. In an embodiment, the non-naturally occurring modification is a 2'-nucleotide sugar modification (e.g., 2'-F).

(c) In an embodiment, the [TH Domain] comprises a nucleotide having a 2'OMe at any one of nucleotide positions 54-60 (e.g., 54, 56, 57, or 59), e.g., (i) wherein the nucleotide position corresponds to 54-60 (e.g., 54, 56, 57, or 59), of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 54-60 (e.g., 54, 56, 57, or 59), according to the CtNS.

(d) In an embodiment, the [TH Domain] comprises a nucleotide having a 2'-F at any one of nucleotide positions 54-60 (e.g., 57, 58, or 60), e.g., (i) wherein the nucleotide position corresponds to 54-60 (e.g., 57, 58, or 60) of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 54-60 (e.g., 57, 58, or 60) according to the CtNS.

(e) In an embodiment, the TREM comprises a non-naturally occurring modification in both of the [DH Domain] and the [TH Domain], wherein (i) the [DH Domain] comprises a nucleotide having a non-naturally occurring modification at any one of nucleotide positions 14-21 (e.g., 14-20, e.g., 16-18), e.g., (i) wherein the nucleotide position corresponds to 14-21 (e.g., 14-20, e.g., 16-18) of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 14-21 (e.g., 14-20, e.g., 16-18) according to the CtNS (ii) the [TH Domain] comprises a nucleotide having a non-naturally occurring modification at any one of nucleotide positions 54-60, e.g., (i) wherein the nucleotide position corresponds to 54-60 of SEQ ID NO: 622 or (ii) wherein the nucleotide position corresponds to 54-60 according to the CtNS. In some embodiments, the non-naturally occurring modification is selected from a 2'OMe or 2'F modification.

Table 21 below summarizes a set of representative TREMs described herein correlated to the Design Guidances outlined above, e.g., Design Guidances 1-6.

Table 21: Exemplary TREMs described herein correlated to Design Guidances described herein

TREM NO.	**SEQ ID NO.**	**Design Guidance**					
		1	**2**	**3**	**4**	**5**	**6**
1	622						
2	623						
3	624						
5	626		c	c	d		
6	627		c	c	d		
7	629		c	c	d		
8	630		c	c	d		
10	631		c	c	d		

11	632		c	c	d		
12	633		c	c	d		a
13	634		c	c	d		
14	635		c	c	d		b
15	636	abe	abc	c	d		
16	637	abe	c	c	d		a
17	638	abe	c	c	d		a
18	639	abe	c	c	d		a
19	640	abe	c	c	d		
20	641	abe	c	c	abde	ab	
21	642	abe	c	c	d	ab	
22	643	abe	c	c	d	ab	
23	644	abe	c	c	d	ab	
24	645	abe	c	c	d		
25	646		abc	c	d		a
26	647		abc	c	d		a
27	648		abc	c	d		a
28	649		abc	c	d		
29	650	abe	c	c	d	ab	
30	651		abc	c	abde	ab	
31	652		abc	c	d	ab	
32	653		abc	c	d	ab	
33	654		abc	c	d	ab	
34	655		abc	c	d		
35	656		c	c	d		a
36	657		c	c	d		a
37	658		c	c	d		a
38	659		c	c	abde	ab	a
39	660		c	c	d	ab	a
40	661		c	c	d	ab	a
41	662		c	c	d	ab	a
42	663		c	c	d		a
43	664		c	c	d		a
44	665		c	c	d		a
45	666		c	c	abde	ab	a
46	667		c	c	d	ab	a
47	668	abe	c	c	d	ab	
48	669		c	c	d	ab	a
49	670		c	c	d	ab	a
50	671		c	c	d		a
51	672		c	c	d		a
52	673		c	c	abde	ab	a
53	674		c	c	d	ab	a
54	675		c	c	d	ab	a
55	676		c	c	d	ab	a

56	677		c	c	d		a
57	678		c	c	abde	ab	
58	679		c	c	d	ab	
59	680		c	c	d	ab	
60	681		c	c	d	ab	
61	682	abe	c	c	d	ab	a
63	684		c	c	d		
64	685		c	c	abde	ab	
65	686		c	c	abde	ab	
66	687		c	c	abde	ab	
67	688		c	c	abde	ab	
68	689		c	c	d	ab	
69	690		c	c	d	ab	
70	691		c	c	d	ab	
71	692		c	c	d	ab	
72	693		c	c	d	ab	
73	694		c	c	d	ab	
74	695		c	c	d		a
75	696		c	c	d		a
76	697		abc	c	d		
77	698		c	c	d	ab	
78	699	abe	c	c	d	ab	a
81	702		c	c	d		a
82	703		c	c	d		a
83	704		abc	c	d		
84	705		c	c	d	ab	
85	706		c	c	d		abce
86	707		c	c	d		abce
87	708		abc	c	d		bc
88	709		c	c	d	ab	bc
89	710	abe	c	c	d		
90	711	abe	c	c	d		
91	712	abe	c	c	d		
92	713		c	c	d		
93	714		c	c	d	ab	
94	715		c	c	d	ab	
95	716		c	c	d	ab	
96	717		c	c	d	ab	

TREM, TREM core fragment and TREM fragment fusions

In an embodiment, a TREM, a TREM core fragment or a TREM fragment disclosed herein comprises an additional moiety, *e.g.*, a fusion moiety. In an embodiment, the fusion

moiety can be used for purification, to alter folding of the TREM, TREM core fragment or TREM fragment, or as a targeting moiety. In an embodiment, the fusion moiety can comprise a tag, a linker, can be cleavable or can include a binding site for an enzyme. In an embodiment, the fusion moiety can be disposed at the N terminal of the TREM or at the C terminal of the TREM, TREM core fragment or TREM fragment. In an embodiment, the fusion moiety can be encoded by the same or different nucleic acid molecule that encodes the TREM, TREM core fragment or TREM fragment.

TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises a consensus sequence provided herein.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula I ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula I corresponds to all species.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula II ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula II corresponds to mammals.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula III ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula III corresponds to humans.

In an embodiment, ZZZ indicates any of the twenty amino acids: alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, methionine, leucine, lysine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

In an embodiment, a TREM disclosed herein comprises a property selected from the following:

a) under physiological conditions residue R_0 forms a linker region, *e.g.*, a Linker 1 region;

b) under physiological conditions residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} form a stem region, *e.g.*, an AStD stem region;

c) under physiological conditions residues R_8-R_9 forms a linker region, *e.g.*, a Linker 2 region;

d) under physiological conditions residues -R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} form a stem-loop region, *e.g.*, a D arm Region;

e) under physiological conditions residue -R_{29} forms a linker region, *e.g.*, a Linker 3 Region;

f) under physiological conditions residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} form a stem-loop region, *e.g.*, an AC arm region;

g) under physiological conditions residue -$[R_{47}]_x$ comprises a variable region, *e.g.*, as described herein;

h) under physiological conditions residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} form a stem-loop region, *e.g.*, a T arm Region; or

i) under physiological conditions residue R_{72} forms a linker region, *e.g.*, a Linker 4 region.

Alanine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ALA} (SEQ ID NO: 562),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}, wherein R is a ribonucleotide residue and the consensus for Ala is: R_0= absent; R_{14}, R_{57}=are independently A or absent; R_{26}= A, C, G or absent; R_5, R_6, R_{15}, R_{16}, R_{21}, R_{30}, R_{31}, R_{32}, R_{34}, R_{37}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{48}, R_{49}, R_{50}, R_{58}, R_{59}, R_{63}, R_{64}, R_{66}, R_{67}= are independently N or absent; R_{11}, R_{35}, R_{65}= are independently A, C, U or absent; R_1, R_9, R_{20}, R_{38}, R_{40}, R_{51}, R_{52}, R_{56}= are independently A, G or absent; R_7, R_{22}, R_{25}, R_{27}, R_{29}, R_{46}, R_{53}, R_{72}= are independently A, G, U or absent; R_{24}, R_{69}= are independently A, U or absent; R_{70}, R_{71}=are independently C or absent; R_3, R_4= are independently C, G or absent; R_{12}, R_{33}, R_{36}, R_{62}, R_{68}= are independently C, G, U or absent; R_{13}, R_{17}, R_{28}, R_{39}, R_{55}, R_{60}, R_{61}= are independently C, U or absent; R_{10}, R_{19}, R_{23}= are independently G or absent; R_2= G, U or absent; R_8, R_{18}, R_{54}= are independently U or absent; $[R_{47}]_x$ = N or absent; wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11,

x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II_{ALA} (SEQ ID NO: 563),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0, R_{18}= are absent;

R_{14}, R_{24}, R_{57}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}, R_{59}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_1, R_5, R_9, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}, R_{72}= are independently A, G, U or absent;

R_6, R_{35}, R_{69}= are independently A, U or absent;

R_{55}, R_{60}, R_{70}, R_{71}= are independently C or absent;

R_3= C, G or absent;

R_{12}, R_{36}, R_{48}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{61}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_4, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_2, R_8, R_{33}= are independently G, U or absent;

R_{21}, R_{54}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III_{ALA} (SEQ ID NO: 564),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0, R_{18}= are absent;

R_{14}, R_{24}, R_{57}, R_{72}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_5, R_9, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}= are independently A, G, U or absent;

R_6, R_{35}= are independently A, U or absent;

R_{55}, R_{60}, R_{61}, R_{70}, R_{71}= are independently C or absent;

R_{12}, R_{48}, R_{59}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_1, R_2, R_3, R_4, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_{33}, R_{36}= are independently G, U or absent;

R_8, R_{21}, R_{54}, R_{69}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Arginine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ARG} (SEQ ID NO: 565),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{57}=A or absent;

R_9,R_{27}=are independently A,C,G or absent;

R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_{11},R_{12},R_{16},R_{21},R_{22},R_{23},R_{25},R_{26},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{51},R_{58},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70},R_{71}=are independently N or absent;

R_{13},R_{17},R_{41}=are independently A,C,U or absent;

R_{19},R_{20},R_{24},R_{40},R_{56}=are independently A,G or absent;

R_{14},R_{15},R_{72}=are independently A,G,U or absent;

R_{18}= A,U or absent;

R_{38}= C or absent;

R_{35},R_{43},R_{61}=are independently C,G,U or absent;

R_{28},R_{55},R_{59},R_{60}=are independently C,U or absent;

R_0,R_{10},R_{52}=are independently G or absent;

R_8,R_{39}=are independently G,U or absent;

R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ARG}$ (SEQ ID NO: 566),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}= absent;

R_{24},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_3,R_7,R_{34},R_{50}=are independently A,C,G or absent;

R_2,R_5,R_6,R_{12},R_{26},R_{32},R_{37},R_{44},R_{58},R_{66},R_{67},R_{68},R_{70}=are independently N or absent;

R_{49},R_{71}=are independently A,C,U or absent;

R_1,R_{15},R_{19},R_{25},R_{27},R_{40},R_{45},R_{46},R_{56},R_{72}=are independently A,G or absent;

R_{14},R_{29},R_{63}=are independently A,G,U or absent;

R_{16},R_{21}=are independently A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_{33},R_{48}=are independently C,G or absent;

R_4,R_9,R_{11},R_{43},R_{62},R_{64},R_{69}=are independently C,G,U or absent;

R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{55},R_{60},R_{65}=are independently C,U or absent;

R_0,R_{10},R_{20},R_{23},R_{51},R_{52}=are independently G or absent;

R_8,R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ARG}$ (SEQ ID NO: 567),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}=is absent;

R_{15},R_{21},R_{24},R_{41},R_{57}=are independently A or absent;

R_{34},R_{44}=are independently A,C or absent;

R_3,R_5,R_{58}=are independently A,C,G or absent;

R_2,R_6,R_{66},R_{70}=are independently N or absent;

R_{37},R_{49}=are independently A,C,U or absent;

R_1,R_{25},R_{29},R_{40},R_{45},R_{46},R_{50}=are independently A,G or absent;

R_{14},R_{63},R_{68}=are independently A,G,U or absent;

R_{16}= A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_7,R_{11},R_{12},R_{26},R_{48}=are independently C,G or absent;

R_{64},R_{67},R_{69}=are independently C,G,U or absent;

R_4,R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{43},R_{55},R_{60},R_{62},R_{65},R_{71}=are independently C,U or absent;

R_0,R_{10},R_{19},R_{20},R_{23},R_{27},R_{33},R_{51},R_{52},R_{56},R_{72}=are independently G or absent;

R_8,R_9,R_{32},R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Asparagine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ASN} (SEQ ID NO: 568),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

R_0,R_{18}=are absent;

R_{41}= A or absent;

R_{14},R_{48},R_{56}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_{12},R_{17},R_{26},R_{29},R_{30},R_{31},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65},R_{66},R_{67},R_{68},R_{70},R_{71}= are independently N or absent;

R_{11},R_{13},R_{22},R_{42},R_{55},R_{59}=are independently A,C,U or absent;

R_9,R_{15},R_{24},R_{27},R_{34},R_{37},R_{51},R_{72}=are independently A,G or absent;

R_1,R_7,R_{25},R_{69}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_{60}= C or absent;

R_{33}= C,G or absent;

R_{21},R_{32},R_{43},R_{64}=are independently C,G,U or absent;

R_3,R_{16},R_{28},R_{35},R_{36},R_{61}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{52}=are independently G or absent;

R_{54}= G,U or absent;

R_8,R_{23},R_{38},R_{39},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ASN}$ (SEQ ID NO: 569),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

$R_{0,}R_{18}$=are absent

$R_{24},R_{41},R_{46},R_{62}$=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{17},R_{29}=are independently N or absent;

$R_{11},R_{26},R_{42},R_{55}$=are independently A,C,U or absent;

$R_1,R_9,R_{12},R_{15},R_{25},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70},R_{72}$=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_5,R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{21},R_{43},R_{71}=are independently C,G,U or absent;

$R_3,R_6,R_{13},R_{22},R_{32},R_{35},R_{36},R_{61},R_{63},R_{64}$=are independently C,U or absent;

$R_7,R_{10},R_{19},R_{20},R_{27},R_{49},R_{52}$=are independently G or absent;

R_{54}= G,U or absent;

$R_2,R_4,R_8,R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ASN}$ (SEQ ID NO: 570),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

$R_{0,}R_{18}$=are absent

R_{24},R_{40},R_{41},R_{46},R_{62}=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{11},R_{26},R_{42},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{12},R_{15},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70}=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{57}= A,U or absent;

R_5,R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{17},R_{21},R_{29}=are independently C,G,U or absent;

R_3,R_6,R_{13},R_{22},R_{32},R_{35},R_{36},R_{43},R_{61},R_{63},R_{64},R_{71}=are independently C,U or absent;

R_7,R_{10},R_{19},R_{20},R_{25},R_{27},R_{49},R_{52},R_{72}=are independently G or absent;

R_{54}= G,U or absent;

R_2,R_4,R_8,R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1,

x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Aspartate TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ASP} (SEQ ID NO: 571),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0=absent

R_{24},R_{71}=are independently A,C or absent;

R_{33},R_{46}=are independently A,C,G or absent;

R_2,R_3,R_4,R_5,R_6,R_{12},R_{16},R_{22},R_{26},R_{29},R_{31},R_{32},R_{44},R_{48},R_{49},R_{58},R_{63},R_{64},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{13},R_{21},R_{34},R_{41},R_{57},R_{65}=are independently A,C,U or absent;

R_9,R_{10},R_{14},R_{15},R_{20},R_{27},R_{37},R_{40},R_{51},R_{56},R_{72}=are independently A,G or absent;

R_7,R_{25},R_{42}=are independently A,G,U or absent;

R_{39}= C or absent;

R_{50},R_{62}=are independently C,G or absent;

R_{30},R_{43},R_{45},R_{55},R_{70}=are independently C,G,U or absent;

R_8,R_{11},R_{17},R_{18},R_{28},R_{35},R_{53},R_{59},R_{60},R_{61}=are independently C,U or absent;

R_{19},R_{52}=are independently G or absent;

R_1= G,U or absent;

R_{23},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ASP}$ (SEQ ID NO: 572),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

$R_{0,}R_{17,}R_{18,}R_{23}$=are independently absent;

R_9,R_{40}=are independently A or absent;

R_{24},R_{71}=are independently A,C or absent;

R_{67},R_{68}=are independently A,C,G or absent;

R_2,R_6,R_{66}=are independently N or absent;

R_{57},R_{63}=are independently A,C,U or absent;

R_{10},R_{14},R_{27},R_{33},R_{37},R_{44},R_{46},R_{51},R_{56},R_{64},R_{72}=are independently A,G or absent;

R_7,R_{12},R_{26},R_{65}=are independently A,U or absent;

R_{39},R_{61},R_{62}=are independently C or absent;

R_3,R_{31},R_{45},R_{70}=are independently C,G or absent;

R_4,R_5,R_{29},R_{43},R_{55}=are independently C,G,U or absent;

R_8,R_{11},R_{13},R_{30},R_{32},R_{34},R_{35},R_{41},R_{48},R_{53},R_{59},R_{60}=are independently C,U or absent;

R_{15},R_{19},R_{20},R_{25},R_{42},R_{50},R_{52}=are independently G or absent;

R_1,R_{22},R_{49},R_{58},R_{69}=are independently G,U or absent;

R_{16},R_{21},R_{28},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ASP}$ (SEQ ID NO: 573),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0,R_{17},R_{18},R_{23}=are absent

R_9,R_{12},R_{40},R_{65},R_{71}=are independently A or absent;

R_2,R_{24},R_{57}=are independently A,C or absent;

R_6,R_{14},R_{27},R_{46},R_{51},R_{56},R_{64},R_{67},R_{68}=are independently A,G or absent;

R_3,R_{31},R_{35},R_{39},R_{61},R_{62}=are independently C or absent;

R_{66}= C,G or absent;

R_5,R_8,R_{29},R_{30},R_{32},R_{34},R_{41},R_{43},R_{48},R_{55},R_{59},R_{60},R_{63}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{20},R_{25},R_{33},R_{37},R_{42},R_{44},R_{45},R_{49},R_{50},R_{52},R_{69},R_{70},R_{72}=are independently G or absent;

R_{22},R_{58}=are independently G,U or absent;

R_1,R_4,R_7,R_{11},R_{13},R_{16},R_{21},R_{26},R_{28},R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Cysteine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{CYS} (SEQ ID NO: 574),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

R_0 =absent

R_{14},R_{39},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_{10},R_{15},R_{27},R_{33},R_{62}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_{12},R_{13},R_{16},R_{24},R_{26},R_{29},R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{63},R_{64},R_{66}, R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{65}= A,C,U or absent;

R_9,R_{25},R_{37},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_7,R_{20},R_{51}=are independently A,G,U or absent;

R_{18},R_{38},R_{55}=are independently C or absent;

R_2= C, G or absent;

R_{21},R_{28},R_{43},R_{50}=are independently C,G,U or absent;

R_{11},R_{22},R_{23},R_{35},R_{36},R_{59},R_{60},R_{61},R_{71},R_{72}=are independently C,U or absent;

R_{1},R_{19}=are independently G or absent;

R_{17}= G,U or absent;

R_{8},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{CYS}$ (SEQ ID NO: 575),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

R_{0},R_{18},R_{23}=are absent;

R_{14},R_{24},R_{26},R_{29},R_{39},R_{41},R_{45},R_{57}=are independently A or absent;

R_{44}= A,C or absent;

R_{27},R_{62}=are independently A,C,G or absent;

R_{16}= A,C,G,U or absent;

R_{30},R_{70}=are independently A,C,U or absent;

R_{5},R_{7},R_{9},R_{25},R_{34},R_{37},R_{40},R_{46},R_{52},R_{56},R_{58},R_{66}=are independently A,G or absent;

R_{20},R_{51}=are independently A,G,U or absent;

R_{35},R_{38},R_{43},R_{55},R_{69}=are independently C or absent;

R_2,R_4,R_{15}=are independently C,G or absent;

R_{13}= C,G,U or absent;

R_6,R_{11},R_{28},R_{36},R_{48},R_{49},R_{50},R_{60},R_{61},R_{67},R_{68},R_{71},R_{72}=are independently C,U or absent;

R_1,R_3,R_{10},R_{19},R_{33},R_{63}=are independently G or absent;

R_8,R_{17},R_{21},R_{64}=are independently G,U or absent;

R_{12},R_{22},R_{31},R_{32},R_{42},R_{53},R_{54},R_{65}=are independently U or absent;

R_{59}= U, or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{CYS}$ (SEQ ID NO: 576),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

R_0,R_{18},R_{23}=are absent

R_{14},R_{24},R_{26},R_{29},R_{34},R_{39},R_{41},R_{45},R_{57},R_{58}=are independently A or absent;

R_{44},R_{70}=are independently A,C or absent;

R_{62}= A,C,G or absent;

R_{16}= N or absent;

R_5,R_7,R_9,R_{20},R_{40},R_{46},R_{51},R_{52},R_{56},R_{66}=are independently A,G or absent;

R_{28},R_{35},R_{38},R_{43},R_{55},R_{67},R_{69}=are independently C or absent;

R_4,R_{15}=are independently C,G or absent;

R_6,R_{11},R_{13},R_{30},R_{48},R_{49},R_{50},R_{60},R_{61},R_{68},R_{71},R_{72}=are independently C,U or absent;

R_1,R_2,R_3,R_{10},R_{19},R_{25},R_{27},R_{33},R_{37},R_{63}=are independently G or absent;

R_8,R_{21},R_{64}=are independently G,U or absent;

R_{12},R_{17},R_{22},R_{31},R_{32},R_{36},R_{42},R_{53},R_{54}, R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glutamine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{GLN} (SEQ ID NO: 577),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

R_0,R_{18}=are absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_9,R_{26},R_{27},R_{33},R_{56}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_{12},R_{13},R_{16},R_{21},R_{22},R_{25},R_{29},R_{30},R_{31},R_{32},R_{34},R_{41},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{23},R_{43},R_{65},R_{71}=are independently A,C,U or absent;

R_{15},R_{40},R_{51},R_{52}=are independently A,G or absent;

R_1,R_7,R_{72}=are independently A,G,U or absent;

R_3,R_{11},R_{37},R_{60},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_{10},R_{19},R_{20}=are independently G or absent;

R_{39}= G,U or absent;

R_8,R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLN}$ (SEQ ID NO: 578),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

R_0,R_{18},R_{23}=are absent

R_{14},R_{24},R_{57}=are independently A or absent;

R_{17},R_{71}=are independently A,C or absent;

R_{25},R_{26},R_{33},R_{44},R_{46},R_{56},R_{69}=are independently A,C,G or absent;

R_4,R_5,R_{12},R_{22},R_{29},R_{30},R_{48},R_{49},R_{63},R_{67},R_{68}=are independently N or absent;

R_{31},R_{43},R_{62},R_{65},R_{70}=are independently A,C,U or absent;

R_{15},R_{27},R_{34},R_{40},R_{41},R_{51},R_{52}=are independently A,G or absent;

R_2,R_7,R_{21},R_{45},R_{50},R_{58},R_{66},R_{72}=are independently A,G,U or absent;

R_3,R_{13},R_{32},R_{37},R_{42},R_{60},R_{64}=are independently C,G,U or absent;

R_6,R_{11},R_{28},R_{35},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_9,R_{10},R_{19},R_{20}=are independently G or absent;

R_1,R_{16},R_{39}=are independently G,U or absent;

R_8,R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLN}$ (SEQ ID NO: 579),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{14},R_{24},R_{41},R_{57}$=are independently A or absent;

R_{17},R_{71}=are independently A,C or absent;

$R_{5},R_{25},R_{26},R_{46},R_{56},R_{69}$=are independently A,C,G or absent;

$R_{4},R_{22},R_{29},R_{30},R_{48},R_{49},R_{63},R_{68}$=are independently N or absent;

$R_{43},R_{62},R_{65},R_{70}$=are independently A,C,U or absent;

$R_{15},R_{27},R_{33},R_{34},R_{40},R_{51},R_{52}$=are independently A,G or absent;

$R_{2},R_{7},R_{12},R_{45},R_{50},R_{58},R_{66}$=are independently A,G,U or absent;

R_{31}= A,U or absent;

R_{32},R_{44},R_{60}=are independently C,G or absent;

$R_{3},R_{13},R_{37},R_{42},R_{64},R_{67}$=are independently C,G,U or absent;

$R_{6},R_{11},R_{28},R_{35},R_{55},R_{59},R_{61}$=are independently C,U or absent;

$R_{9},R_{10},R_{19},R_{20}$=are independently G or absent;

$R_{1},R_{21},R_{39},R_{72}$=are independently G,U or absent;

$R_{8},R_{16},R_{36},R_{38},R_{53},R_{54}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glutamate TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{GLU} (SEQ ID NO: 580),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

R_0=absent;

R_{34},R_{43},R_{68},R_{69}=are independently A,C,G or absent;

R_1,R_2,R_5,R_6,R_9,R_{12},R_{16},R_{20},R_{21},R_{26},R_{27},R_{29},R_{30},R_{31},R_{32},R_{33},R_{41},R_{44},R_{45},R_{46},R_{48},R_{50},R_{51},R_{58},R_{63},R_{64},R_{65},R_{66},R_{70},R_{71}=are independently N or absent;

R_{13},R_{17},R_{23},R_{61}=are independently A,C,U or absent;

R_{10},R_{14},R_{24},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_7,R_{15},R_{25},R_{67},R_{72}=are independently A,G,U or absent;

R_{11},R_{57}=are independently A,U or absent;

R_{39}= C,G or absent;

R_3,R_4,R_{22},R_{42},R_{49},R_{55},R_{62}=are independently C,G,U or absent;

R_{18},R_{28},R_{35},R_{37},R_{53},R_{59},R_{60}=are independently C,U or absent;

R_{19}= G or absent;

R_8,R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLU}$ (SEQ ID NO: 581),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

$R_{0,}R_{18,}R_{23}$=are absent

R_{17},R_{40}=are independently A or absent;

R_{26},R_{27},R_{34},R_{43},R_{68},R_{69},R_{71}=are independently A,C,G or absent;

R_1,R_2,R_5,R_{12},R_{21},R_{31},R_{33},R_{41},R_{45},R_{48},R_{51},R_{58},R_{66},R_{70}=are independently N or absent;

R_{44},R_{61}=are independently A,C,U or absent;

R_9,R_{14},R_{24},R_{25},R_{52},R_{56},R_{63}=are independently A,G or absent;

R_7,R_{15},R_{46},R_{50},R_{67},R_{72}=are independently A,G,U or absent;

R_{29},R_{57}=are independently A,U or absent;

R_{60}= C or absent;

R_{39}= C,G or absent;

R_3,R_6,R_{20},R_{30},R_{32},R_{42},R_{55},R_{62},R_{65}=are independently C,G,U or absent;

R_4,R_8,R_{16},R_{28},R_{35},R_{37},R_{49},R_{53},R_{59}=are independently C,U or absent;

R_{10},R_{19}=are independently G or absent;

R_{22},R_{64}=are independently G,U or absent;

R_{11},R_{13},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLU}$ (SEQ ID NO: 582),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

$R_{0,}R_{17,}R_{18,}R_{23}$=are absent

R_{14},R_{27},R_{40},R_{71}=are independently A or absent;

R_{44}= A,C or absent;

R_{43}= A,C,G or absent;

R_1,R_{31},R_{33},R_{45},R_{51},R_{66}=are independently N or absent;

R_{21},R_{41}=are independently A,C,U or absent;

R_7,R_{24},R_{25},R_{50},R_{52},R_{56},R_{63},R_{68},R_{70}=are independently A,G or absent;

R_5,R_{46}=are independently A,G,U or absent;

R_{29},R_{57},R_{67},R_{72}=are independently A,U or absent;

R_2,R_{39},R_{60}=are independently C or absent;

R_3,R_{12},R_{20},R_{26},R_{34},R_{69}=are independently C,G or absent;

R_6,R_{30},R_{42},R_{48},R_{65}=are independently C,G,U o rabsent;

R_4,R_{16},R_{28},R_{35},R_{37},R_{49},R_{53},R_{55},R_{58},R_{61},R_{62}=are independently C,U or absent;

R_9,R_{10},R_{19},R_{64}=are independently G or absent;

R_{15},R_{22},R_{32}=are independently G,U or absent;

R_8,R_{11},R_{13},R_{36},R_{38},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glycine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{GLY}$ (SEQ ID NO: 583),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

R_0=absent;

R_{24}= A or absent;

R_3,R_9,R_{40},R_{50},R_{51}=are independently A,C,G or absent;

R_4,R_5,R_6,R_7,R_{12},R_{16},R_{21},R_{22},R_{26},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68}=are independently N or absent;

R_{59}= A,C,U or absent;

R_1,R_{10},R_{14},R_{15},R_{27},R_{56}=are independently A,G or absent;

R_{20},R_{25}=are independently A,G,U or absent;

R_{57},R_{72}=are independently A,U or absent;

R_{38},R_{39},R_{60}=are independently C or absent;

R_{52}= C,G or absent;

R_2,R_{19},R_{37},R_{54},R_{55},R_{61},R_{62},R_{69},R_{70}=are independently C,G,U or absent;

R_{11},R_{13},R_{17},R_{28},R_{35},R_{36},R_{71}=are independently C,U or absent;

R_8,R_{18},R_{23},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLY}$ (SEQ ID NO: 584),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{24},R_{27},R_{40},R_{72}$=are independently A or absent;

R_{26}= A,C or absent;

R_3,R_7,R_{68}=are independently A,C,G or absent;

$R_5,R_{30},R_{41},R_{42},R_{44},R_{49},R_{67}$=are independently A,C,G,U or absent;

R_{31},R_{32},R_{34}=are independently A,C,U or absent;

$R_9,R_{10},R_{14},R_{15},R_{33},R_{50},R_{56}$=are independently A,G or absent;

$R_{12},R_{16},R_{22},R_{25},R_{29},R_{46}$=are independently A,G,U or absent;

R_{57}= A,U or absent;

$R_{17},R_{38},R_{39},R_{60},R_{61},R_{71}$=are independently C or absent;

R_6,R_{52},R_{64},R_{66}=are independently C,G or absent;

$R_2,R_4,R_{37},R_{48},R_{55},R_{65}$=are independently C,G,U or absent;

R_{13},R_{35},R_{43},R_{62},R_{69}=are independently C,U or absent;

R_1,R_{19},R_{20},R_{51},R_{70}=are independently G or absent;

R_{21},R_{45},R_{63}=are independently G,U or absent;

R_8,R_{11},R_{28},R_{36},R_{53},R_{54},R_{58},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLY}$ (SEQ ID NO: 585),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

R_0,R_{18},R_{23}=are absent

R_{24},R_{27},R_{40},R_{72}=are independently A or absent;

R_{26}= A,C or absent;

R_3,R_7,R_{49},R_{68}=are independently A,C,G or absent;

R_5,R_{30},R_{41},R_{44},R_{67}=are independently N or absent;

R_{31},R_{32},R_{34}=are independently A,C,U or absent;

R_9,R_{10},R_{14},R_{15},R_{33},R_{50},R_{56}=are independently A,G or absent;

R_{12},R_{25},R_{29},R_{42},R_{46}=are independently A,G,U or absent;

R_{16},R_{57}=are independently A,U or absent;

R_{17},R_{38},R_{39},R_{60},R_{61},R_{71}=are independently C or absent;

R_{6},R_{52},R_{64},R_{66}=are independently C,G or absent;

R_{37},R_{48},R_{65}=are independently C,G,U or absent;

R_{2},R_{4},R_{13},R_{35},R_{43},R_{55},R_{62},R_{69}=are independently C,U or absent;

R_{1},R_{19},R_{20},R_{51},R_{70}=are independently G or absent;

R_{21},R_{22},R_{45},R_{63}=are independently G,U or absent;

R_{8},R_{11},R_{28},R_{36},R_{53},R_{54},R_{58},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

<u>Histidine TREM Consensus sequence</u>

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{HIS} (SEQ ID NO: 586),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

R_{23}=absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_{72}= A,C or absent;

R_9,R_{27},R_{43},R_{48},R_{69}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_{12},R_{25},R_{26},R_{29},R_{30},R_{31},R_{34},R_{42},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68}=are independently N or absent;

R_{13},R_{21},R_{41},R_{44},R_{65}=are independently A,C,U or absent;

R_{40},R_{51},R_{56},R_{70}=are independently A,G or absent;

R_7,R_{32}=are independently A,G,U or absent;

R_{55},R_{60}=are independently C or absent;

R_{11},R_{16},R_{33},R_{64}=are independently C,G,U or absent;

R_2,R_{17},R_{22},R_{28},R_{35},R_{53},R_{59},R_{61},R_{71}=are independently C,U or absent;

R_1,R_{10},R_{15},R_{19},R_{20},R_{37},R_{39},R_{52}=are independently G or absent;

R_0= G,U or absent;

R_8,R_{18},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{HIS}$ (SEQ ID NO: 587),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

$R_{0,}R_{17,}R_{18,}R_{23}$=are absent;

$R_7,R_{12},R_{14},R_{24},R_{27},R_{45},R_{57},R_{58},R_{63},R_{67},R_{72}$=are independently A or absent;

R_3= A,C,U or absent;

R_4,R_{43},R_{56},R_{70}=are independently A,G or absent;

R_{49}= A,U or absent;

$R_2,R_{28},R_{30},R_{41},R_{42},R_{44},R_{48},R_{55},R_{60},R_{66},R_{71}$=are independently C or absent;

R_{25}= C,G or absent;

R_9= C,G,U or absent;

$R_8,R_{13},R_{26},R_{33},R_{35},R_{50},R_{53},R_{61},R_{68}$=are independently C,U or absent;

$R_1,R_6,R_{10},R_{15},R_{19},R_{20},R_{32},R_{34},R_{37},R_{39},R_{40},R_{46},R_{51},R_{52},R_{62},R_{64},R_{69}$=are independently G or absent;

R_{16}= G,U or absent;

$R_5,R_{11},R_{21},R_{22},R_{29},R_{31},R_{36},R_{38},R_{54},R_{59},R_{65}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{HIS}$ (SEQ ID NO: 588),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

$R_{0,}R_{17,}R_{18,}R_{23}$=are absent

$R_7,R_{12},R_{14},R_{24},R_{27},R_{45},R_{57},R_{58},R_{63},R_{67},R_{72}$=are independently A or absent;

R_3= A,C or absent;

R_4,R_{43},R_{56},R_{70}=are independently A,G or absent;

R_{49}= A,U or absent;

$R_2,R_{28},R_{30},R_{41},R_{42},R_{44},R_{48},R_{55},R_{60},R_{66},R_{71}$=are independently C or absent;

$R_8,R_9,R_{26},R_{33},R_{35},R_{50},R_{61},R_{68}$=are independently C,U or absent;

$R_1,R_6,R_{10},R_{15},R_{19},R_{20},R_{25},R_{32},R_{34},R_{37},R_{39},R_{40},R_{46},R_{51},R_{52},R_{62},R_{64},R_{69}$=are independently G or absent;

$R_5,R_{11},R_{13},R_{16},R_{21},R_{22},R_{29},R_{31},R_{36},R_{38},R_{53},R_{54},R_{59},R_{65}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Isoleucine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ILE} (SEQ ID NO: 589),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

R_{23}=absent;

R_{38},R_{41},R_{57},R_{72}=are independently A or absent;

R_1,R_{26}=are independently A,C,G or absent;

R_0,R_3,R_4,R_6,R_{16},R_{31},R_{32},R_{34},R_{37},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{59},R_{62},R_{63},R_{64},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{22},R_{61},R_{65}=are independently A,C,U or absent;

R_9,R_{14},R_{15},R_{24},R_{27},R_{40}=are independently A,G or absent;

R_7,R_{25},R_{29},R_{51},R_{56}=are independently A,G,U or absent;

R_{18},R_{54}=are independently A,U or absent;

R_{60}= C or absent;

R_2,R_{52},R_{70}=are independently C,G or absent;

R_5,R_{12},R_{21},R_{30},R_{33},R_{71}=are independently C,G,U or absent;

R_{11},R_{13},R_{17},R_{28},R_{35},R_{53},R_{55}=are independently C,U or absent;

R_{10},R_{19},R_{20}=are independently G or absent;

R_8,R_{36},R_{39}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ILE}$ (SEQ ID NO: 590),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}$=are independently A or absent;

R_{26},R_{65}=are independently A,C or absent;

R_{58},R_{59},R_{67}=are independently N or absent;

R_{22}= A,C,U or absent;

$R_{6},R_{9},R_{14},R_{15},R_{29},R_{34},R_{43},R_{46},R_{48},R_{50},R_{51},R_{63},R_{69}$=are independently A,G or absent;

R_{37},R_{56}=are independently A,G,U or absent;

R_{54}= A,U or absent;

$R_{28},R_{35},R_{60},R_{62},R_{71}$=are independently C or absent;

R_{2},R_{52},R_{70}=are independently C,G or absent;

R_{5}= C,G,U or absent;

$R_{3},R_{4},R_{11},R_{13},R_{17},R_{21},R_{30},R_{42},R_{44},R_{45},R_{49},R_{53},R_{55},R_{61},R_{64},R_{66}$=are independently C,U or absent;

$R_{1},R_{10},R_{19},R_{20},R_{25},R_{27},R_{31},R_{68}$=are independently G or absent;

R_{7},R_{12},R_{32}=are independently G,U or absent;

$R_{8},R_{16},R_{33},R_{36},R_{39}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ILE}$ (SEQ ID NO: 591),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}$=are independently A or absent;

R_{26},R_{65}=are independently A,C or absent;

R_{22},R_{59}=are independently A,C,U or absent;

$R_6,R_9,R_{15},R_{34},R_{43},R_{46},R_{51},R_{56},R_{63},R_{69}$=are independently A,G or absent;

R_{37}= A,G,U or absent;

$R_{13},R_{28},R_{35},R_{44},R_{55},R_{60},R_{62},R_{71}$=are independently C or absent;

R_2,R_5,R_{70}=are independently C,G or absent;

R_{58},R_{67}=are independently C,G,U or absent;

$R_3,R_4,R_{11},R_{17},R_{21},R_{30},R_{42},R_{45},R_{49},R_{53},R_{61},R_{64},R_{66}$=are independently C,U or absent;

$R_1,R_{10},R_{19},R_{20},R_{25},R_{27},R_{29},R_{31},R_{32},R_{48},R_{50},R_{52},R_{68}$=are independently G or absent;

R_7,R_{12}=are independently G,U or absent;

$R_8,R_{16},R_{33},R_{36},R_{39},R_{54}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Methionine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{MET}$ (SEQ ID NO: 592),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

R_0,R_{23}=are absent;

R_{14},R_{38},R_{40},R_{57}=are independently A or absent;

R_{60}= A,C or absent;

R_{33},R_{48},R_{70}=are independently A,C,G or absent;

R_1,R_3,R_4,R_5,R_6,R_{11},R_{12},R_{16},R_{17},R_{21},R_{22},R_{26},R_{27},R_{29},R_{30},R_{31},R_{32},R_{42},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69},R_{71}=are independently N or absent;

R_{18},R_{35},R_{41},R_{59},R_{65}=are independently A,C,U or absent;

R_9,R_{15},R_{51}=are independently A,G or absent;

R_7,R_{24},R_{25},R_{34},R_{53},R_{56}=are independently A,G,U or absent;

R_{72}= A,U or absent;

R_{37}= C or absent;

R_{10},R_{55}=are independently C,G or absent;

R_2,R_{13},R_{28},R_{43},R_{64}=are independently C,G,U or absent;

R_{36},R_{61}=are independently C,U or absent;

R_{19},R_{20},R_{52}=are independently G or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13,

x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{MET}$ (SEQ ID NO: 593),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

$R_{0,}R_{18,}R_{22,}R_{23}$=are absent

$R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}$=are independently A or absent;

$R_{59},R_{60},R_{62},R_{65}$=are independently A,C or absent;

R_6,R_{45},R_{67}=are independently A,C,G or absent;

R_4= N or absent;

R_{21},R_{42}=are independently A,C,U or absent;

$R_1,R_9,R_{27},R_{29},R_{32},R_{46},R_{51}$=are independently A,G or absent;

$R_{17},R_{49},R_{53},R_{56},R_{58}$=are independently A,G,U or absent;

R_{63}=A,U or absent;

R_3,R_{13},R_{37}=are independently C or absent;

$R_{48},R_{55},R_{64},R_{70}$=are independently C,G or absent;

R_2,R_5,R_{66},R_{68}=are independently C,G,U or absent;

$R_{11},R_{16},R_{26},R_{28},R_{30},R_{31},R_{35},R_{36},R_{43},R_{44},R_{61},R_{71}$=are independently C,U or absent;

$R_{10},R_{12},R_{15},R_{19},R_{20},R_{25},R_{33},R_{52},R_{69}$=are independently G or absent;

R_7,R_{34},R_{50}=are independently G,U or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{MET}$ (SEQ ID NO: 594),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

R_0,R_{18},R_{22},R_{23}=are absent

R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}=are independently A or absent;

R_{59},R_{62},R_{65}=are independently A,C or absent;

R_6,R_{67}=are independently A,C,G or absent;

R_4,R_{21}=are independently A,C,U or absent;

R_1,R_9,R_{27},R_{29},R_{32},R_{45},R_{46},R_{51}=are independently A,G or absent;

R_{17},R_{56},R_{58}=are independently A,G,U or absent;

R_{49},R_{53},R_{63}=are independently A,U or absent;

R_3,R_{13},R_{26},R_{37},R_{43},R_{60}=are independently C or absent;

R_2,R_{48},R_{55},R_{64},R_{70}=are independently C,G or absent;

R_5,R_{66}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{30},R_{31},R_{35},R_{36},R_{42},R_{44},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{12},R_{15},R_{19},R_{20},R_{25},R_{33},R_{52},R_{69}=are independently G or absent;

R_{7},R_{34},R_{50},R_{68}=are independently G,U or absent;

R_{8},R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Leucine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{LEU} (SEQ ID NO: 595),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0=absent;

R_{38},R_{57}=are independently A or absent;

R_{60}= A,C or absent;

R_{1},R_{13},R_{27},R_{48},R_{51},R_{56}=are independently A,C,G or absent;

R_{2},R_{3},R_{4},R_{5},R_{6},R_{7},R_{9},R_{10},R_{11},R_{12},R_{16},R_{23},R_{26},R_{28},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44}, R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{18},R_{21},R_{22},R_{25},R_{35},R_{55}=are independently A,C,U or absent;

R_{14},R_{15},R_{39},R_{72}=are independently A,G or absent;

R_{24},R_{40}=are independently A,G,U or absent;

R_{52},R_{61},R_{64},R_{71}=are independently C,G,U or absent;

R_{36},R_{53},R_{59}=are independently C,U or absent;

R_{19}= G or absent;

R_{20}= G,U or absent;

R_8,R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{LEU}$ (SEQ ID NO: 596),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0 =absent

R_{38},R_{57},R_{72}=are independently A or absent;

R_{60}= A,C or absent;

R_4,R_5,R_{48},R_{50},R_{56},R_{69}=are independently A,C,G or absent;

R_6,R_{33},R_{41},R_{43},R_{46},R_{49},R_{58},R_{63},R_{66},R_{70}=are independently N or absent;

R_{11},R_{12},R_{17},R_{21},R_{22},R_{28},R_{31},R_{37},R_{44},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{14},R_{15},R_{24},R_{27},R_{34},R_{39}=are independently A,G or absent;

R_7,R_{29},R_{32},R_{40},R_{45}=are independently A,G,U or absent;

R_{25}= A,U or absent;

R_{13}= C,G or absent;

R_2,R_3,R_{16},R_{26},R_{30},R_{52},R_{62},R_{64},R_{65},R_{67},R_{68}=are independently C,G,U or absent;

R_{18},R_{35},R_{42},R_{53},R_{59},R_{61},R_{71}=are independently C,U or absent;

R_{19},R_{51}=are independently G or absent;

R_{10},R_{20}=are independently G,U or absent;

R_8,R_{23},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{LEU}$ (SEQ ID NO: 597),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0 =absent

R_{38},R_{57},R_{72}=are independently A or absent;

R_{60}= A,C or absent;

R_4,R_5,R_{48},R_{50},R_{56},R_{58},R_{69}=are independently A,C,G or absent;

R_6,R_{33},R_{43},R_{46},R_{49},R_{63},R_{66},R_{70}=are independently N or absent;

R_{11},R_{12},R_{17},R_{21},R_{22},R_{28},R_{31},R_{37},R_{41},R_{44},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{14},R_{15},R_{24},R_{27},R_{34},R_{39}=are independently A,G or absent;

R_7,R_{29},R_{32},R_{40},R_{45}=are independently A,G,U or absent;

R_{25}= A,U or absent;

R_{13}= C,G or absent;

R_2,R_3,R_{16},R_{30},R_{52},R_{62},R_{64},R_{67},R_{68}=are independently C,G,U or absent;

R_{18},R_{35},R_{42},R_{53},R_{59},R_{61},R_{65},R_{71}=are independently C,U or absent;

R_{19},R_{51}=are independently G or absent;

R_{10},R_{20},R_{26}=are independently G,U or absent;

R_8,R_{23},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

<u>Lysine TREM Consensus sequence</u>

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{LYS} (SEQ ID NO: 598),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

R_0 =absent

R_{14}= A or absent;

R_{40},R_{41}=are independently A,C or absent;

R_{34},R_{43},R_{51}=are independently A,C,G or absent;

R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_{11},R_{12},R_{16},R_{21},R_{26},R_{30},R_{31},R_{32},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65}, R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{13},R_{17},R_{59},R_{71}=are independently A,C,U or absent;

R_9,R_{15},R_{19},R_{20},R_{25},R_{27},R_{52},R_{56}=are independently A,G or absent;

R_{24},R_{29},R_{72}=are independently A,G,U or absent;

R_{18},R_{57}=are independently A,U or absent;

R_{10},R_{33}=are independently C,G or absent;

R_{42},R_{61},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{36},R_{37},R_{53},R_{55},R_{60}=are independently C,U or absent;

R_8,R_{22},R_{23},R_{38},R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{LYS}$ (SEQ ID NO: 599),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

$R_{0,}R_{18,}R_{23}$=are absent

R_{14}= A or absent;

R_{40},R_{41},R_{43}=are independently A,C or absent;

R_3,R_7=are independently A,C,G or absent;

R_1,R_6,R_{11},R_{31},R_{45},R_{48},R_{49},R_{63},R_{65},R_{66},R_{68}=are independently N or absent;

R_2,R_{12},R_{13},R_{17},R_{44},R_{67},R_{71}=are independently A,C,U or absent;

R_9,R_{15},R_{19},R_{20},R_{25},R_{27},R_{34},R_{50},R_{52},R_{56},R_{70},R_{72}=are independently A,G or absent;

R_5,R_{24},R_{26},R_{29},R_{32},R_{46},R_{69}=are independently A,G,U or absent;

R_{57}= A,U or absent;

R_{10},R_{61}=are independently C,G or absent;

R_4,R_{16},R_{21},R_{30},R_{58},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{36},R_{37},R_{42},R_{53},R_{55},R_{59},R_{60},R_{62}=are independently C,U or absent;

R_{33},R_{51}=are independently G or absent;

R_8=G,U or absent;

R_{22},R_{38},R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{LYS}$ (SEQ ID NO: 600),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

$R_{0,}R_{18,}R_{23}$=absent

R_9,R_{14},R_{34},R_{41}=are independently A or absent;

R_{40}= A,C or absent;

R_1,R_3,R_7,R_{31}=are independently A,C,G or absent;

R_{48},R_{65},R_{68}=are independently N or absent;

R_2,R_{13},R_{17},R_{44},R_{63},R_{66}=are independently A,C,U or absent;

R_5,R_{15},R_{19},R_{20},R_{25},R_{27},R_{29},R_{50},R_{52},R_{56},R_{70},R_{72}=are independently A,G or absent;

R_6,R_{24},R_{32},R_{49}=are independently A,G,U or absent;

R_{12},R_{26},R_{46},R_{57}=are independently A,U or absent;

R_{11},R_{28},R_{35},R_{43}=are independently C or absent;

R_{10},R_{45},R_{61}=are independently C,G or absent;

R_4,R_{21},R_{64}=are independently C,G,U or absent;

R_{37},R_{53},R_{55},R_{59},R_{60},R_{62},R_{67},R_{71}=are independently C,U or absent;

R_{33},R_{51}=are independently G or absent;

R_8,R_{30},R_{58},R_{69}=are independently G,U or absent;

R_{16},R_{22},R_{36},R_{38},R_{39},R_{42},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Phenylalanine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{PHE}$ (SEQ ID NO: 601),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

$R_{0,}R_{23}$=are absent

R_9,R_{14},R_{38},R_{39},R_{57},R_{72}=are independently A or absent;

R_{71}= A,C or absent;

R_{41},R_{70}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{16},R_{61},R_{65}=are independently A,C,U or absent;

R_{15},R_{26},R_{27},R_{29},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{51}=are independently A,G,U or absent;

R_{22},R_{24}=are independently A,U or absent;

R_{55},R_{60}=are independently C or absent;

R_2,R_3,R_{21},R_{33},R_{43},R_{50},R_{64}=are independently C,G,U or absent;

R_{11},R_{12},R_{13},R_{17},R_{28},R_{35},R_{36},R_{59}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{25},R_{37},R_{52}=are independently G or absent;

R_1= G,U or absent;

R_8,R_{18},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{PHE}$ (SEQ ID NO: 602),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

$R_{0,}R_{18,}R_{23}$=absent

R_{14},R_{24},R_{38},R_{39},R_{57},R_{72}=are independently A or absent;

R_{46},R_{71}=are independently A,C or absent;

R_4,R_{70}=are independently A,C,G or absent;

R_{45}= A,C,U or absent;

R_6,R_7,R_{15},R_{26},R_{27},R_{32},R_{34},R_{40},R_{41},R_{56},R_{69}=are independently A,G or absent;

R_{29}= A,G,U or absent;

R_5,R_9,R_{67}=are independently A,U or absent;

R_{35},R_{49},R_{55},R_{60}=are independently C or absent;

R_{21},R_{43},R_{62}=are independently C,G or absent;

R_2,R_{33},R_{68}=are independently C,G,U or absent;

R_3,R_{11},R_{12},R_{13},R_{28},R_{30},R_{36},R_{42},R_{44},R_{48},R_{58},R_{59},R_{61},R_{66}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{25},R_{37},R_{51},R_{52},R_{63},R_{64}=are independently G or absent;

R_1,R_{31},R_{50}=are independently G,U or absent;

R_8,R_{16},R_{17},R_{22},R_{53},R_{54},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{PHE}$ (SEQ ID NO: 603),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

R_0,R_{18},R_{22},R_{23}=absent

R_5,R_7,R_{14},R_{24},R_{26},R_{32},R_{34},R_{38},R_{39},R_{41},R_{57},R_{72}=are independently A or absent;

R_{46}= A,C or absent;

R_{70}= A,C,G or absent;

R_4,R_6,R_{15},R_{56},R_{69}=are independently A,G or absent;

R_9,R_{45}=are independently A,U or absent;

R_2,R_{11},R_{13},R_{35},R_{43},R_{49},R_{55},R_{60},R_{68},R_{71}=are independently C or absent;

R_{33}= C,G or absent;

R_3,R_{28},R_{36},R_{48},R_{58},R_{59},R_{61}=are independently C,U or absent;

R_1,R_{10},R_{19},R_{20},R_{21},R_{25},R_{27},R_{29},R_{37},R_{40},R_{51},R_{52},R_{62},R_{63},R_{64}=are independently G or absent;

R_8,R_{12},R_{16},R_{17},R_{30},R_{31},R_{42},R_{44},R_{50},R_{53},R_{54},R_{65},R_{66},R_{67}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Proline TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{PRO} (SEQ ID NO: 604),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

R_0 =absent

R_{14},R_{57}=are independently A or absent;

R_{70},R_{72}=are independently A,C or absent;

R_9,R_{26},R_{27}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{16},R_{21},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{61},R_{62}, R_{63},R_{64},R_{66},R_{67},R_{68}=are independently N or absent;

R_{35},R_{65}=are independently A,C,U or absent;

R_{24},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{25},R_{51}=are independently A,G,U or absent;

R_{55},R_{60}=are independently C or absent;

R_1,R_3,R_{71}=are independently C,G or absent;

R_{11},R_{12},R_{20},R_{69}=are independently C,G,U or absent;

R_{13},R_{17},R_{18},R_{22},R_{23},R_{28},R_{59}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{38},R_{39},R_{52}=are independently G or absent;

R_2= are independently G,U or absent;

R_8,R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{PRO}$ (SEQ ID NO: 605),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

R_0,R_{17},R_{18},R_{22},R_{23}=absent;

R_{14},R_{45},R_{56},R_{57},R_{58},R_{65},R_{68}=are independently A or absent;

R_{61}= A,C,G or absent;

R_{43}=N or absent;

R_{37}= A, C,U or absent;

R_{24},R_{27},R_{33},R_{40},R_{44},R_{63}=are independently A,G or absent;

R_3,R_{12},R_{30},R_{32},R_{48},R_{55},R_{60},R_{70},R_{71},R_{72}=are independently C or absent;

R_5,R_{34},R_{42},R_{66}=are independently C,G or absent;

R_{20}= C,G,U or absent;

R_{35},R_{41},R_{49},R_{62}=are independently C,U or absent;

R_1,R_2,R_6,R_9,R_{10},R_{15},R_{19},R_{26},R_{38},R_{39},R_{46},R_{50},R_{51},R_{52},R_{64},R_{67},R_{69}=are independently G or absent;

R_{11},R_{16}=are independently G,U or absent;

R_4,R_7,R_8,R_{13},R_{21},R_{25},R_{28},R_{29},R_{31},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{PRO}$ (SEQ ID NO: 606),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

R_0,R_{17},R_{18},R_{22},R_{23}=absent

R_{14},R_{45},R_{56},R_{57},R_{58},R_{65},R_{68}=are independently A or absent;

R_{37}= A,C,U or absent;

R_{24},R_{27},R_{40}=are independently A,G or absent;

R_3,R_5,R_{12},R_{30},R_{32},R_{48},R_{49},R_{55},R_{60},R_{61},R_{62},R_{66},R_{70},R_{71},R_{72}=are independently C or absent;

R_{34},R_{42}=are independently C,G or absent;

R_{43}= C,G,U or absent;

R_{41}= C,U or absent;

R_1,R_2,R_6,R_9,R_{10},R_{15},R_{19},R_{20},R_{26},R_{33},R_{38},R_{39},R_{44},R_{46},R_{50},R_{51},R_{52},R_{63},R_{64},R_{67},R_{69}=are independently G or absent;

R_{16}= G,U or absent;

R_4,R_7,R_8,R_{11},R_{13},R_{21},R_{25},R_{28},R_{29},R_{31},R_{35},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

<u>Serine TREM Consensus sequence</u>

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{SER} (SEQ ID NO: 607),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

R_0=absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_2,R_3,R_4,R_5,R_6,R_7,R_9,R_{10},R_{11},R_{12},R_{13},R_{16},R_{21},R_{25},R_{26},R_{27},R_{28},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{42},R_{43}, R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{18}= A,C,U or absent;

R_{15},R_{40},R_{51},R_{56}=are independently A,G or absent;

R_1,R_{29},R_{58},R_{72}=are independently A,G,U or absent;

R_{39}= A,U or absent;

R_{60}= C or absent;

R_{38}= C,G or absent;

R_{17},R_{22},R_{23},R_{71}=are independently C,G,U or absent;

R_8,R_{35},R_{36},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_{19},R_{20}=are independently G or absent;

R_{52}= G,U or absent;

R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{SER}$ (SEQ ID NO: 608),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

$R_{0,}R_{23}$=absent

$R_{14},R_{24},R_{41},R_{57}$=are independently A or absent;

R_{44}= A,C or absent;

R_{25},R_{45},R_{48}=are independently A,C,G or absent;

$R_{2},R_{3},R_{4},R_{5},R_{37},R_{50},R_{62},R_{66},R_{67},R_{69},R_{70}$=are independently N or absent;

R_{12},R_{28},R_{65}=are independently A,C,U or absent;

$R_{9},R_{15},R_{29},R_{34},R_{40},R_{56},R_{63}$=are independently A,G or absent;

$R_{7},R_{26},R_{30},R_{33},R_{46},R_{58},R_{72}$=are independently A,G,U or absent;

R_{39}= A,U or absent;

$R_{11},R_{35},R_{60},R_{61}$=are independently C or absent;

R_{13},R_{38}=are independently C,G or absent;

$R_{6},R_{17},R_{31},R_{43},R_{64},R_{68}$=are independently C,G,U or absent;

$R_{36},R_{42},R_{49},R_{55},R_{59},R_{71}$=are independently C,U or absent;

$R_{10},R_{19},R_{20},R_{27},R_{51}$=are independently G or absent;

$R_{1},R_{16},R_{32},R_{52}$=are independently G,U or absent;

$R_{8},R_{18},R_{21},R_{22},R_{53},R_{54}$=are independently U or absent;

$[R_{47}]_{x}$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{SER}$ (SEQ ID NO: 609),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

$R_{0,}R_{23}$=absent

R_{14},R_{24},R_{41},R_{57},R_{58}=are independently A or absent;

R_{44}= A,C or absent;

R_{25},R_{48}=are independently A,C,G or absent;

R_2,R_3,R_5,R_{37},R_{66},R_{67},R_{69},R_{70}=are independently N or absent;

R_{12},R_{28},R_{62}=are independently A,C,U or absent;

R_7,R_9,R_{15},R_{29},R_{33},R_{34},R_{40},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_4,R_{26},R_{46},R_{50}=are independently A,G,U or absent;

R_{30},R_{39}=are independently A,U or absent;

R_{11},R_{17},R_{35},R_{60},R_{61}=are independently C or absent;

R_{13},R_{38}=are independently C,G or absent;

R_6,R_{64}=are independently C,G,U or absent;

R_{31},R_{42},R_{43},R_{49},R_{55},R_{59},R_{65},R_{68},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{27},R_{51},R_{52}=are independently G or absent;

R_1,R_{16},R_{32},R_{72}=are independently G,U or absent;

R_8,R_{18},R_{21},R_{22},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Threonine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{THR}$ (SEQ ID NO: 610),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

$R_{0,}R_{23}$=absent

R_{14},R_{41},R_{57}=are independently A or absent;

R_{56},R_{70}=are independently A,C,G or absent;

$R_4,R_5,R_6,R_7,R_{12},R_{16},R_{26},R_{30},R_{31},R_{32},R_{34},R_{37},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{72}$=are independently N or absent;

$R_{13},R_{17},R_{21},R_{35},R_{61}$=are independently A,C,U or absent;

$R_1,R_9,R_{24},R_{27},R_{29},R_{69}$=are independently A,G or absent;

R_{15},R_{25},R_{51}=are independently A,G,U or absent;

R_{40},R_{53}=are independently A,U or absent;

R_{33},R_{43}=are independently C,G or absent;

R_2,R_3,R_{59}=are independently C,G,U or absent;

$R_{11},R_{18},R_{22},R_{28},R_{36},R_{54},R_{55},R_{60},R_{71}$=are independently C,U or absent;

$R_{10},R_{20},R_{38},R_{52}$=are independently G or absent;

R_{19}= G,U or absent;

R_8,R_{39}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{THR}$ (SEQ ID NO: 611),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

$R_{0,}R_{18,}R_{23}$=absent

R_{14},R_{41},R_{57}=are independently A or absent;

$R_9,R_{42},R_{44},R_{48},R_{56},R_{70}$=are independently A,C,G or absent;

$R_4,R_6,R_{12},R_{26},R_{49},R_{58},R_{63},R_{64},R_{66},R_{68}$=are independently N or absent;

$R_{13},R_{21},R_{31},R_{37},R_{62}$=are independently A,C,U or absent;

$R_1,R_{15},R_{24},R_{27},R_{29},R_{46},R_{51},R_{69}$=are independently A,G or absent;

$R_7,R_{25},R_{45},R_{50},R_{67}$=are independently A,G,U or absent;

R_{40},R_{53}=are independently A,U or absent;

R_{35}= C or absent;

R_{33},R_{43}=are independently C,G or absent;

$R_2,R_3,R_5,R_{16},R_{32},R_{34},R_{59},R_{65},R_{72}$=are independently C,G,U or absent;

$R_{11},R_{17},R_{22},R_{28},R_{30},R_{36},R_{55},R_{60},R_{61},R_{71}$=are independently C,U or absent;

$R_{10},R_{19},R_{20},R_{38},R_{52}$=are independently G or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{THR}$ (SEQ ID NO: 612),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

R_0,R_{18},R_{23}=absent

R_{14},R_{40},R_{41},R_{57}=are independently A or absent;

R_{44}= A,C or absent;

R_9,R_{42},R_{48},R_{56}=are independently A,C,G or absent;

R_4,R_6,R_{12},R_{26},R_{58},R_{64},R_{66},R_{68}=are independently N or absent;

R_{13},R_{21},R_{31},R_{37},R_{49},R_{62}=are independently A,C,U or absent;

R_1,R_{15},R_{24},R_{27},R_{29},R_{46},R_{51},R_{69}=are independently A,G or absent;

R_7,R_{25},R_{45},R_{50},R_{63},R_{67}=are independently A,G,U or absent;

R_{53}= A,U or absent;

R_{35}= C or absent;

R_2,R_{33},R_{43},R_{70}=are independently C,G or absent;

R_5,R_{16},R_{34},R_{59},R_{65}=are independently C,G,U or absent;

R_3,R_{11},R_{22},R_{28},R_{30},R_{36},R_{55},R_{60},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{38},R_{52}=are independently G or absent;

R_{32}= G,U or absent;

R_8,R_{17},R_{39},R_{54},R_{72}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Tryptophan TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{TRP} (SEQ ID NO: 613),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

R_0= absent;

R_{24},R_{39},R_{41},R_{57}=are independently A or absent;

R_2,R_3,R_{26},R_{27},R_{40},R_{48}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{29},R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{49},R_{51},R_{58},R_{63},R_{66},R_{67},R_{68}=are independently N or absent;

R_{13},R_{14},R_{16},R_{18},R_{21},R_{61},R_{65},R_{71}=are independently A,C,U or absent;

R_1,R_9,R_{10},R_{15},R_{33},R_{50},R_{56}=are independently A,G or absent;

R_7,R_{25},R_{72}=are independently A,G,U or absent;

R_{37},R_{38},R_{55},R_{60}=are independently C or absent;

R_{12},R_{35},R_{43},R_{64},R_{69},R_{70}=are independently C,G,U or absent;

R_{11},R_{17},R_{22},R_{28},R_{59},R_{62}=are independently C,U or absent;

R_{19},R_{20},R_{52}=are independently G or absent;

R_8,R_{23},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{TRP}$ (SEQ ID NO: 614),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

R_0,R_{18},R_{22},R_{23}=absent

R_{14},R_{24},R_{39},R_{41},R_{57},R_{72}=are independently A or absent;

R_3,R_4,R_{13},R_{61},R_{71}=are independently A,C or absent;

R_6,R_{44}=are independently A,C,G or absent;

R_{21}= A,C,U or absent;

R_2,R_7,R_{15},R_{25},R_{33},R_{34},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_{58}= A,G,U or absent;

R_{46}= A,U or absent;

R_{37},R_{38},R_{55},R_{60},R_{62}=are independently C or absent;

R_{12},R_{26},R_{27},R_{35},R_{40},R_{48},R_{67}=are independently C,G or absent;

R_{32},R_{43},R_{68}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{31},R_{49},R_{59},R_{65},R_{70}=are independently C,U or absent;

R_{1},R_{9},R_{10},R_{19},R_{20},R_{50},R_{52},R_{69}=are independently G or absent;

R_{5},R_{8},R_{29},R_{30},R_{42},R_{51},R_{64},R_{66}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{TRP}$ (SEQ ID NO: 615),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

R_{0},R_{18},R_{22},R_{23}=absent

R_{14},R_{24},R_{39},R_{41},R_{57},R_{72}=are independently A or absent;

R_3,R_4,R_{13},R_{61},R_{71}=are independently A,C or absent;

R_6,R_{44}=are independently A,C,G or absent;

R_{21}= A,C,U or absent;

R_2,R_7,R_{15},R_{25},R_{33},R_{34},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_{58}= A,G,U or absent;

R_{46}= A,U or absent;

R_{37},R_{38},R_{55},R_{60},R_{62}=are independently C or absent;

R_{12},R_{26},R_{27},R_{35},R_{40},R_{48},R_{67}=are independently C,G or absent;

R_{32},R_{43},R_{68}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{31},R_{49},R_{59},R_{65},R_{70}=are independently C,U or absent;

R_1,R_9,R_{10},R_{19},R_{20},R_{50},R_{52},R_{69}=are independently G or absent;

R_5,R_8,R_{29},R_{30},R_{42},R_{51},R_{64},R_{66}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

<u>Tyrosine TREM Consensus sequence</u>

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{TYR} (SEQ ID NO: 616),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

R_0 =absent

R_{14},R_{39},R_{57}=are independently A or absent;

R_{41},R_{48},R_{51},R_{71}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_9,R_{10},R_{12},R_{13},R_{16},R_{25},R_{26},R_{30},R_{31},R_{32},R_{42},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66}, R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{22},R_{65}=are independently A,C,U or absent;

R_{15},R_{24},R_{27},R_{33},R_{37},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{29},R_{34},R_{72}=are independently A,G,U or absent;

R_{23},R_{53}=are independently A,U or absent;

R_{35},R_{60}=are independently C or absent;

R_{20}= C,G or absent;

R_1,R_2,R_{28},R_{61},R_{64}=are independently C,G,U or absent;

R_{11},R_{17},R_{21},R_{43},R_{55}=are independently C,U or absent;

R_{19},R_{52}=are independently G or absent;

R_8,R_{18},R_{36},R_{38},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{TYR}$ (SEQ ID NO: 617),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

$R_{0,}R_{18,}R_{23}$=absent

R_7,R_9,R_{14},R_{24},R_{26},R_{34},R_{39},R_{57}=are independently A or absent;

R_{44},R_{69}=are independently A,C or absent;

R_{71}= A,C,G or absent;

R_{68}= N or absent;

R_{58}= A,C,U or absent;

R_{33},R_{37},R_{41},R_{56},R_{62},R_{63}=are independently A,G or absent;

R_6,R_{29},R_{72}=are independently A,G,U or absent;

R_{31},R_{45},R_{53}=are independently A,U or absent;

R_{13},R_{35},R_{49},R_{60}=are independently C or absent;

R_{20},R_{48},R_{64},R_{67},R_{70}=are independently C,G or absent;

R_1,R_2,R_5,R_{16},R_{66}=are independently C,G,U or absent;

R_{11},R_{21},R_{28},R_{43},R_{55},R_{61}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{25},R_{27},R_{40},R_{51},R_{52}=are independently G or absent;

R_3,R_4,R_{30},R_{32},R_{42},R_{46}=are independently G,U or absent;

R_8,R_{12},R_{17},R_{22},R_{36},R_{38},R_{50},R_{54},R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{TYR}$ (SEQ ID NO: 618),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

$R_{0,}R_{18,}R_{23}$=absent

$R_7,R_9,R_{14},R_{24},R_{26},R_{34},R_{39},R_{57},R_{72}$=are independently A or absent;

R_{44},R_{69}=are independently A,C or absent;

R_{71}= A,C,G or absent;

$R_{37},R_{41},R_{56},R_{62},R_{63}$=are independently A,G or absent;

R_6,R_{29},R_{68}=are independently A,G,U or absent;

R_{31},R_{45},R_{58}=are independently A,U or absent;

$R_{13},R_{28},R_{35},R_{49},R_{60},R_{61}$=are independently C or absent;

$R_5,R_{48},R_{64},R_{67},R_{70}$=are independently C,G or absent;

R_1,R_2=are independently C,G,U or absent;

$R_{11},R_{16},R_{21},R_{43},R_{55},R_{66}$=are independently C,U or absent;

$R_{10},R_{15},R_{19},R_{20},R_{25},R_{27},R_{33},R_{40},R_{51},R_{52}$=are independently G or absent;

$R_3,R_4,R_{30},R_{32},R_{42},R_{46}$=are independently G,U or absent;

$R_8,R_{12},R_{17},R_{22},R_{36},R_{38},R_{50},R_{53},R_{54},R_{59},R_{65}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-

271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Valine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{VAL}$ (SEQ ID NO: 619),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

R_0,R_{23}=absent;

R_{24},R_{38},R_{57}=are independently A or absent;

R_9,R_{72}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_7,R_{12},R_{15},R_{16},R_{21},R_{25},R_{26},R_{29},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{61},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{35},R_{59}=are independently A,C,U or absent;

R_{10},R_{14},R_{27},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_1,R_3,R_{51},R_{53}=are independently A,G,U or absent;

R_{39}= C or absent;

R_{13},R_{30},R_{55}=are independently C,G,U or absent;

R_{11},R_{22},R_{28},R_{60},R_{71}=are independently C,U or absent;

R_{19}= G or absent;

R_{20}= G ,U or absent;

R_8,R_{18},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{VAL}$ (SEQ ID NO: 620),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

$R_{0,}R_{18,}R_{23}$=absent;

$R_{24,}R_{38,}R_{57}$=are independently A or absent;

$R_{64,}R_{70,}R_{72}$=are independently A,C,G or absent;

$R_{15,}R_{16,}R_{26,}R_{29,}R_{31,}R_{32,}R_{43,}R_{44,}R_{45,}R_{49,}R_{50,}R_{58,}R_{62,}R_{65}$=are independently N or absent;

$R_{6,}R_{17,}R_{34,}R_{37,}R_{41,}R_{59}$=are independently A,C,U or absent;

$R_{9,}R_{10,}R_{14,}R_{27,}R_{40,}R_{46,}R_{51,}R_{52,}R_{56}$=are independently A,G or absent;

$R_{7,}R_{12,}R_{25,}R_{33,}R_{53,}R_{63,}R_{66,}R_{68}$=are independently A,G,U or absent;

R_{69}= A,U or absent;

R_{39}= C or absent;

$R_{5,}R_{67}$=are independently C,G or absent;

$R_{2,}R_{4,}R_{13,}R_{48,}R_{55,}R_{61}$=are independently C,G,U or absent;

$R_{11,}R_{22,}R_{28,}R_{30,}R_{35,}R_{60,}R_{71}$=are independently C,U or absent;

R_{19}= G or absent;

R_1,R_3,R_{20},R_{42}=are independently G,U or absent;

R_8,R_{21},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{VAL}$ (SEQ ID NO: 621),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

R_0,R_{18},R_{23}=absent

R_{24},R_{38},R_{40},R_{57},R_{72}=are independently A or absent;

R_{29},R_{64},R_{70}=are independently A,C,G or absent;

R_{49},R_{50},R_{62}=are independently N or absent;

R_{16},R_{26},R_{31},R_{32},R_{37},R_{41},R_{43},R_{59},R_{65}=are independently A,C,U or absent;

R_9,R_{14},R_{27},R_{46},R_{52},R_{56},R_{66}=are independently A,G or absent;

R_7,R_{12},R_{25},R_{33},R_{44},R_{45},R_{53},R_{58},R_{63},R_{68}=are independently A,G,U or absent;

R_{69}= A,U or absent;

R_{39}= C or absent;

R_5,R_{67}=are independently C,G or absent;

R_2,R_4,R_{13},R_{15},R_{48},R_{55}=are independently C,G,U or absent;

R_6,R_{11},R_{22},R_{28},R_{30},R_{34},R_{35},R_{60},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{51}=are independently G or absent;

R_1,R_3,R_{20},R_{42}=are independently G,U or absent;

R_8,R_{17},R_{21},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Variable region consensus sequence

In an embodiment, a TREM disclosed herein comprises a variable region at position R_{47}. In an embodiment, the variable region is 1-271 ribonucleotides in length (*e.g.* 1-250, 1-225, 1-200, 1-175, 1-150, 1-125, 1-100, 1-75, 1-50, 1-40, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 10-271, 20-271, 30-271, 40-271, 50-271, 60-271, 70-271, 80-271, 100-271, 125-271, 150-271, 175-271, 200-271, 225-271, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 110, 125, 150, 175, 200, 225, 250, or 271 ribonucleotides). In an embodiment, the variable region comprises any one, all or a combination of Adenine, Cytosine, Guanine or Uracil.

In an embodiment, the variable region comprises a ribonucleic acid (RNA) sequence encoded by a deoxyribonucleic acid (DNA) sequence disclosed in Table 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4.

Table 4: Exemplary variable region sequences.

	SEQ ID NO	SEQUENCE

1	452	AAAATATAAATATATTTC
2	453	AAGCT
3	454	AAGTT
4	455	AATTCTTCGGAATGT
5	456	AGA
6	457	AGTCC
7	458	CAACC
8	459	CAATC
9	460	CAGC
10	461	CAGGCGGGTTCTGCCCGCGC
11	462	CATACCTGCAAGGGTATC
12	463	CGACCGCAAGGTTGT
13	464	CGACCTTGCGGTCAT
14	465	CGATGCTAATCACATCGT
15	466	CGATGGTGACATCAT
16	467	CGATGGTTTACATCGT
17	468	CGCCGTAAGGTGT
18	469	CGCCTTAGGTGT
19	470	CGCCTTTCGACGCGT
20	471	CGCTTCACGGCGT
21	472	CGGCAGCAATGCTGT
22	473	CGGCTCCGCCTTC
23	474	CGGGTATCACAGGGTC
24	475	CGGTGCGCAAGCGCTGT
25	476	CGTACGGGTGACCGTACC
26	477	CGTCAAAGACTTC
27	478	CGTCGTAAGACTT
28	479	CGTTGAATAAACGT
29	480	CTGTC
30	481	GGCC
31	482	GGGGATT
32	483	GGTC
33	484	GGTTT
34	485	GTAG
35	486	TAACTAGATACTTTCAGAT
36	487	TACTCGTATGGGTGC
37	488	TACTTTGCGGTGT
38	489	TAGGCGAGTAACATCGTGC
39	490	TAGGCGTGAATAGCGCCTC
40	491	TAGGTCGCGAGAGCGGCGC
41	492	TAGGTCGCGTAAGCGGCGC
42	493	TAGGTGGTTATCCACGC
43	494	TAGTC

44	495	TAGTT
45	496	TATACGTGAAAGCGTATC
46	497	TATAGGGTCAAAAACTCTATC
47	498	TATGCAGAAATACCTGCATC
48	499	TCCCCATACGGGGGC
49	500	TCCCGAAGGGGTTC
50	501	TCTACGTATGTGGGC
51	502	TCTCATAGGAGTTC
52	503	TCTCCTCTGGAGGC
53	504	TCTTAGCAATAAGGT
54	505	TCTTGTAGGAGTTC
55	506	TGAACGTAAGTTCGC
56	507	TGAACTGCGAGGTTCC
57	508	TGAC
58	509	TGACCGAAAGGTCGT
59	510	TGACCGCAAGGTCGT
60	511	TGAGCTCTGCTCTC
61	512	TGAGGCCTCACGGCCTAC
62	513	TGAGGGCAACTTCGT
63	514	TGAGGGTCATACCTCC
64	515	TGAGGGTGCAAATCCTCC
65	516	TGCCGAAAGGCGT
66	517	TGCCGTAAGGCGT
67	518	TGCGGTCTCCGCGC
68	519	TGCTAGAGCAT
69	520	TGCTCGTATAGAGCTC
70	521	TGGACAATTGTCTGC
71	522	TGGACAGATGTCCGT
72	523	TGGACAGGTGTCCGC
73	524	TGGACGGTTGTCCGC
74	525	TGGACTTGTGGTC
75	526	TGGAGATTCTCTCCGC
76	527	TGGCATAGGCCTGC
77	528	TGGCTTATGTCTAC
78	529	TGGGAGTTAATCCCGT
79	530	TGGGATCTTCCCGC
80	531	TGGGCAGAAATGTCTC
81	532	TGGGCGTTCGCCCGC
82	533	TGGGCTTCGCCCGC
83	534	TGGGGGATAACCCCGT
84	535	TGGGGGTTTCCCCGT
85	536	TGGT
86	537	TGGTGGCAACACCGT

87	538	TGGTTTATAGCCGT
88	539	TGTACGGTAATACCGTACC
89	540	TGTCCGCAAGGACGT
90	541	TGTCCTAACGGACGT
91	542	TGTCCTATTAACGGACGT
92	543	TGTCCTTCACGGGCGT
93	544	TGTCTTAGGACGT
94	545	TGTGCGTTAACGCGTACC
95	546	TGTGTCGCAAGGCACC
96	547	TGTTCGTAAGGACTT
97	548	TTCACAGAAATGTGTC
98	549	TTCCCTCGTGGAGT
99	550	TTCCCTCTGGGAGC
100	551	TTCCCTTGTGGATC
101	552	TTCCTTCGGGAGC
102	553	TTCTAGCAATAGAGT
103	554	TTCTCCACTGGGGAGC
104	555	TTCTCGAGAGGGAGC
105	556	TTCTCGTATGAGAGC
106	557	TTTAAGGTTTTCCCTTAAC
107	558	TTTCATTGTGGAGT
108	559	TTTCGAAGGAATCC
109	560	TTTCTTCGGAAGC
110	561	TTTGGGGCAACTCAAC

Corresponding Nucleotide Positions

To determine if a selected nucleotide position in a candidate sequence corresponds to a selected position in a reference sequence (e.g., SEQ ID NO: 622, SEQ ID NO: 623, SEQ ID NO: 624), one or more of the following Evaluations is performed.

Evaluation A:

1.The candidate sequence is aligned with each of the consensus sequences in Tables 9 and 10. The consensus sequence(s) having the most positions aligned (and which has at least 60% of the positions of the candidate sequence aligned) is selected.

The alignment is performed as is follows. The candidate sequence and an isodecoder consensus sequence from Tables 10A-10B are aligned based on a global pairwise alignment calculated with the Needleman–Wunsch algorithm when run with match scores from Table 11, a mismatch penalty of -1, a gap opening penalty of -1, and a gap extension penalty of -0.5, and no

penalty for end gaps. The alignment with the highest overall alignment score is then used to determine the percent similarity between the candidate and the consensus sequence by counting the number of matched positions in the alignment, dividing it by the larger of the number of non-N bases in the candidate sequence or the consensus sequence, and multiplying the result by 100. In cases where multiple alignments (of the candidate and a single consensus sequence) tie for the same score, the percent similarity is the largest percent similarity calculated from the tied alignments. This process is repeated for the candidate sequence with each of the remaining isodecoder consensus sequences in Tables 10A-10B, and the alignment resulting in the greatest percent similarity is selected. If this alignment has a percent similarity equal to or greater than 60%, it is considered a valid alignment and used to relate positions in the candidate sequence to those in the consensus sequence, otherwise the candidate sequence is considered to have not aligned to any of the isodecoder consensus sequences. If there is a tie at this point, all tied consensus sequences are taken forward to step 2 in the analysis.

2. Using the selected consensus sequence(s) from step 1, one determines the consensus sequence position number that aligns with the selected position (e.g., a modified position) in the candidate sequence. One then assigns the position number of the aligned position in the consensus sequence to the selected position in the candidate sequence, in other words, the selected position in the candidate sequence is numbered according to the numbering of the consensus sequence. If there were tied consensus sequences from step one, and they give different position numbers in this step 2, then all such position numbers are taken forward to step 5.

3. The reference sequence is aligned with the consensus sequence chosen in step 1. The alignment is performed as described in step 1.

4. From the alignment in step 3, one determines the consensus sequence position number that aligns with the selected position (e.g., a modified position) in the reference sequence. One then assigns the position number of the aligned position in the consensus sequence to the selected position in the reference sequence, in other words, the selected position in the reference sequence is numbered according to the numbering of the consensus sequence. If there is a tie at this point, all tied consensus sequences are taken forward to step 5 in the analysis.

5. If a value for a position number determined for the reference sequence in step 2 is the same as the value for the position number determined for the candidate sequence in step 4, the positions are defined as corresponding.

Evaluation B:

The reference sequence (e.g., a TREM sequence described herein) and the candidate sequence are aligned with one another. The alignment is performed as follows.

The reference sequence and the candidate sequence are aligned based on a global pairwise alignment calculated with the Needleman–Wunsch algorithm when run with match scores from Table 11, a mismatch penalty of -1, a gap opening penalty of -1, and a gap extension penalty of -0.5, and no penalty for end gaps. The alignment with the highest overall alignment score is then used to determine the percent similarity between the candidate and reference sequence by counting the number of matched based in the alignment, dividing it by the larger of the number of non-N bases in the candidate or reference sequence, and multiplying the result by 100. In cases where multiple alignments tie for the same score, the percent similarity is the largest percent similarity calculated from the tied alignments. If this alignment has a percent similarity equal to or greater than 60%, it is considered a valid alignment and used to relate positions in the candidate sequence to those in the reference sequence, otherwise the candidate sequence is considered to have not aligned to the reference sequence.

If the selected nucleotide position in the reference sequence (e.g., a modified position) is paired with a selected nucleotide position (e.g., a modified position) in the candidate sequence, the positions are defined as corresponding.

Evaluation C:

The candidate sequence is assigned a nucleotide position number according to the comprehensive tRNA numbering system (CtNS), also referred to as the tRNAviz method (e.g., as described in Lin et al., Nucleic Acids Research, 47:W1, pages W542-W547, 2 July 2019), which serves as a global numbering system for tRNA molecules. The alignment is performed as follows.

1. The candidate sequence is assigned a nucleotide position according to the tRNAviz method. For a novel sequence not present in the tRNAviz database, the numbering for the closest sequence in the database is obtained. For example, if a TREM differs at any given nucleotide

position from a sequence in the database, the numbering for the tRNA having the wildtype sequence at said given nucleotide position is used.

2. The reference sequence is assigned a nucleotide position according to the method described in 1.

3. If a value for a position number determined for the reference sequence in step 1 is the same as the value for the position number determined for the candidate sequence in step 2, the positions are defined as corresponding.

If the selected position in the reference sequence and the candidate sequence are found to be corresponding in at least one of Evaluations A, B, and C, the positions correspond. For example, if two positions are found to be corresponding under Evaluation A, but do not correspond under Evaluation B or Evaluation C, the positions are defined as corresponding. Similarly, if two positions are found to be corresponding under Evaluation B, but do not correspond under Evaluation A or Evaluation C, the positions are defined as corresponding. In addition, if two positions are found to be corresponding under Evaluation C, but do not correspond under Evaluation A or Evaluation B, the positions are defined as corresponding

The numbering given above is used for ease of presentation and does not imply a required sequence. If more than one Evaluation is performed, they can be performed in any order.

Table 10A. Consensus sequence computationally generated for each isodecoder by aligning members of the isodecoder family

SEQ ID NO.	Amino Acid	Anticodon	Consensus sequence
1200	Ala	AGC	GGGGAATTAGCTCAAGTGGTAGAGCGCTTG CTTAGCATGCAAGAGGTAGTGGGATCGATG CCCACATTCTCCA
1201	Ala	CGC	GGGGATGTAGCTCAGTGGTAGAGCGCATGC TTCGCATGTATGAGGTCCCGGGTTCGATCCC CGGCATCTCCA
1202	Ala	TGC	GGGGGTGTAGCTCAGTGGTAGAGCGCATGC TTTGCATGTATGAGGCCCCGGGTTCGATCCC CGGCACCTCCA
1203	Arg	ACG	GGGCCAGTGGCGCAATGGATAACGCGTCTG ACTACGGATCAGAAGATTCCAGGTTCGACTC CTGGCTGGCTCG

1204	Arg	CCG	GGCCGCGTGGCCTAATGGATAAGGCGTCTG ATTCCGGATCAGAAGATTGAGGGTTCGAGTC CCTTCGTGGTCG
1205	Arg	CCT	GCCCCAGTGGCCTAATGGATAAGGCACTGG CCTCCTAAGCCAGGGATTGTGGGTTCGAGTC CCACCTGGGGTA
1206	Arg	TCG	GACCGCGTGGCCTAATGGATAAGGCGTCTG ACTTCGGATCAGAAGATTGAGGGTTCGAGTC CCTCCGTGGTCG
1207	Arg	TCT	GGCTCTGTGGCGCAATGGATNAGCGCATTG GACTTCTAATTCAAAGGTTGCGGGTTCGAGT CCCNCCAGAGTCG
1208	Asn	GTT	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTTAACCGNAAAGGTTGGTGGTTCGAGC CCACCCAGGGACG
1209	Asp	GTC	TCCTCGTTAGTATAGTGGTGAGTATCCCCGC CTGTCACGCGGGAGACCGGGGTTCGATTCCC CGACGGGGAG
1210	Cys	GCA	GGGGGTATAGCTCAGNGGGTAGAGCATTTG ACTGCAGATCAAGAGGTCCCCGGTTCAAATC CGGGTGCCCCCT
1211	Gln	CTG	GGTTCCATGGTGTAATGGTNAGCACTCTGGA CTCTGAATCCAGCGATCCGAGTTCAAGTCTC GGTGGAACCT
1212	Gln	TTG	GGTCCCATGGTGTAATGGTTAGCACTCTGGA CTTTGAATCCAGCGATCCGAGTTCAAATCTC GGTGGGACCT
1213	Glu	CTC	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCG CTCTCACCGCCGCGGCCCGGGTTCGATTCCC GGTCAGGGAA
1214	Glu	TTC	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCG CTTTCACCGCNGCGGCCCGGGTTCGATTCCC GGTCAGGGAA
1215	Gly	CCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCC TCCCACGCNGGAGACCCGGGTTCGATTCCCG GCCAATGCA
1216	Gly	GCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCC TGCCACGCGGGAGGCCCGGGTTCGATTCCCG GCCAATGCA
1217	Gly	TCC	GCGTTGGTGGTATAGTGGTGAGCATAGCTGC CTTCCAAGCAGTTGACCCGGGTTCGATTCCC GGCCAACGCA
1218	Ile	AAT	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGT GCTAATAACGCCAAGGTCGCGGGTTCGATCC CCGTACGGGCCA

1219	Ile	TAT	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGT ACTTATAATGCCGAGGTTGTGAGTTCGAGCC TCACCTGGAGCA
1220	Leu	AAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTG GATTAAGGCTCCAGTCTCTTCGGGGGCGTGG GTTCGAATCCCACCGCTGCCA
1221	Leu	CAA	GTCAGGATGGCCGAGTGGTCNTAAGGCGCC AGACTCAAGTTCTGGTCTCCGNATGGAGGCG TGGGTTCGAATCCCACTTCTGACA
1222	Leu	CAG	GTCAGGATGGCCGAGCGGTCTAAGGCGCTG CGTTCAGGTCGCAGTCTCCCCTGGAGGCGTG GGTTCGAATCCCACTCCTGACA
1223	Leu	TAA	ACCAGGATGGCCGAGTGGTTAAGGCGTTGG ACTTAAGATCCAATGGACAGATGTCCGCGTG GGTTCGAACCCCACTCCTGGTA
1224	Leu	TAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTG GATTTAGGCTCCAGTCTCTTCGGNGGCGTGG GTTCGAATCCCACCGCTGCCA
1225	Lys	CTT	GCCCGGCTAGCTCAGTCGGTAGAGCATGAG ACTCTTAATCTCAGGGTCGTGGGTTCGAGCC CCACGTTGGGCGNNN
1226	Lys	TTT	GCCTGGATAGCTCAGTCGGTAGAGCATCAG ACTTTTAATCTGAGGGTCCAGGGTTCAAGTC CCTGTTCAGGCG
1227	Met	CAT	GCCCTCTTAGCGCAGTNGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAGCCT CAGAGAGGGCA
1228	Phe	GAA	GCCGAAATAGCTCAGTTGGGAGAGCGTTAG ACTGAAGATCNTAAAGGTCCCTGGTTCAATC CCGGGTTTCGGCA
1229	Pro	AGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCT TAGGATGCGAGAGGTCCCGGGTTCAAATCC CGGACGAGCCC
1230	Pro	CGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCT TCGGGTGCGAGAGGTCCCGGGTTCAAATCCC GGACGAGCCC
1231	Pro	TGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCT TTGGGTGCGAGAGGTCCCGGGTTCAAATCCC GGACGAGCCC
1232	Ser	AGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGG ACTAGAAATCCATTGGGGTTTCCCCGCGCAG GTTCGAATCCTGCCGACTACG
1233	Ser	CGA	GCTGTGATGGCCGAGTGGTTAAGGCGTTGG ACTCGAAATCCAATGGGGTCTCCCCGCGCAG GTTCGAATCCTGCTCACAGCG

1234	Ser	GCT	GACGAGGNNTGGCCGAGTGGTTAAGGCGAT GGACTGCTAATCCATTGTGCTCTGCACGCGT GGGTTCGAATCCCATCCTCGTCG
1235	Ser	TGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGG ACTTGAAATCCATTGGGGTCTCCCCGCGCAG GTTCGAATCCTGCCGGCTACG
1236	Thr	AGT	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC CCAGCGGGGCCT
1237	Thr	CGT	GGCNCTGTGGCTNAGTNGGNTAAAGCGCCG GTCTCGTAAACCNGGAGATCNTGGGTTCGA ATCCCANCNGGGCCT
1238	Thr	TGT	GGCTCCATAGCTCAGNGGGTTAGAGCACTG GTCTTGTAAACCAGGGGTCGCGAGTTCAAAT CTCGCTGGGGCCT
1239	Trp	CCA	GACCTCGTGGCGCAACGGTAGCGCGTCTGA CTCCAGATCAGAAGGTTGCGTGTTCAAATCA CGTCGGGGTCA
1240	Tyr	GTA	CCTTCGATAGCTCAGCTGGTAGAGCGGAGG ACTGTAGATCCTTAGGTCGCTGGTTCGATTC CGGCTCGAAGGA
1241	Val	AAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCGC CTAACACGCGAAAGGTCCCCGGTTCGAAAC CGGGCGGAAACA
1242	Val	CAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCGC CTCACACGCGAAAGGTCCCCGGTTCGAAAC CGGGCGGAAACA
1243	Val	TAC	GGTTCCATAGTGTAGTGGTTATCACGTCTGC TTTACACGCAGAAGGTCCTGGGTTCGAGCCC CAGTGGAACCA
1244	iMet	CAT	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGG CCCATAACCCAGAGGTCGATGGATCGAAAC CATCCTCTGCTA

Table 10B. Consensus sequence computationally generated for each isodecoder by aligning members of the isodecoder family

SEQ ID NO	Amino Acid	Anticodon	Consensus sequence
1245	Ala	AGC	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGC TTAGCATGCAAGAGGTAGTGGGATCGATGCC CACATTCTCCANNN
1246	Ala	CGC	GGGGATGTAGCTCAGTGGTAGAGCGCATGCT TCGCATGTATGAGGTCCCGGGTTCGATCCCC GGCATCTCCANNN

1247	Ala	TGC	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCT TTGCATGTATGAGGCCCCGGGTTCGATCCCC GGCACCTCCANNN
1248	Arg	ACG	GGGCCAGTGGCGCAATGGATAACGCGTCTGA CTACGGATCAGAAGATTCCAGGTTCGACTCC TGGCTGGCTCGNNN
1249	Arg	CCG	GGCCGCGTGGCCTAATGGATAAGGCGTCTGA TTCCGGATCAGAAGATTGAGGGTTCGAGTCC CTTCGTGGTCGNNN
1250	Arg	CCT	GCCCCAGTGGCCTAATGGATAAGGCACTGGC CTCCTAAGCCAGGGATTGTGGGTTCGAGTCC CACCTGGGGTANNN
1251	Arg	TCG	GACCGCGTGGCCTAATGGATAAGGCGTCTGA CTTCGGATCAGAAGATTGAGGGTTCGAGTCC CTCCGTGGTCGNNN
1252	Arg	TCT	GGCTCTGTGGCGCAATGGATNAGCGCATTGG ACTTCTAATTCAAAGGTTGCGGGTTCGAGTC CCNCCAGAGTCGNNN
1253	Asn	GTT	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTTAACCGNAAAGGTTGGTGGTTCGAGC CCACCCAGGGACGNNN
1254	Asp	GTC	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCC TGTCACGCGGGAGACCGGGGTTCGATTCCCC GACGGGGAGNNN
1255	Cys	GCA	GGGGGTATAGCTCAGNGGGTAGAGCATTTGA CTGCAGATCAAGAGGTCCCCGGTTCAAATCC GGGTGCCCCCTNNN
1256	Gln	CTG	GGTTCCATGGTGTAATGGTNAGCACTCTGGA CTCTGAATCCAGCGATCCGAGTTCAAGTCTC GGTGGAACCTNNN
1257	Gln	TTG	GGTCCCATGGTGTAATGGTTAGCACTCTGGA CTTTGAATCCAGCGATCCGAGTTCAAATCTC GGTGGGACCTNNN
1258	Glu	CTC	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCG CTCTCACCGCCGCGGCCCGGGTTCGATTCCC GGTCAGGGAANNN
1259	Glu	TTC	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCG CTTTCACCGCNGCGGCCCGGGTTCGATTCCC GGTCAGGGAANNN
1260	Gly	CCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCT CCCACGCNGGAGACCCGGGTTCGATTCCCGG CCAATGCANNN
1261	Gly	GCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCT GCCACGCGGGAGGCCCGGGTTCGATTCCCGG CCAATGCANNN

1262	Gly	TCC	GCGTTGGTGGTATAGTGGTGAGCATAGCTGC CTTCCAAGCAGTTGACCCGGGTTCGATTCCC GGCCAACGCANNN
1263	Ile	AAT	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGT GCTAATAACGCCAAGGTCGCGGGTTCGATCC CCGTACGGGCCANNN
1264	Ile	TAT	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGT ACTTATAATGCCGAGGTTGTGAGTTCGAGCC TCACCTGGAGCANNN
1265	Leu	AAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG TTCGAATCCCACCGCTGCCANNN
1266	Leu	CAA	GTCAGGATGGCCGAGTGGTCNTAAGGCGCCA GACTCAAGTTCTGGTCTCCGNATGGAGGCGT GGGTTCGAATCCCACTTCTGACANNN
1267	Leu	CAG	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG GTTCGAATCCCACTCCTGACANNN
1268	Leu	TAA	ACCAGGATGGCCGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGACAGATGTCCGCGTGG GTTCGAACCCCACTCCTGGTANNN
1269	Leu	TAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCTCTTCGGNGGCGTGGG TTCGAATCCCACCGCTGCCANNN
1270	Lys	CTT	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGA CTCTTAATCTCAGGGTCGTGGGTTCGAGCCCC ACGTTGGGCGNNNNNN
1271	Lys	TTT	GCCTGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC TGTTCAGGCGNNN
1272	Met	CAT	GCCCTCTTAGCGCAGTNGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAGCCT CAGAGAGGGCANNN
1273	Phe	GAA	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCNTAAAGGTCCCTGGTTCAATCC CGGGTTTCGGCANNN
1274	Pro	AGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT AGGATGCGAGAGGTCCCGGGTTCAAATCCCG GACGAGCCCNNN
1275	Pro	CGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT CGGGTGCGAGAGGTCCCGGGTTCAAATCCCG GACGAGCCCNNN
1276	Pro	TGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT TGGGTGCGAGAGGTCCCGGGTTCAAATCCCG GACGAGCCCNNN

1277	Ser	AGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGA CTAGAAATCCATTGGGGTTTCCCCGCGCAGG TTCGAATCCTGCCGACTACGNNN
1278	Ser	CGA	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGA CTCGAAATCCAATGGGGTCTCCCCGCGCAGG TTCGAATCCTGCTCACAGCGNNN
1279	Ser	GCT	GACGAGGNNTGGCCGAGTGGTTAAGGCGAT GGACTGCTAATCCATTGTGCTCTGCACGCGT GGGTTCGAATCCCATCCTCGTCGNNN
1280	Ser	TGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGA CTTGAAATCCATTGGGGTCTCCCCGCGCAGG TTCGAATCCTGCCGGCTACGNNN
1281	Thr	AGT	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC CCAGCGGGGCCTNNN
1282	Thr	CGT	GGCNCTGTGGCTNAGTNGGNTAAAGCGCCGG TCTCGTAAACCNGGAGATCNTGGGTTCGAAT CCCANCNGGGCCTNNN
1283	Thr	TGT	GGCTCCATAGCTCAGNGGGTTAGAGCACTGG TCTTGTAAACCAGGGGTCGCGAGTTCAAATC TCGCTGGGGCCTNNN
1284	Trp	CCA	GACCTCGTGGCGCAACGGTAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAATCAC GTCGGGGTCANNN
1285	Tyr	GTA	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGATCCTTAGGTCGCTGGTTCGATTCCG GCTCGAAGGANNN
1286	Val	AAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TAACACGCGAAAGGTCCCCGGTTCGAAACCG GGCGGAAACANNN
1287	Val	CAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCC TCACACGCGAAAGGTCCCCGGTTCGAAACCG GGCGGAAACANNN
1288	Val	TAC	GGTTCCATAGTGTAGTGGTTATCACGTCTGCT TTACACGCAGAAGGTCCTGGGTTCGAGCCCC AGTGGAACCANNN
1289	iMet	CAT	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGG CCCATAACCCAGAGGTCGATGGATCGAAACC ATCCTCTGCTANNN

Table 11: Score values alignment

Row	Candidate nucleotide	Reference nucleotide	Match score
1	A	A	1

2	T	T	1
3	U	T	1
4	C	C	1
5	G	G	1
6	A	N	0
7	T	N	0
8	C	N	0
9	G	N	0
10	N	A	0
11	N	T	0
12	N	C	0
13	N	G	0
14	N	N	0

Premature termination codons (PTC) and ORFs comprising PTCs

Mutations underlie many diseases. For example, a point mutation in the open reading frame (ORF) of a gene which creates a premature stop codon (PTC) can result in altered expression and/or activity of a polypeptide encoded by the gene. Table 15 provides single mutations in codons encoding amino acids which can result in a stop codon. In an embodiment, a PTC disclosed herein comprises a mutation disclosed in Table 15.

In an embodiment, the codon having the first sequence or the PTC comprises a mutation disclosed in Table 15. In an embodiment, the non-mutated, e.g., wildtype, codon sequence of the codon having the first sequence or the PTC is an original codon sequence provided in Table 15 and the amino acid corresponding to the non-mutated codon is an original AA provided in Table 15.

In an embodiment, the TREM, TREM core fragment or TREM fragment recognizes a stop codon and mediates incorporation of the original AA provided in Table 15 at the position of the stop codon. In an embodiment, the TREM, TREM core fragment or TREM fragment recognizes a stop codon and mediates incorporation of an amino acid belonging to the same group as the original AA, e.g., as provided in Table 16. Other genetic abnormalities, such as insertions and/or deletions can also result in a PTC in an ORF.

Table 15. Select amino acids and stop codons

Original AA	Original codon	One mutation to stop codon

TRP	UGG	UGA
TYR	UAU	UAA
	UAC	UAG
CYS	UGU	UGA
	UGC	UGA
GLU	GAA	UAA
	GAG	UAG
LYS	AAA	UAA
	AAG	UAG
GLN	CAA	UAA
	CAG	UAG
SER	UCA	UGA
	UCG	UAG
LEU	UUA	UAA OR UGA
	UUG	UAG
ARG	CGA	UGA
GLY	GGA	UGA

Table 16: Amino acids and amino acid groupings

Group	**Amino acid**
Nonpolar, aliphatic R group	leucine methionine isoleucine glycine alanine valine
Polar, uncharged R group	serine threonine cysteine proline asparagine glutamine
positively charged r group	lysine arginine histidine
Negatively charged R group	aspartate glutamate
Nonpolar, aromatic R group	phenylalanine tyrosine tryptophan

Disclosed herein, inter alia, are endogenous ORFs comprising a codon having a first sequence, e.g., a mutation, e.g., a PTC. An ORF having a PTC, e.g., as described herein, can be

present, or part of in any gene. As an example, the ORF can be present or be part of any gene in the human genome.

In an embodiment, a PTC disclosed herein is present in a gene disclosed in any one of Tables 17, 18, or 20. Exemplary genes having ORFs comprising a PTC are provided in Table 3.

Table 17: Exemplary genes with ORFs having a PTC

A2ML1	ARFGEF1	CACNA1G	CNOT1	DLG4
AARS1	ARFGEF2	CACNA1S	COG1	DLL1
AARS2	ARHGAP21	CACNA2D1	COL11A2	DNA2
ABCA13	ARHGEF9	CACNA2D2	COL13A1	DNM1L
ABCB11	ARMC4	CACNB2, NSUN6	COL4A1	DNMT1
ABCG5	ARV1	CAD	COL4A2	DNMT3A
ABHD5	ARX	CAMTA1	COL4A4	DNMT3B
ACAD8	ASCC3	CARS2	COL9A1	DPH1
ACADL	ASH1L	CCDC140	COQ4	DPYD-AS1
ACSF3	ASPH	CCDC8	COQ6	DSEL
ACTA2	ASXL2	CCM2	COX14	DSPP
ACTC1,	ATAD3A	CD40LG	CPE	DUOXA1
ACTN2	ATP2A2	CDAN1	CPEB1-AS1	DUOXA2
ACVR1	ATP6V1B1	CDH15	CREBBP	DVL1
ADAR	ATP8A2	CDK11A	CRELD1	EARS2
ADAT3	AUH	CEBPA	CSNK2A1	EBF3
ADCY5	AUTS2	CELF5	CSNK2B	EBP
ADIPOQ	AVPR2	CELSR2	CSTA	EDAR
ADIPOQ-AS1	B3GLCT	CEP135	CTNND2	EFHC1
ADIPOR1	B4GAT1	CEP164	CTSA	EFNB1
AFF2	BCAP31	CEP83	CTSC	EFTUD2
ALG11	BCL11A	CETP	CUL3	EIF2B5
ALG14	BCL11B	CFI	CYLD	ELANE
ALG6	BCORL1	CHAMP1	CYP11A1	EMC1
ALOXE3	BEND2	CHAT	DAG1	EMC1-AS1
AMER1	BGN	CHD1	DARS2	ENO3
AMH	BMP4	CHD4	DCX	ENTPD5
AMMECR1	BRD4	CHD8	DDHD2	EP300
AMN	BRPF1	CHRM2	DDR2	EPM2A
ANK2	BRSK2	CHRNB1	DEAF1	ERLIN2
ANK3	BUB1B	CIC	DENND5A	EVC
ANKS6	BUB1B-PAK6	CLCN7	DGAT1	EZH2
ANOS1	C8G	CLTC	DHFR	FAM111A

AP1S1	CACNA1E	CNGA3	DIAPH3	FAM126A
AP3B2	CACNA1F	CNKSR2	DISP1	FAN1
FANCD2	GJB6	ISLR2	LOC110673972	MTR
FANCE	GJC2	ITGA3	LOC112997540	MYCBP2
FASTKD2	GK	ITGA8	LOC113788297	MYCNOS
FAT1	GLI2	ITGB6	LOC349160	MYH7B
FBN2	GNAI1	JMJD1C	LONP1	MYL3
FBP1	GNB1L	KANK1	LORICRIN	MYOM1
FDXR	GNE	KANSL1	LPIN1	MYPN
FGA	GNRH1	KBTBD13	LPIN2	MYT1L
FGD1	GNS	KCNA2	LRP2	NAA15
FGF10	GPAA1	KCNB1	LRRTM4	NAGA
FGFR1	GPD1L	KCND2	MAB21L2	NARS2
FGFR2	GRIN2A	KCNE3	MAF	NAXE
FIBP	GTPBP3	KCNMA1	MARS1	NCAPH2
FLAD1	HACE1	KCNQ5	MARS2	NCF2
FLG-AS1	HADH	KCTD7	MASP1	NDP
FLVCR1	HADHB	KIDINS220	MBOAT7	NDP-AS1
FLVCR2	HDAC4	KIF21B	MCM3AP	NDRG1
FMN2	HERC1	KIF6	MCM3AP-AS1	NDUFA2, TMCO6
FOXA2	HESX1	KIT	MED13	NDUFAF1
FOXC1	HIBCH	KLHL40	MED17	NDUFAF5
FOXC2	HNF4A	KLHL41	MEGF10	NDUFAF6
FOXC2-AS1	HNRNPH2	KNL1	MET	NDUFAF7
FOXP2	HPRT1	KRAS	MGAT2	NDUFS1
FREM1	HRG	LAMB1	MIB1	NDUFS3
FRYL	HUWE1	LAMB2	MICU1	NEFH
FTL	IARS1	LAMC3	MIR302CHG	NEK8
FUS	IBA57	LARP7	MIR5004	NEXMIF
GABRG2	IDH2	LARS1	MIR6501	NFIA
GAN	IFNAR1	LCT	MITD1	NFKB1
GATA2	IFT122	LEMD3	MMP13	NHEJ1
GATA4	IFT80	LGI4	MMP21	NICN1
GATAD1	IGF2	LIAS	MNX1	NID1
GDF5	ILDR1	LINS1	MNX1-AS2	NKX2-1
GDF5-AS1	ILK, TAF10	LIPC	MPDU1	NLRP1
GFM1	INF2	LIPT1	MRPS22	NLRP3
GH-LCR	INS-IGF2	LOC101448202	MSL3	NOD2
GHRHR	INSR	LOC106804612, HBA2	MSRB3	NONO

GHSR	IRAK1BP1	LOC107303338	MT-ND2	NOTCH3
GJA1	IRAK3	RARS2	SETD1B	SPTLC1
NPHP4	PLEKHG5	RAX	SETD2	SRD5A3
NPR2	PLEKHM2	RBM10	SETX	SRPX2
NR2F2	PLK4	RELN	SFTA3	SSBP2
NR5A1	PLPBP	RERE	SHANK2	ST3GAL3
NRL, PCK2	PNKD	RFT1	SHH	ST3GAL5
NRXN1	PNPLA1	RMND1	SIN3A	STAMBP
NT5DC1	POC1A	RNASEH1	SIX3	STAT3
NTRK2	POLG2, MILR1	RNF17	SKI	STIL
NUBPL	POMGNT2	ROR2	SLC13A5	STX11
NUS1	PPM1D	RP2	SLC16A1	STX1B
OCRL	PPP3CA	RPL11	SLC16A2	SUCLA2
OPTN	PRDM1	RPS19	SLC17A8	SYN1
P4HA1	PRDM12	RRM2B	SLC18A3	SYN2
PAK6	PREPL	RS1	SLC20A2	SYNJ1
PBX1	PRICKLE1	RUNX2	SLC25A4	TAB2
PCARE	PRKAG2	RXYLT1	SLC25A46	TACR3
PCDH12	PROS1	S100PBP	SLC2A1	TBCD
PDCD10	PRPF31	SALL4	SLC39A8	TBL1XR1
PDE11A-AS1	PRPF8	SAMD9	SLC52A2	TBX1
PDE4D	PRPS1	SAR1B	SLC6A3	TBX18
PDE6A	PRSS1, TRB	SASH3	SLC6A8	TCIRG1
PDHX	PSAT1	SBF2	SLC6A9	TELO2
PDLIM3	PSMD12	SBF2-AS1	SLC7A9	TFAP2A
PDP1	PSTPIP1	SCAMP4	SMAD2	TFG
PDSS1	PTCHD1	SCLT1	SMAD9	TGIF1
PEX5	PTF1A	SCN10A	SMARCA2	THAP1
PHF21A	PTPN23	SCN11A	SMC3	TINF2
PHF8	PTPRQ	SCN1B	SMOC2	TLK2
PHKA2	PTRH2	SCN3A	SNTA1	TMEM43
PHKB	PUS1	SCN4A	SNX14	TMIE
PIEZO1	PYCR2	SCN4B	SNX22	TMPO
PIGG	QARS1	SCN8A	SOCS1	TMPRSS15
PIGL	RAB3GAP1, ZRANB3	SCO2	SOX11	TMTC3
PIGM	RAB3GAP2	SCYL1	SOX17	TNFAIP3
PIGP	RAC1	SEMA4A	SPATA5	TNFRSF11A
PIK3CA	RAF1	SEPTIN9	SPATA7	TOE1
PIN4, ERCC6L	RAG1	SET	SPRED1	TOR1AIP1
PLAT	RARB	SETD1A	SPTBN2	TPK1

TPM1	UTP14C	ZEB1		
TRAPPC9	VPS53	ZFHX4		
TRIM37	WDR19	ZFPM2		
TRIM59-IFT80	WDR26	ZFPM2-AS1		
TRIO	WDR62	ZIC1		
TRIP12	WDR81	ZIC2		
TRIP4	WNT1	ZMYND11		
TRPM1	WNT10A	ZNF335		
TSEN54	WRAP53	ZNF423		
TUBA4A	WWOX	ZNF469		
TUBGCP4	YARS1			
TUBGCP6	YARS2			
TWNK	YY1			
TXNRD2	ZAP70			
UBA2	ZBTB20			
UBA5	ZBTB24			
UMOD	ZC4H2			
UNC5B	ZDHHC9			

Additional exemplary genes containing a PTC include FVIII, FIX, CFTR, MeCP2, NAGLU, DMD, GAA, RP1, RP2, ABCA4, PCDH15, REP1, GLA, MUT, TP53, and ATM. In an embodiment, the PTC is present within the FVIII gene and comprises an R mutation, e.g., an R2228X mutation. In an embodiment, the PTC is present within the FIX gene and comprises an R mutation, e.g., an R29X mutation, an R116X mutation, an R248X mutation, an R252X mutation, an R333X mutation, and/or an R338X mutation. In an embodiment, the PTC is present within the CFTR gene and comprises an R mutation, e.g., an R553X mutation. In an embodiment, the PTC is present within the MeCP2 gene and comprises an R mutation, e.g., an R168X mutation. In an embodiment, the PTC is present within the NAGLU gene and comprises an R mutation, e.g., an R626X mutation. In an embodiment, t the PTC is present within the DMD gene and comprises an R mutation, e.g., an R3881X mutation. In an embodiment, the PTC is present within the GAA gene and comprises an R mutation, e.g., an R854X mutation. In an embodiment, the PTC is present within the RP1 gene and comprises an R mutation, e.g., an R667X mutation. In an embodiment, the PTC is present within the RP2 gene and comprises an R mutation, e.g., an R120X mutation. In an embodiment, the PTC is present within the ABCA4 gene and comprises an R mutation, e.g., an R2030X mutation. In an embodiment, the PTC is

present within the PCD gene and comprises an R mutation, e.g., an R245X mutation. In an embodiment, the PTC is present within the REP1 gene and comprises an R mutation, e.g., an R270X mutation. In an embodiment, the PTC is a mutation in the GLA gene, e.g., an R220X mutation and/or an R227X mutation. In an embodiment, the PTC is present within the MUT gene and comprises an R mutation, e.g., an R228X mutation, an R403X mutation, an R467X mutation, and/or an R727X mutation. In an embodiment, the PTC is present within the TP53 gene and comprises an R mutation, e.g., an R578X mutation. In an embodiment the PTC is present within the ATM gene and comprises an R mutation, e.g., an R35X mutation.

Diseases or disorders associated with a PTC

A TREM composition disclosed herein can be used treat a disorder or disease associated with a PTC, e.g., as described herein. Exemplary diseases or disorders associated with a PTC are listed in Tables 18, 19, and 20.

In an embodiment, the subject has a disease or disorder provided in any one of Tables 4-6. In an embodiment, the cell is associated with, e.g., is obtained from a subject who has, a disorder or disease listed in any one of Tables 18-20.

For example, the disorder or disease can be chosen from the left column of Table 18. As another example, the disorder or disease is chosen from the left column of Table 18 and, in embodiments the PTC is in a gene chosen from the right column of Table 18, e.g., any one of the genes provided in the right column of Table 18. In some embodiments, the PTC is in a gene corresponding to the disorder or disease provided in the left column of Table 18. As a further non-limiting example, the PTC can be at a position provided in Table 18.

As another example, the disorder or symptom is chosen from a disorder or disease provided in Table 19.

As yet another exmaple, the disorder or symptom is chosen from a disorder or disease provided in Table 20. In an embodiment, the disorder or symptom is chosen from a disorder or disease provided in Table 20 and, in embodiments, the PTC is in any gene provided in Table 20. In an embodiment, the disorder or symptom is chosen from a disorder or disease provided in Table 20 and the PTC is in a corresponding gene provided in Table 20, e.g., a gene corresponding to the disease or disorder. In an embodiment, the disorder or symptom is chosen

from a disorder or disease provided in Table 20 and the PTC is not in a gene provided in Table 20.

In an embodiment of any of the methods disclosed herein, the PTC is at any position within the ORF of the gene, e.g., upstream of the naturally occurring stop codon.

Table 18: Exemplary diseases or disorders

Disease/disorder or protein	Exemplary Point Mutation
G to A point mutations	
Dihydropyrimidine dehydrogenase deficiency	NM 000110.3(DPYD):c.1905+1G>A
Noonan syndrome	NM 005633.3(SOS1):c.2536G>A (p.Glu846Lys)
Lynch syndrome	NM 000251.2(MSH2):c.212-1G>A
Breast-ovarian cancer, familial **1**	NM 007294.3(BRCA1):c.963G>A (p.Trp321Ter)
Cystic fibrosis	NM 000492.3(CFTR):c.57G>A (p.Trpl9Ter)
Anemia, due to G6PD deficiency	NM 000402.4(G6PD):c.292G>A (p.Val98Met)
AVPR2 Nephrogenic diabetes insipidus, X-linked	NM 000054.4(AVPR2):c.878G>A (p.Trp293Ter)
FANCC Fanconi anemia, complementation group C	NM 000054.4(AVPR2):c.878G>A (p.Trp293Ter)
FANCC Fanconi anemia, complementation group C	NM 000136.2(FANCC):c.1517G>A (p.Trp506Ter)
IL2RG X-linked severe combined immunodeficiency	NM 000206.2(IL2RG):c.710G>A (p.Trp237Ter)
F8 Hereditary factor VIII deficiency disease	NM 000132.3(F8):c.3144G>A (p.Trpl048Ter)
LDLR Familial hypercholesterolemia	NM 000527.4(LDLR):c.1449G>A (p.Trp483Ter)
CBS Homocystinuria due to CBS deficiency	NM 000071.2(CBS):c.162G>A (p.Trp54Ter)
HBB betaThalassemia	NM 000518.4(HBB):c.114G>A (p.Trp38Ter)
ALDOB Hereditary fmctosuria	NM 000035.3(ALDOB):c.888G>A (p.Trp296Ter)
DMD Duchenne muscular dystrophy	NM 004006.2(DMD):c.3747G>A (p.Trpl249Ter)
SMAD4 Juvenile polyposis syndrome	NM 005359.5(SMAD4):c.906G>A (p.Trp302Ter)
BRCA2 Familial cancer ofbreastlBreast-ovarian cancer, familial 2	NM 000059.3(BRCA2):c.582G>A (p.Trpl94Ter)

GRIN2A Epilepsy, focal, with speech disorder and with or without mental retardation	NM 000833.4(GRIN2A):c.3813G>A (p.Trpl271Ter)
SCN9A Indifference to pain, congenital, autosomal recessive	NM 002977.3(SCN9A):c.2691G>A (p.Trp897Ter)
TARDBP Amyotrophic lateral sclerosis type 10	NM 007375.3(TARDBP):c.943G>A (p.Ala315Thr)
CFTR Cystic fibrosislHereditary pancreatitislnot providedlataluren response - Efficacy	NM 000492.3(CFTR):c.3846G>A (p.Trpl282Ter)
UBE3A Angelman syndrome	NM 130838. l(UBE3A):c.2304G>A (p.Trp768Ter)
SMPD**1** Niemann-Pick disease, type A	NM 000543.4(SMPD1):c.168G>A (p.Trp56Ter)
USH2A Usher syndrome, type 2A	NM 206933.2(USH2A):c.9390G>A (p.Trp3130Ter)
MENl Hereditary cancer-predisposing syndrome	NM 130799.2(MEN1):c.1269G>A (p.Trp423Ter)
C8orf37 Retinitis pigmentosa 64	NM 177965.3(C8orf37):c.555G>A (p.Trpl85Ter)
MLHl Lynch syndrome	NM 000249.3(MLH1):c.1998G>A (p.Trp666Ter)
TSC2 Tuberous sclerosis 21Tuberous sclerosis syndrome 46	NM 000548.4(TSC2):c.2108G>A (p.Trp703Ter)
NFl Neurofibromatosis, type **1**	NM 000267.3(NF1):c.7044G>A (p.Trp2348Ter)
MSH6 Lynch syndrome	NM 000179.2(MSH6):c.3020G>A (p.Trpl007Ter)
SMNl Spinal muscular atrophy, type III Kugelberg- Welander disease	NM 000344.3(SMN1):c.305G>A (p.Trpl02Ter)
SH3TC2 Charcot-Marie-Tooth disease, type 4C	NM 024577.3(SH3TC2):c.920G>A (p.Trp307Ter)
DNAH5 Primary ciliary dyskinesia	NM 001369.2(DNAH5):c.8465G>A (p.Trp2822Ter)
MECP2 Rett syndrome	NM 004992.3(MECP2):c.311G>A (p.Trpl04Ter)
ADGRVl Usher syndrome, type 2C	NM 032119.3(ADGRV1):c.7406G>A (p.Trp2469Ter)
AHil Joubert syndrome 3	NM 017651.4(AHI1):c.2174G>A (p.Trp725Ter)
PRKN	NM 004562.2(PRKN):c.1358G>A

Parkinson disease 2	(p.Trp453Ter)
COL3Al Ehlers-Danlos syndrome, type 4	NM 000090.3(COL3Al):c.3833G>A (p.Trpl278Ter)
BRCAl Familial cancer ofbreastlBreast-ovarian cancer, familial 1	NM 007294.3(BRCA1):c.5511G>A (p.Trpl837Ter)
MYBPC3 Primary familial hypertrophic cardiomyopathy	NM 000256.3(MYBPC3):c.3293G>A (p.Trpl098Ter)
APC Familial adenomatous polyposis 1	NM 000038.5(APC):c.1262G>A (p.Trp421Ter)
BMPR2 Primary pulmonary hypertension	NM 001204.6(BMPR2):c.893G>A (p.W298*)
T to C point mutations	
Wilson disease	NM_000053.3(ATP7B):c.3443T>C (p.Ile **1 1** 48Thr)
Leukodystrophy, hypomyelinating, 2	NM_020435.3(GJC2):c.857T>C (p.Met286Thr)
Alport syndrome, X-linked recessive	NM_000495.4(COL4A5):c.438+2T>C
Leigh disease	NC 012920.l:m.9478T>C
Gaucher disease, type **1**	NM_001005741.2(GBA):c.751T>C (p.Tyr251His)
Renal dysplasia, retinal pigmentary dystrophy, cerebellar ataxia and skeletal dysplasia	NM_0l4714.3(IFT140):c.4078T>C (p.Cysl360Arg)
Marfan syndrome	NM_000138.4(FBN1):c.3793T>C (p.Cysl265Arg)
Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase	NM_000155.3(GALT):c.482T>C (p.Leul61Pro)
Familial hypercholesterolemia	NM_000527.4(LDLR):c.694+2T>C
Episodic pain syndrome, familial, 3	NM_001287223.l(SCN11A):c.1142T>C (p.Ile381Thr)
Navajo neurohepatopathy	NM_002437.4(MPV17):c.186+2T>C
Congenital muscular dystrophy, LMNA-related	NM_l 70707.3(LMNA):c.l139T>C (p.Leu380Ser)
Hereditary factor VIII deficiency disease	NM_000132.3(F8):c.5372T>C (p.Metl 791Thr)
Insulin-dependent diabetes mellitus secretory diarrhea syndrome	NM_0l4009.3(FOXP3):c.970T>C (p.Phe324Leu)
Hereditary factor IX deficiency disease	NM_000133.3(F9):c.1328T>C (p.Ile443Thr)
Familial cancer of breast, Breast-ovarian cancer, familial 2, Hereditary cancer predisposing syndrome	NM_000059.3(BRCA2):c.316+2T>C

Cardiac arrhythmia	NM_000238.3(KCNH2):c.1945+6T>C
Tangier disease	NM_005502.3(ABCA1):c.4429T>C (p.Cysl477Arg)
Dilated cardiomyopathy lAA	NM_001103.3(ACTN2):c.683T>C (p.Met228Thr)
Mental retardation 3, X-linked	NM_005334.2(HCFC1):c.-970T>C
Limb-girdle muscular dystrophy, type 2B	NM_003494.3(DYSF):c.1284+2T>C
Macular dystrophy, vitelliform, 5	NM_0l6247.3(IMPG2):c.370T>C (p.Phel24Leu)
Retinitis pigmentosa	NM_000322.4(PRPH2):c.736T>C (p.Trp246Arg)

Table 19: Additional exemplary disorders

5q-syndrome	Adams-Oliver syndrome 1
Adams-Oliver syndrome 3	Adams-Oliver syndrome 5
Adams-Oliver syndrome 6	Alagille syndrome 1
Autoimmune lymphoproliferative syndrome type IA	Autoimmune lymphoproliferative syndrome type V
Autosomal dominant deafness-2A	Brain malformations with or without urinary tract defects (BRMUTD)
Carney complex type 1	CHARGE syndrome
Cleidocranial dysplasia	Currarino syndrome
Denys-Drash syndrome / Frasier syndrome	Developmental delay
intellectual disability	obesity
and dysmorphic features (DIDOD)	DiGeorge syndrome (TBXl-associated)
Dravet syndrome	Duane-radial ray syndrome
Ehlers-Danlos syndrome (classic-like)	Ehlers-Danlos syndrome (vascular type)
Feingold syndrome 1	Frontotemporal lobar degeneration with TDP43 inclusions (FTFD-TDP)
GRN-related	GFUT1 deficiency syndrome
Greig cephalopolysyndactyly syndrome	Hereditary hemorrhagic telangiectasia type 1

Holoprosencephaly 3	Holoprosencephaly 4
Holoprosencephaly 5	Holt-Oram syndrome
Hypoparathyroidism	sensorineural deafness
and renal disease (HDR)	Kleefstra syndrome 1
Klippel-Trenaunay syndrome (AAGF-related)	Feri-Weill dyschondrosteosis
Marfan syndrome	Mental retardation and distinctive facial features with or without cardiac defects (MRFACD)
Mental retardation	autosomal dominant 1
Mental retardation	autosomal dominant 19
Mental retardation	autosomal dominant 29
Nail-patella syndrome (NPS)	Phelan-McDermid syndrome
Pitt-Hopkins syndrome	Primary pulmonary hypertension 1
Rett syndrome (congenital variant)	Smith-Magenis syndrome (RAI1-associated)
Sotos syndrome 1	Sotos syndrome 2
Stickler syndrome type I	Supravalvular aortic stenosis
SYNGAP1 -related intellectual disability	Treacher Collins syndrome
Trichorhinophalangeal syndrome type I	Ulnar-mammary syndrome
van der Woude syndrome 1	Waardenburg syndrome type 1
Waardenburg syndrome type 2A	Waardenburg syndrome type 4C.

Table 20: Exemplary genes with ORFs comprising a PTC and exemplary disorders

Gene	**Disease/Disorder**
AAAS	Glucocorticoid deficiency with achalasia
AAGAB	Keratosis palmoplantaris papulosa
AASS	Hyperlysinemia
ABCA1	Tangier disease

ABCA12, SNHG31	Autosomal recessive congenital ichthyosis 4B
ABCA3	3, Surfactant metabolism dysfunction, pulmonary
ABCA4	Bietti crystalline corneoretinal dystrophy, Cone-rod degeneration, Cone-rod dystrophy 3, Macular dystrophy, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 19, Stargardt disease, Stargardt disease 1
ABCB4	Cholestasis, Progressive familial intrahepatic cholestasis 3, intrahepatic, of pregnancy 3
ABCC2	Dubin-Johnson syndrome
ABCC6	Cutis laxa, Generalized arterial calcification of infancy 2, Papule, Pseudoxanthoma elasticum, forme fruste
ABCC8	1, Familial hyperinsulinism, Hyperinsulinemic hypoglycemia, familial
ABCC9	Arrhythmogenic right ventricular cardiomyopathy, Cardiomyopathy, Cardiovascular phenotype, Dilated cardiomyopathy 1O, Primary dilated cardiomyopathy
ABCD1	Adrenoleukodystrophy, Spastic gait, Spastic paraplegia
ABHD12	Polyneuropathy, and cataract, ataxia, hearing loss, retinitis pigmentosa
ABRAXAS1	Hereditary breast and ovarian cancer syndrome
ACAD9	Acyl-CoA dehydrogenase family, deficiency of, member 9
ACADM	Medium-chain acyl-coenzyme A dehydrogenase deficiency
ACADS	Deficiency of butyryl-CoA dehydrogenase
ACADVL	Very long chain acyl-CoA dehydrogenase deficiency
ACAN	Osteochondritis dissecans, Spondyloepiphyseal dysplasia, kimberley type
ACAT1	Deficiency of acetyl-CoA acetyltransferase
ACBD5	RETINAL DYSTROPHY WITH LEUKODYSTROPHY
ACBD6, LHX4, LHX4-AS1	Short stature-pituitary and cerebellar defects-small sella turcica syndrome
ACE	Renal dysplasia
ACOX1	Peroxisomal acyl-CoA oxidase deficiency
ACP5	Spondyloenchondrodysplasia with immune dysregulation
ACP5, ZNF627	Spondyloenchondrodysplasia with immune dysregulation
ACTA1	Congenital myopathy with excess of thin filaments
ACTB	Baraitser-Winter syndrome
ACVRL1	Hereditary hemorrhagic telangiectasia type 1, Primary pulmonary hypertension, Pulmonary arterial hypertension related to hereditary hemorrhagic telangiectasia, Telangiectasia, hereditary hemorrhagic, type 2
ACY1	Neurological conditions associated with aminoacylase 1 deficiency
ADA	Severe combined immunodeficiency disease, Severe combined immunodeficiency due to ADA deficiency
ADAM10	Reticulate acropigmentation of Kitamura
ADAMTS17	Weill-Marchesani syndrome 4
ADAMTS2	Ehlers-Danlos syndrome dermatosparaxis type
ADAMTSL4	Ectopia lentis et pupillae

ADAMTSL4	Ectopia lentis, Ectopia lentis 2, Ectopia lentis et pupillae, autosomal recessive, isolated
ADCY3	BODY MASS INDEX QUANTITATIVE TRAIT LOCUS 19
ADCY3, CENPO	BODY MASS INDEX QUANTITATIVE TRAIT LOCUS 19
ADGRG1	Polymicrogyria, bilateral frontoparietal
ADGRG2	Congenital bilateral aplasia of vas deferens from CFTR mutation, Vas deferens, X-linked, congenital bilateral aplasia of
ADGRG6	Arthrogryposis multiplex congenita, Lethal congenital contracture syndrome 9
ADGRV1	4, Febrile seizures, Rare genetic deafness, Retinal dystrophy, Usher syndrome, familial, type 2C
ADNP	Helsmoortel-Van der Aa Syndrome, History of neurodevelopmental disorder, Inborn genetic diseases
AEBP1	2, CLASSIC-LIKE, EHLERS-DANLOS SYNDROME
AGA	Aspartylglucosaminuria
AGK	Sengers syndrome
AGK, DENND11	Cataract, Sengers syndrome, autosomal recessive congenital 5
AGL	Glycogen storage disease, Glycogen storage disease IIIa, Glycogen storage disease IIIb, Glycogen storage disease type III
AGPAT2	Congenital generalized lipodystrophy type 1
AGRN	Congenital myasthenic syndrome
AGT	Renal dysplasia
AGTR1	Renal dysplasia
AGXT	Primary hyperoxaluria, type I
AHDC1	Delayed speech and language development, Global developmental delay, Intellectual disability, Muscular hypotonia, Neonatal hypotonia, Sleep apnea, Xia-Gibbs syndrome
AHI1	Joubert syndrome, Joubert syndrome 3, Retinal dystrophy, Retinitis pigmentosa
AHR	Retinitis pigmentosa 85
AIRE	Autoimmune polyglandular syndrome type 1, Polyglandular autoimmune syndrome, type 1, with reversible metaphyseal dysplasia
ALB	Analbuminemia
ALDH18A1	Cutis laxa-corneal clouding-oligophrenia syndrome
ALDH3A2	SjÃ¶gren-Larsson syndrome
ALDH5A1	Succinate-semialdehyde dehydrogenase deficiency
ALDH7A1	Pyridoxine-dependent epilepsy, Seizures
ALDOB	Hereditary fructosuria
ALG1	ALG1-CDG, Congenital disorder of glycosylation
ALG3	ALG3-CDG
ALMS1	Alstrom syndrome
ALOX12B	Autosomal recessive congenital ichthyosis 2
ALPK3	CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC 27, Hypertrophic cardiomyopathy
ALPL	Hypophosphatasia, Infantile hypophosphatasia

ALS2	Amyotrophic lateral sclerosis type 2, Infantile-onset ascending hereditary spastic paralysis, Juvenile primary lateral sclerosis
ALX4	Parietal foramina 2
AMPD2	Pontocerebellar hypoplasia, type 9
AMT	Non-ketotic hyperglycinemia
ANAPC1	Rothmund-Thomson syndrome type 1
ANGPTL3, DOCK7	2, Hypobetalipoproteinemia, familial
ANKRD1	ANKRD1-related dilated cardiomyopathy, Cardiovascular phenotype, Primary dilated cardiomyopathy
ANKRD11	Abnormal facial shape, Clinodactyly of the 5th finger, Conductive hearing impairment, Delayed speech and language development, Global developmental delay, Inborn genetic diseases, Intellectual disability, KBG syndrome, Ptosis, Seizures, Short foot, Short palm, Unilateral cryptorchidism
ANO10	Autosomal recessive cerebellar ataxia, Spinocerebellar ataxia, autosomal recessive 10
ANO5	ANO5-Related Disorders, Achilles tendon contracture, Elevated serum creatine phosphokinase, Gnathodiaphyseal dysplasia, Limb-girdle muscular dystrophy, Lower limb amyotrophy, Lower limb muscle weakness, Miyoshi muscular dystrophy 3, Muscular Diseases, Polycystic kidney dysplasia, type 2L
ANTXR1	Odontotrichomelic syndrome
AP1B1	Autosomal recessive keratitis-ichthyosis-deafness syndrome
AP3B1	Hermansky-Pudlak syndrome 2
AP4B1, AP4B1-AS1	Inborn genetic diseases, Spastic paraplegia 47, autosomal recessive
AP4M1	Spastic paraplegia 50, autosomal recessive
AP5Z1	Spastic paraplegia 48, autosomal recessive
APC	Adenomatous colonic polyposis, Adenomatous polyposis coli with congenital cholesteatoma, Brain tumor-polyposis syndrome 2, Carcinoma of colon, Colon adenocarcinoma, Colorectal cancer, Craniopharyngioma, Desmoid disease, Desmoid tumors, Duodenal polyposis, Familial adenomatous polyposis, Familial adenomatous polyposis 1, Familial multiple polyposis syndrome, Gardner syndrome, Gastric polyposis, Hepatocellular carcinoma, Hereditary cancer-predisposing syndrome, Hyperplastic colonic polyposis, Intestinal polyp, Malignant Colorectal Neoplasm, Neoplasm of stomach, Neoplasm of the large intestine, Periampullary adenoma, hereditary, susceptibility to
APOA1, APOA1-AS	Familial hypoalphalipoproteinemia
APOB	1, Familial hypobetalipoproteinemia, Hypobetalipoproteinemia, familial, normotriglyceridemic
APOC2	APOLIPOPROTEIN C-II (NIJMEGEN), Apolipoprotein C2 deficiency
APOC2, APOC4-APOC2	APOLIPOPROTEIN C-II (PADOVA), Apolipoprotein C2 deficiency
APTX	Ataxia-oculomotor apraxia type 1
AR	Androgen resistance syndrome, Bulbo-spinal atrophy X-linked, Partial androgen insensitivity syndrome

ARCN1	Short stature, and developmental delay, micrognathia, rhizomelic, with microcephaly
ARG1, MED23	Arginase deficiency
ARHGEF18	Retinitis pigmentosa 78
ARID1A	Mental retardation, autosomal dominant 14
ARID1B	Absent speech, Blepharophimosis, Coffin-Siris syndrome 1, Constipation, Decreased body weight, Failure to thrive, Inborn genetic diseases, Intellectual disability, Long eyelashes, Microcephaly, Recurrent respiratory infections, Seizures, Short stature, Thick lower lip vermilion, Thin upper lip vermilion, moderate
ARID2	COFFIN-SIRIS SYNDROME 6
ARL2BP	Retinitis pigmentosa 82 with or without situs inversus
ARMC2	Male infertility with teratozoospermia due to single gene mutation, SPERMATOGENIC FAILURE 38, Sperm tail anomaly
ARMC2, ARMC2-AS1	Male infertility with teratozoospermia due to single gene mutation, SPERMATOGENIC FAILURE 38
ARMC5	Acth-independent macronodular adrenal hyperplasia 2
ARSA	Metachromatic leukodystrophy, Pseudoarylsulfatase A deficiency, late infantile
ARSB	Metachromatic leukodystrophy, Mucopolysaccharidosis type 6
ART4	Blood group, Dombrock system
ASAH1	Farber disease, Spinal muscular atrophy-progressive myoclonic epilepsy syndrome
ASL	Argininosuccinate lyase deficiency
ASPA, SPATA22	Canavan Disease, Familial Form, Spongy degeneration of central nervous system
ASPM	Microcephaly, Primary autosomal recessive microcephaly, Primary autosomal recessive microcephaly 1, Primary autosomal recessive microcephaly 5
ASS1	Citrullinemia type I
ASXL1	Bohring-Opitz syndrome, Inborn genetic diseases
ASXL3	Bainbridge-Ropers syndrome
ATF6	Achromatopsia, Achromatopsia 7
ATL1	Hereditary spastic paraplegia 3A
ATM	Ataxia-telangiectasia syndrome, Familial cancer of breast, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms
ATM, C11orf65, ATP13A2	Ataxia-telangiectasia syndrome, Ataxia-telangiectasia without immunodeficiency, Breast cancer, Familial cancer of breast, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Neoplasm of the breast, susceptibility to Kufor-Rakeb syndrome
ATP1A2	Abnormality of neuronal migration, Arthrogryposis multiplex congenita, Epilepsy, Hydrops fetalis
ATP2A1	Brody myopathy
ATP2C1	Familial benign pemphigus
ATP6V0A2	ALG9 congenital disorder of glycosylation, Cutis laxa with osteodystrophy
ATP6V0A4	Renal tubular acidosis, autosomal recessive, distal
ATP7A	Cutis laxa, Menkes kinky-hair syndrome, X-linked

ATP7B	Inborn genetic diseases, Wilson disease
ATRX	1, Alpha thalassemia-X-linked intellectual disability syndrome, Intellectual disability, Mental retardation-hypotonic facies syndrome, Mental retardation-hypotonic facies syndrome X-linked, X-linked
AXIN2	Oligodontia-colorectal cancer syndrome
B3GALNT1	p phenotype
B3GALNT2	11, Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type a
B3GALT6	Spondylo-epi-(meta)-physeal dysplasia
B4GALNT1	Hereditary spastic paraplegia 26, Inborn genetic diseases
B4GALT7	Ehlers-Danlos syndrome progeroid type
B9D1	Joubert syndrome, Meckel syndrome, Meckel-Gruber syndrome, type 9
B9D2	Joubert syndrome
BAG3	BAG3-related, Cardiovascular phenotype, Dilated cardiomyopathy 1HH, Inborn genetic diseases, Myofibrillar myopathy, Primary dilated cardiomyopathy
BAP1	Hereditary cancer-predisposing syndrome, Tumor susceptibility linked to germline BAP1 mutations
BARD1	Breast cancer, Familial cancer of breast, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Triple-Negative Breast Cancer Finding, susceptibility to
BBS1	Bardet-Biedl syndrome
BBS1, ZDHHC24	Bardet-Biedl syndrome, Bardet-Biedl syndrome 1
BBS10	Bardet-Biedl syndrome, Bardet-Biedl syndrome 1, Bardet-Biedl syndrome 10, Bardet-biedl syndrome 6/10, Inborn genetic diseases, Retinal dystrophy, Retinitis pigmentosa, digenic
BBS2	Bardet-Biedl syndrome, Bardet-Biedl syndrome 2, Bardet-biedl syndrome 1/2, Bardet-biedl syndrome 2/6, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 74, digenic
BBS5	Bardet-Biedl syndrome 5
BBS9	Bardet-Biedl syndrome
BCKDHA	Maple syrup urine disease, Maple syrup urine disease type 1A
BCKDHB	CLASSIC, MAPLE SYRUP URINE DISEASE, Maple syrup urine disease, Maple syrup urine disease type 1B, TYPE IB
BCOR	Oculofaciocardiodental syndrome
BCS1L	BCS1L-Related Disorders, GRACILE syndrome, Leigh syndrome, Mitochondrial complex III deficiency, Pili torti-deafness syndrome, nuclear type 1
BEST1	Bestrophinopathy, Retinal dystrophy, Vitelliform macular dystrophy type 2, autosomal recessive
BET1	Progressive muscle weakness, Seizures
BFSP1	Cataract 33, multiple types
BLM	Bloom syndrome, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome
BMP1	Osteogenesis imperfecta, type xiii
BMP2	AND SKELETAL ANOMALIES WITH OR WITHOUT CARDIAC ANOMALIES, FACIAL DYSMORPHISM, SHORT STATURE

BMPR1A	Hereditary cancer-predisposing syndrome, Juvenile polyposis syndrome
BMPR2	Primary pulmonary hypertension
BNC1	PREMATURE OVARIAN FAILURE 16
BOLA3	Multiple mitochondrial dysfunctions syndrome 2
BPNT2	Chondrodysplasia with joint dislocations, GPAPP type
BPTF	NEURODEVELOPMENTAL DISORDER WITH DYSMORPHIC FACIES AND DISTAL LIMB ANOMALIES
BRAT1	Inborn genetic diseases, NEURODEVELOPMENTAL DISORDER WITH CEREBELLAR ATROPHY AND WITH OR WITHOUT SEIZURES, Rigidity and multifocal seizure syndrome, lethal neonatal
BRCA1	Breast and/or ovarian cancer, Breast carcinoma, Breast-ovarian cancer, COMPLEMENTATION GROUP S, Dysgerminoma, FANCONI ANEMIA, Familial cancer of breast, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Infiltrating duct carcinoma of breast, Neoplasm of ovary, Neoplasm of the breast, Ovarian Neoplasms, Ovarian Serous Surface Papillary Adenocarcinoma, Ovarian cancer, Pancreatic cancer, Pancreatic cancer 4, Porokeratosis punctata palmaris et plantaris, Rhabdomyosarcoma (disease), bilateral breast cancer, breast cancer, familial 1, susceptibility to
BRCA2	Asthma, BRCA2-Related Disorders, Breast and/or ovarian cancer, Breast carcinoma, Breast-ovarian cancer, Cancer of the pancreas, Colorectal cancer, Diffuse intrinsic pontine glioma, Ectopic ossification, Familial cancer of breast, Fanconi anemia, Focal seizures, Genetic non-acquired premature ovarian failure, Glioma susceptibility 3, Headache, Hereditary Cancer Syndrome, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Inborn genetic diseases, Malignant tumor of prostate, Medulloblastoma, Migraine, Muscle weakness, Neoplasm of the breast, Nephrolithiasis, Obesity, Ovarian Neoplasms, Ovarian cancer, Pancreatic cancer 2, Polydactyly, Short attention span, Striae distensae, Tracheoesophageal fistula, Tumor susceptibility linked to germline BAP1 mutations, Wilms tumor 1, complementation group D1, familial 1, familial 2
BRIP1	BRIP1-Related Disorders, Breast cancer, Carcinoma of colon, Familial cancer of breast, Fanconi anemia, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Neoplasm of ovary, Neoplasm of the breast, Ovarian Cancers, Ovarian Neoplasms, Tracheoesophageal fistula, complementation group J, early-onset
BRWD3	Mental retardation, X-linked 93
BSND	Bartter disease type 4a
BTD	Biotinidase deficiency
BTK	Agammaglobulinemia, X-linked agammaglobulinemia, X-linked agammaglobulinemia with growth hormone deficiency, non-Bruton type
C11orf65, ATM	Ataxia-telangiectasia syndrome, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome
C12orf4	AUTOSOMAL RECESSIVE 66, Attention deficit hyperactivity disorder, Intellectual disability, MENTAL RETARDATION, Muscular hypotonia
C12orf65	Combined oxidative phosphorylation deficiency 7, Spastic paraplegia
C19orf12	Neurodegeneration with brain iron accumulation 4, Spastic paraplegia 43, autosomal recessive

C1QB	C1q deficiency
C1S	Complement component c1s deficiency
C2	Complement component 2 deficiency
C2CD3	Orofaciodigital syndrome xiv
C5	Leiner disease
C6	Complement component 6 deficiency, Immunodeficiency due to a late component of complement deficiency
C7	Complement component 7 deficiency
C8B	Complement component 6 deficiency, Type II complement component 8 deficiency
C8orf37	Cone-rod dystrophy 16
C8orf37	Retinitis pigmentosa 64
CA2	Osteopetrosis with renal tubular acidosis
CABP4	Congenital stationary night blindness, type 2B
CACNA1A	42, Bulbar palsy, Epileptic encephalopathy, Episodic ataxia, Episodic ataxia type 2, Recurrent respiratory infections, and epilepsy, early infantile, type 2
CACNA1C	Long QT syndrome
CACNA2D4	Abnormality of the eye, Retinal cone dystrophy 4
CAPN1	Spastic paraplegia 76, autosomal recessive
CAPN3	Absent Achilles reflex, Absent muscle fiber calpain-3, Arrhythmia, Calf muscle hypertrophy, Congenital muscular dystrophy, Contractures of the joints of the lower limbs, Difficulty walking, EMG: myopathic abnormalities, EMG: neuropathic changes, Elbow flexion contracture, Elevated serum creatine phosphokinase, Limb-Girdle Muscular Dystrophy, Limb-girdle muscle weakness, Limb-girdle muscular dystrophy, Migraine, Muscle weakness, Muscular Diseases, Muscular dystrophy, Myositis, Paresthesia, Positive Romberg sign, Progressive spinal muscular atrophy, Recessive, Shoulder girdle muscle weakness, eosinophilic, type 2A
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia
CASP14	Ichthyosis, autosomal recessive 12, congenital
CASQ2	2, Ventricular tachycardia, catecholaminergic polymorphic
CASR	Hypocalciuric hypercalcemia, Inborn genetic diseases, familial, type 1
CAST	Peeling skin with leukonychia, acral punctate keratoses, and knuckle pads, cheilitis
CAST, ERAP1	Peeling skin with leukonychia, acral punctate keratoses, and knuckle pads, cheilitis
CAT	Acatalasemia, Acatalasia, japanese type
CATSPER1	Spermatogenic failure 7
CAV1	Lipodystrophy, congenital generalized, type 3
CAV3, SSUH2	Long QT syndrome
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia
CBS	CYSTATHIONINE BETA-SYNTHETASE POLYMORPHISM, Classic homocystinuria, Homocystinuria
CC2D1A	Mental Retardation, Mental retardation, Psychosocial, autosomal recessive 3

CC2D2A	Joubert syndrome, Joubert syndrome 9, Meckel syndrome type 6, Meckel-Gruber syndrome
CCBE1	Hennekam lymphangiectasia-lymphedema syndrome 1
CCDC103	Primary ciliary dyskinesia
CCDC28B	Bardet-Biedl syndrome, Bardet-Biedl syndrome 1, modifier of
CCDC39	14, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
CCDC40	15, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
CCDC47	Global developmental delay with dysmorphic features, Trichohepatoneurodevelopmental syndrome, and woolly hair, liver dysfunction, pruritus
CCDC65	27, Ciliary dyskinesia, Kartagener syndrome, Primary ciliary dyskinesia, primary
CCDC78	4, Myopathy, centronuclear
CCDC88C	Congenital hydrocephalus 1
CCN6	Progressive pseudorheumatoid dysplasia
CCNH, RASA1	Capillary malformation-arteriovenous malformation
CCNO	29, Ciliary dyskinesia, Kartagener syndrome, Primary ciliary dyskinesia, primary
CCNQ	Syndactyly-telecanthus-anogenital and renal malformations syndrome
CD19	Common variable immunodeficiency 3
CD247	Immunodeficiency due to defect in cd3-zeta
CD36	Malaria, Platelet glycoprotein IV deficiency, cerebral, susceptibility to
CD46	Atypical hemolytic-uremic syndrome 2
CD55	CROMER BLOOD GROUP SYSTEM, Dr(a-) PHENOTYPE, Protein-losing enteropathy (disease)
CDC14A	Deafness, Rare genetic deafness, autosomal recessive 32
CDC73	Parathyroid adenoma, Parathyroid carcinoma
CDH1	Blepharocheilodontic syndrome 1, Breast cancer, Endometrial carcinoma, Familial cancer of breast, Hereditary cancer-predisposing syndrome, Hereditary diffuse gastric cancer, Malignant tumor of prostate, Neoplasm of ovary, lobular
CDH11	Brachioskeletogenital syndrome
CDH23	Deafness, Inborn genetic diseases, MULTIPLE TYPES, PITUITARY ADENOMA 5, Rare genetic deafness, Usher syndrome type 1D, autosomal recessive 12
CDH23, C10orf105	Rare genetic deafness
CDH23, CDH23-AS1	DIGENIC, TYPE ID/F, USHER SYNDROME, Usher syndrome type 1, Usher syndrome type 1D
CDH3	Congenital hypotrichosis with juvenile macular dystrophy, EEM syndrome, Hypotrichosis with juvenile macular dystrophy, Macular dystrophy
CDHR1	Cone-rod dystrophy 15, Leber congenital amaurosis, Retinal dystrophy, Retinitis pigmentosa 65
CDK10	AL KAISSI SYNDROME
CDK13	Congenital heart defects, and intellectual developmental disorder, dysmorphic facial features
CDK5RAP2	Primary autosomal recessive microcephaly 3

CDKL5	Angelman syndrome-like, Atypical Rett syndrome, Early infantile epileptic encephalopathy 2, Epileptic encephalopathy, Inborn genetic diseases
CDKN2A	Hereditary cancer-predisposing syndrome, Hereditary cutaneous melanoma, Melanoma-pancreatic cancer syndrome, Neoplasm
CDSN, PSORS1C1	Peeling skin syndrome 1
CEL	Maturity-onset diabetes of the young type 8
CELA2A	Coronary artery disease, Diabetes, Familial partial lipodystrophy 6, Hypertensive disorder, Hypertriglyceridemia
CENPF	Stromme syndrome
CENPJ	Congenital microcephaly, Intellectual disability, Perisylvian polymicrogyria, Primary autosomal recessive microcephaly, Primary autosomal recessive microcephaly 1, Primary autosomal recessive microcephaly 6, Seckel syndrome 4, Type III lissencephaly, moderate
CEP120	JOUBERT SYNDROME 31
CEP152	Seckel syndrome
CEP290	Abnormality of the kidney, Bardet-Biedl syndrome 14, Blindness, CEP290-Related Disorders, Cerebellar cyst, Cerebellar vermis hypoplasia, Global developmental delay, Hyperechogenic kidneys, Joubert syndrome, Joubert syndrome 5, Leber congenital amaurosis 10, Meckel syndrome, Meckel-Gruber syndrome, Nephronophthisis, Polycystic kidney dysplasia, Retinal dystrophy, Senior-Loken syndrome 6, type 4
CEP290, C12orf29	Bardet-Biedl syndrome 14, Joubert syndrome, Joubert syndrome 5, Meckel-Gruber syndrome, Nephronophthisis
CEP41	Joubert syndrome 15
CEP78	Cone-rod degeneration, Cone-rod dystrophy and hearing loss 1, Sensorineural hearing loss
CFAP251	Male infertility with teratozoospermia due to single gene mutation, Non-syndromic male infertility due to sperm motility disorder, SPERMATOGENIC FAILURE 18, SPERMATOGENIC FAILURE 33, asthenozoospermia, dysplasia of the mitochondrial sheath, multiple morphologic abnormalities of the sperm flagellum
CFAP410	Axial spondylometaphyseal dysplasia, RETINAL DYSTROPHY WITH OR WITHOUT MACULAR STAPHYLOMA
CFAP43	SPERMATOGENIC FAILURE 19
CFAP44	SPERMATOGENIC FAILURE 20
CFHR5	CFHR5 deficiency
CFTR	Bronchiectasis with or without elevated sweat chloride 1, CFTR-related disorders, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis, Hereditary pancreatitis, Inborn genetic diseases, ataluren response - Efficacy
CFTR, CFTR-AS1	CFTR-related disorders, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis
CFTR, LOC111674472	Bronchiectasis with or without elevated sweat chloride 1, CFTR-related disorders, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis, Hereditary pancreatitis
CFTR, LOC111674475	Bronchiectasis with or without elevated sweat chloride 1, CFTR-related disorders, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis, Hereditary pancreatitis, Inborn genetic diseases, ataluren response - Efficacy

CFTR, LOC111674477	Cystic fibrosis
CFTR, LOC113633877	Bronchiectasis with or without elevated sweat chloride 1, CFTR-related disorders, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis, Hereditary pancreatitis
CFTR, LOC113664106	Bronchiectasis with or without elevated sweat chloride 1, Congenital bilateral aplasia of vas deferens from CFTR mutation, Cystic fibrosis, Hereditary pancreatitis
CHD2	CHD2-Related Disorder, Epileptic encephalopathy, History of neurodevelopmental disorder, childhood-onset
CHD7	CHARGE association, Hypogonadism with anosmia, Hypogonadotropic hypogonadism 5 with or without anosmia
CHEK2	3, Astrocytoma, B Lymphoblastic Leukemia/Lymphoma, Breast and colorectal cancer, Breast cancer, CHEK2-Related Cancer Susceptibility, Colitis, Congenital heart defects, Diffuse intrinsic pontine glioma, Familial cancer of breast, Hematochezia, Hereditary breast and ovarian cancer syndrome, Hereditary cancer, Hereditary cancer-predisposing syndrome, Inflammation of the large intestine, Leiomyosarcoma, Li-Fraumeni syndrome, Li-Fraumeni syndrome 2, Malignant tumor of prostate, Neoplasm of the breast, Not Otherwise Specified, Osteosarcoma, Ovarian Neoplasms, Prostate cancer, Thrombocytopenia, multiple types, somatic, susceptibility to
CHM	Retinal dystrophy
CHRDL1	Megalocornea
CHRNA1	Congenital myasthenic syndrome
CHRNA2	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNA3	CHRNA3-related condition
CHRND	Lethal multiple pterygium syndrome
CHRNE	4a, Congenital myasthenic syndrome, Congenital myasthenic syndrome 4C, Myasthenic syndrome, congenital, slow-channel
CHRNE, C17orf107	4a, 4b, Congenital myasthenic syndrome, Congenital myasthenic syndrome 4C, Myasthenic syndrome, congenital, fast-channel, slow-channel
CHRNG	Autosomal recessive multiple pterygium syndrome, CHRNG-Related Disorders, Inborn genetic diseases, Lethal multiple pterygium syndrome
CHST14	Ehlers-Danlos syndrome, musculocontractural type
CHST3	Spondyloepiphyseal dysplasia with congenital joint dislocations
CHSY1	Temtamy preaxial brachydactyly syndrome
CIB1	3, EPIDERMODYSPLASIA VERRUCIFORMIS, SUSCEPTIBILITY TO
CIITA	Bare lymphocyte syndrome 2
CKAP2L	Filippi syndrome
CLCN1	Autosomal dominant intermediate Charcot-Marie-Tooth disease, Congenital myotonia, EMG: myopathic abnormalities, Muscular Diseases, Myotonia congenita, autosomal dominant form, autosomal recessive form
CLCN2	Epilepsy, Leukoencephalopathy with ataxia, juvenile myoclonic 8
CLCN5	Nephrolithiasis, X-linked recessive, X-linked recessive nephrolithiasis with renal failure
CLDN1, CLDN16	Neonatal ichthyosis-sclerosing cholangitis syndrome

CLIC5	Deafness, autosomal recessive
CLN3	Juvenile neuronal ceroid lipofuscinosis, Neuronal ceroid lipofuscinosis
CLN5, FBXL3	Neuronal ceroid lipofuscinosis, Neuronal ceroid lipofuscinosis 5
CLRN1	Rare genetic deafness, Retinal dystrophy, Retinitis pigmentosa, Usher syndrome, type 3A
CNGA1, LOC101927157	Retinal dystrophy, Retinitis pigmentosa 49
CNGB1	Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 45
CNGB3	Abnormality of the eye, Achromatopsia, Achromatopsia 3, CNGB3-Related Disorders, Cone-rod dystrophy, Leber congenital amaurosis, Recessive, Retinal dystrophy, Retinitis pigmentosa, Stargardt Disease
CNNM2	Hypomagnesemia 6, renal
CNNM4	Jalili syndrome
CNTNAP1	Lethal congenital contracture syndrome 7
CNTNAP2	Pitt-Hopkins-like syndrome 1
COASY	Neurodegeneration with brain iron accumulation 6
COG4	Congenital disorder of glycosylation type 2J
COG5	Congenital disorder of glycosylation type 2i
COG5, DUS4L, DUS4L-BCAP29	Congenital disorder of glycosylation type 2i
COL10A1	Metaphyseal chondrodysplasia, Schmid type
COL11A1	Fibrochondrogenesis 1
COL12A1	Ullrich congenital muscular dystrophy 2
COL17A1	Epidermolysis bullosa, Junctional epidermolysis bullosa, junctional, localisata variant, non-Herlitz type
COL18A1	GLAUCOMA, Knobloch syndrome 1, PRIMARY CLOSED-ANGLE
COL18A1, SLC19A1	Knobloch syndrome 1, Macular dystrophy, Retinal dystrophy, Retinitis pigmentosa
COL1A1	Ehlers-Danlos syndrome, Infantile cortical hyperostosis, Osteogenesis imperfecta, Osteogenesis imperfecta type I, Osteogenesis imperfecta type III, Osteogenesis imperfecta with normal sclerae, Postmenopausal osteoporosis, dominant form, procollagen proteinase deficient, recessive perinatal lethal
COL1A2	COL1A2-Related Disorder, Ehlers-Danlos syndrome, Inborn genetic diseases, Osteogenesis imperfecta type I, autosomal recessive, cardiac valvular form, classic type
COL2A1	Spondyloperipheral dysplasia-short ulna syndrome, Stickler syndrome type 1
COL3A1	Ehlers-Danlos syndrome, type 4
COL4A3, MFF-DT	Alport syndrome, autosomal recessive
COL4A5	Alport syndrome 1, X-linked recessive
COL5A1	Ehlers-Danlos syndrome, classic type
COL5A2	Ehlers-Danlos syndrome, Ehlers-Danlos syndrome classic type 2, classic type
COL6A1	Bethlem myopathy 1
COL6A2	Bethlem myopathy 1, Ullrich congenital muscular dystrophy 1

COL6A3	Bethlem myopathy 1
COL7A1	Dystrophic epidermolysis bullosa, Epidermolysis bullosa pruriginosa, Recessive dystrophic epidermolysis bullosa, Transient bullous dermolysis of the newborn, autosomal dominant
COL9A2	Stickler syndrome, type 5
COLEC10	3MC syndrome 3
COLEC10, LOC101927513	3MC syndrome 3
COLQ	Congenital myasthenic syndrome, Endplate acetylcholinesterase deficiency
COQ2	Coenzyme Q10 deficiency, primary, primary 1
COQ8A	4, ADCK3-Related Disorders, Coenzyme Q10 deficiency, primary
COQ9	5, Coenzyme Q10 deficiency, primary
COX15	Cardioencephalomyopathy, Leigh syndrome, Leigh syndrome due to mitochondrial complex IV deficiency, due to cytochrome c oxidase deficiency 2, fatal infantile
CP	Ceruloplasmin belfast, Deficiency of ferroxidase, Hemosiderosis, due to aceruloplasminemia, systemic
CPAMD8	Anterior segment dysgenesis 8
CPLANE1	Global developmental delay, Jaundice, Joubert syndrome, Joubert syndrome 1, Joubert syndrome 17, Orofaciodigital syndrome type 6, Typical Joubert syndrome MRI findings
CPOX	Coproporphyria
CPS1	Congenital hyperammonemia, type I
CPSF1	MYOPIA 27
CPT2	Carnitine palmitoyltransferase II deficiency, infantile, lethal neonatal, myopathic, stress-induced
CRB1	Leber congenital amaurosis 8
CRB2	Focal segmental glomerulosclerosis 9, Steroid-resistant nephrotic syndrome
CRIPT	Ateleiotic dwarfism, Short stature with microcephaly and distinctive facies
CRPPA	7, Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, Muscular dystrophy-dystroglycanopathy (limb-girdle), type A7, type c
CRTAP	Osteogenesis imperfecta type 7
CRX	Leber congenital amaurosis 7
CRYAB	Alpha-B crystallinopathy, Dilated cardiomyopathy 1II
CRYBA4, CRYBB1	Cataract, autosomal recessive 3, congenital nuclear
CRYBB2	Cataract 3, Congenital cataract, multiple types
CSGALNACT1	MILD, SKELETAL DYSPLASIA, WITH JOINT LAXITY AND ADVANCED BONE AGE
CSPP1	Joubert syndrome 21, Meckel-Gruber syndrome
CSRP3	Cardiovascular phenotype
CSTB	Inborn genetic diseases, Progressive myoclonic epilepsy, Unverricht-Lundborg syndrome
CTC1	Cerebroretinal microangiopathy with calcifications and cysts, Cerebroretinal microangiopathy with calcifications and cysts 1, Dyskeratosis congenita

CTCF	Mental retardation, autosomal dominant 21
CTNNB1	EXUDATIVE VITREORETINOPATHY 7, Exudative vitreoretinopathy 1, Hepatocellular carcinoma, Inborn genetic diseases, Mental retardation, autosomal dominant 19
CTNND1, TMX2-CTNND1	Blepharocheilodontic syndrome 2
CTNS	Cystinosis, Juvenile nephropathic cystinosis, Nephropathic cystinosis, Ocular cystinosis
CTSD	Neuronal ceroid lipofuscinosis 10
CTSH	Variant of unknown significance
CTU2	AND AMBIGUOUS GENITALIA SYNDROME, FACIAL DYSMORPHISM, MICROCEPHALY, RENAL AGENESIS
CUBN	Megaloblastic anemia due to inborn errors of metabolism
CUL4B	Cabezas type, Syndromic X-linked mental retardation
CUL7	Three M syndrome 1
CWC27	Retinitis pigmentosa with or without skeletal anomalies
CWF19L1	Spinocerebellar ataxia, autosomal recessive 17
CYB5R3	Methemoglobinemia type 2
CYBB	Chronic granulomatous disease, X-linked
CYP11B1, LOC106799833	Deficiency of steroid 11-beta-monooxygenase
CYP17A1	20-lyase deficiency, Combined partial 17-alpha-hydroxylase/17, Complete combined 17-alpha-hydroxylase/17, Deficiency of steroid 17-alpha-monooxygenase
CYP1B1	A, Anterior segment dysgenesis 6, CYP1B1-Related Disorders, Congenital glaucoma, Congenital ocular coloboma, Glaucoma, Glaucoma 3, Irido-corneo-trabecular dysgenesis, b, congenital, primary congenital, primary infantile
CYP21A2, LOC106780800	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency
CYP21A2, TNXB, LOC106780800	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency
CYP24A1	1, Hypercalcemia, infantile
CYP26C1	Optic nerve hypoplasia
CYP27A1	Cholestanol storage disease
CYP27B1	Vitamin D-dependent rickets, type 1
CYP2C19	CYP2C19: no function, Clopidogrel response, Mephenytoin, Proguanil, Toxicity/ADR, amitriptyline response - Efficacy, citalopram response - Efficacy, clomipramine response - Efficacy, clopidogrel response - Efficacy, poor metabolism of
CYP2D6	Debrisoquine, Deutetrabenazine response, Tamoxifen response, Toxicity/ADR, Tramadol response, amitriptyline response - Dosage, antidepressants response - Dosage, clomipramine response - Dosage, desipramine response - Dosage, doxepin response - Dosage, imipramine response - Dosage, nortriptyline response - Dosage, poor metabolism of, tamoxifen response - Efficacy, trimipramine response - Dosage

CYP2U1	Spastic paraplegia 56, autosomal recessive
CYP4F22	Autosomal recessive congenital ichthyosis 5
CZ1P-ASNS, ASNS	Asparagine synthetase deficiency
DBH	Orthostatic hypotension 1
DBT	Maple syrup urine disease, Maple syrup urine disease type 2
DCAF17	Hypogonadism, alopecia, diabetes mellitus, mental retardation and electrocardiographic abnormalities
DCLRE1C	Severe combined immunodeficiency, Severe combined immunodeficiency due to DCLRE1C deficiency, partial
DCN	Congenital Stromal Corneal Dystrophy
DDHD1	Spastic paraplegia 28, autosomal recessive
DDRGK1	Shohat type, Spondyloepimetaphyseal dysplasia
DDX3X	Delayed speech and language development, Global developmental delay, History of neurodevelopmental disorder, Mental retardation, Microcephaly, X-linked 102
DDX41	Acute myeloid leukemia, Myeloproliferative/lymphoproliferative neoplasms, familial (multiple types), susceptibility to
DEPDC5	DEPDC5-Related Disorder, Familial focal epilepsy with variable foci
DES	Muscular dystrophy, Myofibrillar myopathy 1, Neuromuscular disease, Primary dilated cardiomyopathy, limb-girdle, type 2R
DGKE	Nephrotic syndrome, type 7
DGUOK	Mitochondrial DNA depletion syndrome, Mitochondrial DNA-depletion syndrome 3, Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 4, hepatocerebral, hepatocerebral form due to DGUOK deficiency
DHCR7	2-3 toe syndactyly, Congenital microcephaly, Elevated 7-dehydrocholesterol, History of neurodevelopmental disorder, Inborn genetic diseases, Small for gestational age, Smith-Lemli-Opitz syndrome
DHH	46, XY sex reversal, type 7
DHTKD1	2-aminoadipic 2-oxoadipic aciduria
DIAPH1	Seizures, and microcephaly syndrome, cortical blindness
DICER1	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome, Hereditary cancer-predisposing syndrome
DIPK1A, RPL5	Diamond-Blackfan anemia 6
DLD	Maple syrup urine disease, type 3
DLG3	X-Linked mental retardation 90
DLL3, PLEKHG2	Leukodystrophy and acquired microcephaly with or without dystonia, Spondylocostal dysostosis 1, autosomal recessive
DLX3	Amelogenesis imperfecta, Tricho-dento-osseous syndrome, type IV
DLX4	Orofacial cleft 15
DMD	Becker muscular dystrophy, Duchenne muscular dystrophy
DMP1	Autosomal recessive hypophosphatemic vitamin D refractory rickets
DNAAF2	Primary ciliary dyskinesia

DNAAF4, DNAAF4-CCPG1	Primary ciliary dyskinesia
DNAH1	Non-syndromic male infertility due to sperm motility disorder, SPERMATOGENIC FAILURE 18
DNAH11	7, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
DNAH17	SPERMATOGENIC FAILURE 39
DNAH5	3, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
DNAI1	Kartagener syndrome, Primary ciliary dyskinesia
DNAI2	9, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
DNAJB2	5, Charcot-Marie-Tooth disease, Spinal muscular atrophy, autosomal recessive, distal
DNAJC12	Hyperphenylalaninemia, mild, non-bh4-deficient
DNAL1	16, Ciliary dyskinesia, Primary ciliary dyskinesia, primary
DNM2	Charcot-Marie-Tooth disease, dominant intermediate B
DNMBP	CATARACT 48
DOCK6	Adams-Oliver syndrome 2
DOCK6, LOC105372273	Adams-Oliver syndrome, Adams-Oliver syndrome 2
DOCK8	Hyperimmunoglobulin E recurrent infection syndrome, Inborn genetic diseases, autosomal recessive
DOK7	Congenital myasthenic syndrome, Inborn genetic diseases, Myasthenia, Pena-Shokeir syndrome type I, familial, limb-girdle
DOLK	Congenital disorder of glycosylation type 1M
DONSON	AND LIMB ABNORMALITIES, MICROCEPHALY, Microcephaly-micromelia syndrome, SHORT STATURE
DPY19L2	Spermatogenic failure 9
DPYD	Dihydropyrimidine dehydrogenase deficiency, fluorouracil response - Other
DRAM2	Cone-rod dystrophy 21, Retinal dystrophy
DRC1	21, Ciliary dyskinesia, Kartagener syndrome, Primary ciliary dyskinesia, primary
DSC2	11, Arrhythmogenic right ventricular cardiomyopathy, Arrhythmogenic right ventricular dysplasia, familial, type 11, with mild palmoplantar keratoderma and woolly hair
DSC2, DSCAS	Arrhythmogenic right ventricular cardiomyopathy, type 11
DSG1	Palmoplantar keratoderma i, focal, or diffuse, striate
DSG1, DSG1-AS1	Erythroderma, and hyper-ige, congenital, hypotrichosis, with palmoplantar keratoderma
DSG2	Arrhythmogenic right ventricular cardiomyopathy, Cardiac arrest, Cardiomyopathy, Cardiovascular phenotype, Dilated Cardiomyopathy, Dominant, Hypertrophic cardiomyopathy, type 10
DSG2, DSG2-AS1	Dilated cardiomyopathy 1BB
DSG4, DSG1-AS1	Hypotrichosis 6

DSP	Arrhythmogenic right ventricular cardiomyopathy, Arrhythmogenic right ventricular dysplasia/cardiomyopathy, Cardiac arrest, Cardiomyopathy, Cardiovascular phenotype, DSP-Related Disorders, Dilated cardiomyopathy with woolly hair and keratoderma, Keratosis palmoplantaris striata II, Left ventricular noncompaction cardiomyopathy, Lethal acantholytic epidermolysis bullosa, Long QT syndrome 1, Primary dilated cardiomyopathy, Skin fragility-woolly hair-palmoplantar keratoderma syndrome, Ventricular tachycardia, and tooth agenesis, dilated, keratoderma, type 8, with woolly hair
DST	Epidermolysis bullosa simplex, Neuropathy, autosomal recessive 2, hereditary sensory and autonomic, type VI
DUOX2	Congenital hypothyroidism, Familial thyroid dyshormonogenesis, Inborn genetic diseases, Nongoitrous Euthyroid Hyperthyrotropinemia, Thyroid dyshormonogenesis 6
DVL3	Robinow syndrome, autosomal dominant 1, autosomal dominant 3
DYNC2H1	Jeune thoracic dystrophy, Short Rib Polydactyly Syndrome, Short-rib polydactyly syndrome type III, Short-rib thoracic dysplasia 3 with or without polydactyly
DYNC2I1	Short-rib thoracic dysplasia 8 with or without polydactyly
DYNC2I2	Jeune thoracic dystrophy, Short-rib thoracic dysplasia 11 with or without polydactyly
DYNC2LI1	Short-rib thoracic dysplasia 15 with polydactyly
DYRK1A	Mental retardation, autosomal dominant 7
DYSF	Autosomal recessive limb-girdle muscular dystrophy type 2B, Miyoshi muscular dystrophy 1, Myopathy, Qualitative or quantitative defects of dysferlin, distal, with anterior tibial onset
ECEL1	Distal arthrogryposis type 5D, Inborn genetic diseases
ECHS1	Inborn genetic diseases, Mitochondrial short-chain enoyl-coa hydratase 1 deficiency
ECM1	Lipid proteinosis
EDA	Hypohidrotic X-linked ectodermal dysplasia
EDARADD	Ectodermal dysplasia 11b, autosomal recessive, hypohidrotic/hair/tooth type
EDN3	Congenital central hypoventilation, Dominant, Hirschsprung Disease, Hirschsprung disease, Waardenburg syndrome, Waardenburg syndrome type 4B
EDNRB, EDNRB-AS1	Rare genetic deafness
EFEMP2	Autosomal recessive cutis laxa type 1B, Autosomal recessive cutis laxa type IA
EHMT1	Kleefstra syndrome 1
EIF2AK3	Wolcott-Rallison dysplasia
EIF2AK4	Pulmonary venoocclusive disease 2, autosomal recessive
EIF2B2	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy
EIF2S3	MEHMO syndrome
ELN	Inborn genetic diseases, Supravalvar aortic stenosis
ELOVL4	Retinal dystrophy, Stargardt Disease 3
ELP1	Familial dysautonomia
ELP2	ELP2-Related Disorders, Mental retardation, autosomal recessive 58

EMD	Cardiovascular phenotype, Emery-Dreifuss muscular dystrophy 1, Neuromuscular disease, X-linked
ENAM	Amelogenesis imperfecta, Amelogenesis imperfecta - hypoplastic autosomal dominant - local, type IC
ENG	Hereditary hemorrhagic telangiectasia, Hereditary hemorrhagic telangiectasia type 1
ENG, LOC102723566	Hereditary hemorrhagic telangiectasia type 1
EOGT	Adams-Oliver syndrome, Adams-Oliver syndrome 4
EPB42	Spherocytosis type 5
EPCAM	Diarrhea 5, congenital, with tufting enteropathy
EPG5	Vici syndrome
EPHB4	Capillary malformation-arteriovenous malformation 2
EPHB4, SLC12A9	Capillary malformation-arteriovenous malformation 2
EPOR	Primary familial polycythemia due to EPO receptor mutation
ERCC2	Metachromatic leukodystrophy variant, Trichothiodystrophy 1, Xeroderma pigmentosum, group D, photosensitive
ERCC3	Xeroderma pigmentosum, complementation group b
ERCC4	Cockayne syndrome, Fanconi anemia, Hutchinson-Gilford syndrome, Pre-B-cell acute lymphoblastic leukemia, XFE progeroid syndrome, Xeroderma pigmentosum, complementation group Q, group F
ERCC5, BIVM-ERCC5	Xeroderma pigmentosum, group G
ERCC6	Cerebrooculofacioskeletal syndrome 1, Cockayne syndrome B, DE SANCTIS-CACCHIONE SYNDROME
ERCC8	Cockayne syndrome type A
ERCC8, ERCC8-AS1	Cockayne syndrome type A
ERCC8, NDUFAF2	Cockayne syndrome type A, MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 10
ERF	Craniosynostosis 1, Craniosynostosis 4
ERI1	Abnormality of finger, Coarse facial features, Global developmental delay, Unilateral renal agenesis
ESCO2	Roberts-SC phocomelia syndrome
ESRP1	AUTOSOMAL RECESSIVE 109, DEAFNESS
ESRRB	Rare genetic deafness
ETFDH	Multiple acyl-CoA dehydrogenase deficiency
ETHE1	Ethylmalonic encephalopathy
EVC2	Curry-Hall syndrome, Ellis-van Creveld syndrome
EXOSC3	Pontocerebellar hypoplasia, type 1b
EXPH5	Epidermolysis bullosa, autosomal recessive, nonspecific
EXT1	Chondrosarcoma, Multiple congenital exostosis, Multiple exostoses type 1, sporadic
EXT2	Multiple exostoses type 2

EYA1	Branchiootic syndrome, Melnick-Fraser syndrome, Rare genetic deafness
EYA4	Deafness, Dilated cardiomyopathy 1J, Rare genetic deafness, autosomal dominant 10
EYA4, TARID	EYA4-Related Disorders
EYS	Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 25
F13A1	Factor XIII subunit A deficiency
F13B	Factor XIII, b subunit, deficiency of
F2	Prothrombin deficiency, congenital
F5	Factor V deficiency
F8	Hereditary factor VIII deficiency disease
F9	Hereditary factor IX deficiency disease, Thrombophilia, X-linked, due to factor IX defect
FA2H	Spastic paraplegia 35
FAH	Tyrosinemia type I
FAM161A	Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 28
FAM20A	Amelogenesis imperfecta type 1G
FANCA	Fanconi anemia, complementation group A
FANCB	Fanconi anemia, complementation group B
FANCC	Fanconi anemia, Hereditary cancer-predisposing syndrome, complementation group C
FANCC, AOPEP	Fanconi anemia, Hereditary cancer-predisposing syndrome, Tracheoesophageal fistula, complementation group C
FANCF	Fanconi anemia, complementation group F
FANCM	Fanconi anemia, Malignant germ cell tumor of ovary, SPERMATOGENIC FAILURE 28
FARS2	Combined oxidative phosphorylation deficiency 14
FARSB	Interstitial lung and liver disease, Rajab interstitial lung disease with brain calcifications
FAS	Autoimmune lymphoproliferative syndrome
FAT4	Van Maldergem syndrome
FBN1	Acromicric dysplasia, Acute aortic dissection, Cardiovascular phenotype, Ectopia lentis, Familial thoracic aortic aneurysm, Familial thoracic aortic aneurysm and aortic dissection, Geleophysic dysplasia 2, Inborn genetic diseases, MASS syndrome, Marfan Syndrome/Loeys-Dietz Syndrome/Familial Thoracic Aortic Aneurysms and Dissections, Marfan lipodystrophy syndrome, Marfan syndrome, Stiff skin syndrome, Weill-Marchesani syndrome 2, autosomal dominant, isolated
FBN1, LOC113939944	Marfan Syndrome/Loeys-Dietz Syndrome/Familial Thoracic Aortic Aneurysms and Dissections, Marfan syndrome
FBXL4	Inborn genetic diseases, Mitochondrial DNA depletion syndrome, Mitochondrial DNA depletion syndrome 13 (encephalomyopathic type)
FERMT1	Kindler's syndrome
FEZF1-AS1, FEZF1	Hypogonadotropic hypogonadism 22 with anosmia
FGD4	Charcot-Marie-Tooth disease, Charcot-Marie-Tooth disease type 4
FGF16	Metacarpal 4-5 fusion

FGF3	Deafness with labyrinthine aplasia microtia and microdontia (LAMM)
FGG	Afibrinogenemia, Hypofibrinogenemia, congenital
FH	Fumarase deficiency, Hereditary cancer-predisposing syndrome, Hereditary leiomyomatosis and renal cell cancer
FIG4	Charcot-Marie-Tooth disease, Charcot-Marie-Tooth disease type 4, Yunis-Varon syndrome, type 4J
FKBP10	Bruck syndrome 1, Osteogenesis imperfecta type 12
FKBP14, FKBP14-AS1	Congenital muscular dystrophy, Ehlers-Danlos syndrome with progressive kyphoscoliosis, Inborn genetic diseases, Joint hypermobility, Muscular hypotonia, Pes valgus, Thoracolumbar scoliosis, and hearing loss, myopathy
FKRP	Limb-girdle muscular dystrophy-dystroglycanopathy, type C5
FKTN	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, Congenital muscular dystrophy-dystroglycanopathy without mental retardation, FKTN-Related Disorders, Fukuyama congenital muscular dystrophy, Limb-girdle muscular dystrophy-dystroglycanopathy, Walker-Warburg congenital muscular dystrophy, type A4, type B4, type C4
FLCN	Hereditary cancer-predisposing syndrome, Multiple fibrofolliculomas, Pneumothorax, primary spontaneous
FLG	2, Dermatitis, FLG-Related Disorder, Ichthyosis vulgaris, atopic, susceptibility to
FLNA	Periventricular nodular heterotopia 1
FLNB	Spondylocarpotarsal synostosis syndrome
FLNC	26, 4, Cardiomyopathy, Dilated Cardiomyopathy, Dominant, Myofibrillar myopathy, Myopathy, distal, familial hypertrophic, filamin C-related
FLNC, FLNC-AS1	26, 4, Cardiomyopathy, Dilated Cardiomyopathy, Dominant, Myofibrillar myopathy, Myopathy, distal, familial hypertrophic, filamin C-related
FLT4	7, CONGENITAL HEART DEFECTS, MULTIPLE TYPES
FMR1	Intellectual disability
FOXF1	Persistent fetal circulation syndrome
FOXG1	History of neurodevelopmental disorder, Rett syndrome, congenital variant
FOXL2	Blepharophimosis, and epicanthus inversus, and epicanthus inversus syndrome type 1, ptosis
FOXN1	AUTOSOMAL DOMINANT, INFANTILE, T-CELL LYMPHOPENIA, T-cell immunodeficiency, WITH OR WITHOUT NAIL DYSTROPHY, and nail dystrophy, congenital alopecia
FOXP1	Mental retardation with language impairment and with or without autistic features
FOXRED1	Leigh syndrome, Mitochondrial complex I deficiency, nuclear type 1
FRAS1	Fraser syndrome 1
FREM2	Cryptophthalmos, FRASER SYNDROME 2, Fraser syndrome 1, isolated, unilateral or bilateral
FSHB	Hypogonadotropic hypogonadism 24 without anosmia
FSIP2	SPERMATOGENIC FAILURE 34
FSIP2, FSIP2-AS1	SPERMATOGENIC FAILURE 34
FTCD	GLUTAMATE FORMIMINOTRANSFERASE DEFICIENCY
FTSJ1	Mental retardation 9, X-linked

FUCA1	Fucosidosis
FYCO1	Cataract 18
FZD4, PRSS23	Exudative retinopathy, Familial exudative vitreoretinopathy
G6PC	Glycogen storage disease, Glycogen storage disease due to glucose-6-phosphatase deficiency type IA
GAA	Glycogen storage disease, type II, Pompe disease
GABRA1	19, Epilepsy, Epileptic encephalopathy, early infantile, juvenile myoclonic 5
GABRA6	GABRA6-Related Disorder
GALC	Galactosylceramide beta-galactosidase deficiency
GALM	GALACTOSEMIA IV
GALNS	MPS-IV-A, Morquio syndrome, Mucopolysaccharidosis
GALT	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase
GAMT	Cerebral creatine deficiency syndrome, Deficiency of guanidinoacetate methyltransferase
GAREM2, HADHA	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Mitochondrial trifunctional protein deficiency
GATA1	Acute megakaryoblastic leukemia
GATA3	Hypoparathyroidism-deafness-renal disease syndrome
GATA6	Abnormality of cardiovascular system morphology, Congenital diaphragmatic hernia, Pancreatic agenesis and congenital heart disease, Persistent truncus arteriosus
GATAD1, PEX1	Deafness enamel hypoplasia nail defects, Peroxisome biogenesis disorder 1A (Zellweger)
GATAD2B	GATAD2B-Related Disorder, Mental retardation, autosomal dominant 18
GBA	Acute neuronopathic Gaucher's disease, Gaucher disease, Gaucher disease type 3C, Gaucher's disease, Subacute neuronopathic Gaucher's disease, type 1
GBA, LOC106627981	Gaucher disease, Gaucher's disease, perinatal lethal, type 1
GBE1	Glycogen storage disease, Glycogen storage disease IV, classic hepatic, fatal perinatal neuromuscular, type IV
GCDH	Glutaric aciduria, type 1
GCH1	Dystonia 5
GCK	Maturity onset diabetes mellitus in young, Maturity-onset diabetes of the young, type 2
GDAP1	Charcot-Marie-Tooth disease, recessive intermediate A, type 4A
GDF1, CERS1	Heterotaxia
GDF9	PREMATURE OVARIAN FAILURE 14
GFER	Mitochondrial diseases
GHR	Laron syndrome with elevated serum GH-binding protein, Laron-type isolated somatotropin defect
GJB1	Charcot-Marie-Tooth Neuropathy X, Charcot-Marie-Tooth disease

GJB2	Bilateral conductive hearing impairment, Bilateral sensorineural hearing impairment, Deafness, Dominant, GJB2-Related Disorders, GJB2/GJB3, GJB2/GJB6, Hearing impairment, Hearing loss, Hystrix-like ichthyosis with deafness, Inborn genetic diseases, Keratitis ichthyosis and deafness syndrome, Keratitis-ichthyosis-deafness syndrome, Knuckle pads, Mutilating keratoderma, Nonsyndromic Hearing Loss, Nonsyndromic hearing loss and deafness, Palmoplantar keratoderma-deafness syndrome, Rare genetic deafness, Recessive, Severe sensorineural hearing impairment, X-linked 2, autosomal dominant, autosomal dominant 3a, autosomal recessive 1A, autosomal recessive 1b, deafness AND leukonychia syndrome, digenic
GJB3	Deafness, autosomal dominant 2b
GLA, RPL36A-HNRNPH2	Fabry disease
GLB1	GLB1-Related Disorders, GM1 gangliosidosis, GM1 gangliosidosis type 2, GM1 gangliosidosis type 3, GM1-gangliosidosis, Infantile GM1 gangliosidosis, MPS-IV-B, Mucopolysaccharidosis, type I, with cardiac involvement
GLDC	Non-ketotic hyperglycinemia
GLDN	Lethal congenital contracture syndrome 11
GLI3	Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, Postaxial polydactyly, Preaxial polydactyly 4, type A1/B
GLIS3	Diabetes mellitus, neonatal, with congenital hypothyroidism
GLMN	Glomuvenous malformations
GLRA1	Hyperekplexia 1
GNAS	Progressive osseous heteroplasia, Pseudohypoparathyroidism, Pseudopseudohypoparathyroidism
GNAT2	Achromatopsia 4
GNB5	Intellectual developmental disorder with cardiac arrhythmia, Language delay and attention deficit-hyperactivity disorder/cognitive impairment with or without cardiac arrhythmia
GNPAT	Rhizomelic chondrodysplasia punctata type 2
GNPTAB	GNPTAB-Related Disorders, Inborn genetic diseases, MUCOLIPIDOSIS III ALPHA/BETA, Mucolipidosis, Mucolipidosis type II, Pseudo-Hurler polydystrophy
GNPTG	Mucolipidosis, Mucolipidosis type III gamma
GORAB	Geroderma osteodysplastica
GOSR2, LRRC37A2	Progressive myoclonic epilepsy
GPC3	Simpson-Golabi-Behmel syndrome, Wilms tumor 1
GPC4	Keipert syndrome
GPC6	Autosomal recessive omodysplasia
GPC6, GPC6-AS2	Autosomal recessive omodysplasia
GPI	Hemolytic anemia, due to glucose phosphate isomerase deficiency, nonspherocytic
GPNMB	3, AMYLOIDOSIS, PRIMARY LOCALIZED CUTANEOUS
GPR143	Ocular albinism, type I
GPR179	Congenital stationary night blindness, Retinal dystrophy, type 1E

GPSM2	Chudley-McCullough syndrome, GPSM2-Related Disorders, Rare genetic deafness
GRHL2	Deafness, autosomal dominant 28
GRHL3	Van der Woude syndrome 2
GRHPR	Nephrocalcinosis, Nephrolithiasis, Primary hyperoxaluria, type II
GRIN2B	Mental retardation, autosomal dominant 6
GRIP1	FRASER SYNDROME 3
GRN	Frontotemporal dementia
GRXCR1	Deafness, Rare genetic deafness, autosomal recessive 25
GSDME	Deafness, autosomal dominant 5
GUCY2C, C12orf60	Meconium ileus
GUSB	Mucopolysaccharidosis type 6, Mucopolysaccharidosis type 7
GYG1	Glycogen storage disease XV, Polyglucosan body myopathy 2
GYS1	Glycogen storage disease 0, muscle
GYS2	Glycogen storage disease, Glycogen storage disease due to hepatic glycogen synthase deficiency
GZF1	AND MYOPIA, JOINT LAXITY, SHORT STATURE
H1-4	Inborn genetic diseases, RAHMAN SYNDROME
H6PD	Cortisone reductase deficiency 1
HADHA	HADHA-Related Disorders, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Mitochondrial trifunctional protein deficiency
HADHA, GAREM2	HADHA-Related Disorders, Inborn genetic diseases, LCHAD Deficiency, Lchad deficiency with maternal acute fatty liver of pregnancy, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, Mitochondrial trifunctional protein deficiency
HAX1	Severe congenital neutropenia 3, autosomal recessive
HBA2, LOC106804612	Alpha plus thalassemia
HBB, LOC106099062, LOC107133510	Anemia, Beta thalassemia major, Beta-plus-thalassemia, Beta-thalassemia, Erythrocytosis 6, Fetal hemoglobin quantitative trait locus 1, HBB-Related Disorders, Hb SS disease, Heinz body anemia, Hemoglobin E, Hemoglobin E disease, Hemoglobin E/beta thalassemia disease, Hemoglobin M disease, Hemoglobinopathy, Malaria, Susceptibility to malaria, alpha Thalassemia, beta Thalassemia, beta^0^ Thalassemia, dominant inclusion body type, familial, resistance to
HBB, LOC107133510, LOC110006319	beta Thalassemia
HCN4	Brugada syndrome 8, Sick sinus syndrome 2, autosomal dominant
HEXA	Inborn genetic diseases, Tay-Sachs disease
HEXB	Sandhoff disease, infantile
HFM1	Premature ovarian failure 9
HGD	Alkaptonuria
HGSNAT	MPS-III-C, Mucopolysaccharidosis, Retinitis pigmentosa 73, Sanfilippo syndrome

HIVEP2	Angelman syndrome-like, Mental retardation, autosomal dominant 43
HJV	Hemochromatosis type 2A
HLCS	Holocarboxylase synthetase deficiency
HMCN1	Age-related macular degeneration 1
HMGB3	Microphthalmia, syndromic 13
HMGCL	Deficiency of hydroxymethylglutaryl-CoA lyase
HNF1A	20, Clear cell carcinoma of kidney, Diabetes mellitus, Diabetes mellitus type 1, Hepatic adenomas, Maturity onset diabetes mellitus in young, Maturity-onset diabetes of the young, familial, insulin-dependent, type 3
HNF1B	Familial hypoplastic, Renal cysts and diabetes syndrome, glomerulocystic kidney
HNRNPK	AU-KLINE SYNDROME
HNRNPU	Epileptic encephalopathy
HOXA1	Athabaskan brainstem dysgenesis syndrome, Bosley-Salih-Alorainy syndrome
HOXA11	Radioulnar synostosis with amegakaryocytic thrombocytopenia 1
HOXD13	Synpolydactyly 1
HPGD	1, HPGD-Related Disorders, Hypertrophic osteoarthropathy, autosomal recessive, primary
HPS1	Hermansky-Pudlak syndrome, Hermansky-Pudlak syndrome 1
HPS5	Hermansky-Pudlak syndrome, Hermansky-Pudlak syndrome 5
HPS6	Hermansky-Pudlak syndrome, Hermansky-Pudlak syndrome 6
HPSE2	Urofacial syndrome 1
HR	Atrichia with papular lesions
HSD17B10	HSD10 disease
HSD17B4	Bifunctional peroxisomal enzyme deficiency, Perrault syndrome
HSPA9	4, Anemia, Even-plus syndrome, sideroblastic
HSPB1	Charcot-Marie-Tooth disease, Charcot-Marie-Tooth disease axonal type 2F, Distal hereditary motor neuronopathy type 2B
HSPG2	Lethal Kniest-like syndrome, Schwartz-Jampel syndrome
HYAL1	Deficiency of hyaluronoglucosaminidase
HYDIN	5, Ciliary dyskinesia, primary
ICAM4	Landsteiner-Wiener phenotype
IDS	MPS-II, Mucopolysaccharidosis
IDS, LOC106050102	MPS-II, Mucopolysaccharidosis
IDUA	Hurler syndrome, MPS-I-H/S, MPS-I-S, Mucopolysaccharidosis, Mucopolysaccharidosis type 1
IDUA, SLC26A1	Hurler syndrome, MPS-I-H/S, MPS-I-S, Mucopolysaccharidosis, Mucopolysaccharidosis type 1
IFIH1	Aicardi-Goutieres syndrome 7, Singleton-Merten syndrome 1
IFNGR1	Disseminated atypical mycobacterial infection, IFN-gamma receptor 1 deficiency, Immunodeficiency 27b, Inherited Immunodeficiency Diseases
IFNGR2	Immunodeficiency 28
IFT140	Retinitis pigmentosa 80

IFT140, LOC105371046	Jeune thoracic dystrophy, Joubert syndrome with Jeune asphyxiating thoracic dystrophy, Renal dysplasia, cerebellar ataxia and skeletal dysplasia, retinal pigmentary dystrophy
IFT172	Short-rib thoracic dysplasia 10 with or without polydactyly
IFT52	Short Rib Polydactyly Syndrome, Short-rib thoracic dysplasia 16 with or without polydactyly
IGF1	Growth delay due to insulin-like growth factor type 1 deficiency
IGF1R	Inborn genetic diseases
IGFALS	Acid-labile subunit deficiency
IGHM	Agammaglobulinemia, non-Bruton type
IGHMBP2	1, Autosomal dominant distal hereditary motor neuropathy, Charcot-Marie-Tooth disease, Distal spinal muscular atrophy, Inborn genetic diseases, Spinal muscular atrophy, autosomal recessive, axonal, distal, type 2S
IGLL1	Agammaglobulinemia 2, autosomal recessive
IGSF1	Hypothyroidism, and testicular enlargement, central
IGSF3	Lacrimal duct defect
IKBKG	Ectodermal dysplasia and immunodeficiency 1, Immunodeficiency without anhidrotic ectodermal dysplasia, Incontinentia pigmenti, atypical
IL12B	Immunodeficiency 29
IL12RB1	Immunodeficiency 30
IL2RB	Ichthyosis (disease)
IL2RG	Combined immunodeficiency, X-linked, X-linked severe combined immunodeficiency
IL36RN	Pustular psoriasis, generalized
IL7R	B cell-positive, NK cell-positive, Severe combined immunodeficiency, T cell-negative, autosomal recessive
INPP5E	Retinal dystrophy
INPPL1	Opsismodysplasia
INTU	Mohr syndrome, Orofaciodigital syndrome 17
IQCB1	Renal dysplasia and retinal aplasia
IQCE	POLYDACTYLY, POSTAXIAL, TYPE A7
IQSEC2	Mental retardation, Severe intellectual deficiency, X-linked 1
IRAK4	Immunodeficiency due to interleukin-1 receptor-associated kinase-4 deficiency
IRF2BPL	ABNORMAL MOVEMENTS, AND SEIZURES, LOSS OF SPEECH, NEURODEVELOPMENTAL DISORDER WITH REGRESSION, Neurodevelopmental disorder
IRF6	Van der Woude syndrome
IRS4	9, CONGENITAL, HYPOTHYROIDISM, NONGOITROUS
ISCA2	Multiple mitochondrial dysfunctions syndrome 4
ISG15	Immunodeficiency 38 with basal ganglia calcification
ITGA7	Muscular dystrophy, congenital, due to integrin alpha-7 deficiency
ITGB2	Leukocyte adhesion deficiency
ITGB4	Epidermolysis bullosa junctionalis with pyloric atresia
ITPA	35, Epileptic encephalopathy, Inosine triphosphatase deficiency, early infantile
ITPR1	Gillespie syndrome

IVD	Isovaleric acidemia, Isovaleryl-CoA dehydrogenase deficiency, type III
JAG1	Alagille syndrome 1, Arteriohepatic dysplasia, Heart, malformation of
JAK3	B cell-positive, NK cell-negative, Severe combined immunodeficiency, Severe combined immunodeficiency disease, T cell-negative, autosomal recessive
KAT6A	History of neurodevelopmental disorder, Mental retardation, autosomal dominant 32
KAT6B	Blepharophimosis - intellectual disability syndrome, SBBYS type
KAT6B, DUPD1	Blepharophimosis - intellectual disability syndrome, Genitopatellar syndrome, Inborn genetic diseases, SBBYS type
KATNIP	Joubert syndrome 26
KCNA1	Episodic ataxia type 1
KCNA5	7, Atrial fibrillation, familial
KCNC1	Epilepsy, progressive myoclonic 7
KCNE1	Long QT syndrome
KCNH2	Cardiac arrhythmia, Cardiovascular phenotype, Congenital long QT syndrome, Long QT syndrome, Long QT syndrome 1/2, Long QT syndrome 2, digenic
KCNK18	Migraine, with or without aura 13
KCNQ1	Cardiac arrhythmia, Cardiovascular phenotype, Congenital long QT syndrome, Jervell and Lange-Nielsen syndrome, Jervell and Lange-Nielsen syndrome 1, KCNQ1-Related Disorders, LQT1 subtype, Long QT syndrome, Long QT syndrome 1, Rare genetic deafness, Romano-Ward syndrome, recessive
KCNQ1-AS1, KCNQ1	Jervell and Lange-Nielsen syndrome 1
KCNQ1, KCNQ1-AS1	Cardiovascular phenotype, Long QT syndrome, Long QT syndrome 1
KCNQ1, KCNQ1OT1	Congenital long QT syndrome, LQT1 subtype, Long QT syndrome
KCNQ2	Benign familial neonatal seizures 1, Early infantile epileptic encephalopathy, Early infantile epileptic encephalopathy 7, Epileptic encephalopathy, Inborn genetic diseases, Seizures
KCNQ3	Intellectual disability, Seizures
KCNQ4	Autosomal dominant nonsyndromic deafness 2A
KCNT1	5, Early infantile epileptic encephalopathy 14, Epilepsy, nocturnal frontal lobe
KCNV2	Cone dystrophy with supernormal rod response, Progressive cone dystrophy (without rod involvement), Retinal dystrophy, Stargardt disease
KDM5B	Intellectual disability, autosomal recessive 65
KDM5C	Claes-Jensen type, Mental retardation, X-linked, syndromic
KDM6A	Kabuki syndrome 2
KERA	Cornea plana 2
KHDC3L	2, Hydatidiform mole, recurrent
KIAA0586	Congenital cerebellar hypoplasia, Intellectual disability, Joubert syndrome, Joubert syndrome 23, Retinal dystrophy, Rod-cone dystrophy, Short-rib thoracic dysplasia 14 with polydactyly
KIAA0753	Orofaciodigital syndrome XV
KIAA0825	POLYDACTYLY, POSTAXIAL, Postaxial polydactyly type A1, TYPE A10
KIAA1549	RETINITIS PIGMENTOSA 86

KIF11	Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation
KIF7	Acrocallosal syndrome, Joubert syndrome 12
KIFBP	Goldberg-Shprintzen megacolon syndrome
KISS1R	Hypogonadotropic hypogonadism 8 without anosmia
KIZ	Retinitis pigmentosa 69
KMT2A	Wiedemann-Steiner syndrome
KMT2B	Dystonia 28, childhood-onset
KMT2C	Kleefstra syndrome due to a point mutation
KMT2D	CHARGE association, Kabuki syndrome, Kabuki syndrome 1
KMT2E	Epilepsy, Leukoencephalopathy, Macrocephalus, O''''DONNELL-LURIA-RODAN SYNDROME, See cases, intellectual deficiency
KPTN	Mental retardation, autosomal recessive 41
KRIT1	Cavernous malformations of CNS and retina, Cerebral cavernous malformation, Cerebral cavernous malformations 1
KRT1	Ichthyosis histrix, curth-macklin type
KRT10	Bullous ichthyosiform erythroderma
KRT10, TMEM99	Bullous ichthyosiform erythroderma
KRT14	Epidermolysis bullosa simplex, autosomal recessive
KRT5	Dowling-Degos disease 1
KRT6A	Pachyonychia congenita 3
KRT85	'pure' hair-nail type, Ectodermal dysplasia
KYNU	AND LIMB DEFECTS SYNDROME 2, CARDIAC, Congenital NAD deficiency disorder, RENAL, VERTEBRAL
L1CAM	MASA syndrome, Spastic paraplegia
L2HGDH	L-2-hydroxyglutaric aciduria
LACC1	JUVENILE ARTHRITIS
LAMA2	Inborn genetic diseases, Laminin alpha 2-related dystrophy, Merosin deficient congenital muscular dystrophy
LAMA3	Junctional epidermolysis bullosa gravis of Herlitz
LAMA4	Dilated cardiomyopathy 1JJ
LAMB3	Amelogenesis imperfecta, Junctional epidermolysis bullosa, Junctional epidermolysis bullosa gravis of Herlitz, non-Herlitz type, type IA
LAMC2	Junctional epidermolysis bullosa, Junctional epidermolysis bullosa gravis of Herlitz, non-Herlitz type
LAMP2	Cardiomyopathy, Danon disease, Hypertrophic cardiomyopathy, Primary dilated cardiomyopathy
LARGE1	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6
LBR	Disproportionate short stature, Femoral bowing, Pelger-HuÃ«t anomaly, Regressive spondylometaphyseal dysplasia, Retrognathia, Rhizomelic arm shortening, Rhizomelic leg shortening, Short long bone
LDB3	Cardiomyopathy, Myofibrillar myopathy, ZASP-related
LDLR	Familial hypercholesterolemia, Familial hypercholesterolemia 1, Homozygous familial hypercholesterolemia

LDLRAP1	Familial hypercholesterolemia 4
LEP	Leptin deficiency or dysfunction
LFNG	Spondylocostal dysostosis 3, autosomal recessive
LGI1	Familial temporal lobe epilepsy 1
LHFPL5	Rare genetic deafness
LHX3	Non-acquired combined pituitary hormone deficiency with spine abnormalities
LIFR	StÃ¼ve-Wiedemann syndrome
LIG4	LIG4-Related Disorders, Lig4 syndrome
LIPA	Lysosomal acid lipase deficiency
LIPE	Familial partial lipodystrophy 6
LIPE, LIPE-AS1, LOC101930071	Familial partial lipodystrophy 6
LIPH	Hypotrichosis 7, Woolly hair, autosomal recessive 2, with or without hypotrichosis
LIPN	Autosomal recessive congenital ichthyosis 8
LMBR1	Acheiropodia
LMBRD1	Inborn genetic diseases, Methylmalonic aciduria and homocystinuria type cblF
LMNA	Cardiovascular phenotype, Charcot-Marie-Tooth disease, Primary dilated cardiomyopathy, type 2
LMOD3	Nemaline myopathy 10
LMX1B	Nail-patella syndrome
LOC100507346, PTCH1	Gorlin syndrome, Medulloblastoma
LOC101927055, TTN	Dilated cardiomyopathy 1G, Limb-girdle muscular dystrophy, Primary dilated cardiomyopathy, type 2J
LOC101927157, CNGA1	Retinitis pigmentosa, Retinitis pigmentosa 49
LOC101927188, LAMA1	Poretti-Boltshauser syndrome
LOC102723566, ENG	Hereditary hemorrhagic telangiectasia type 1
LOC106694316, MPO	Myeloperoxidase deficiency
LOC110006319, HBB, LOC107133510	beta Thalassemia
LOXHD1	Deafness, Rare genetic deafness, autosomal recessive 77
LPL	Hyperlipoproteinemia, Lpl-arita, type I
LRAT	EARLY-ONSET SEVERE, JUVENILE, LRAT-RELATED, Leber congenital amaurosis, Leber congenital amaurosis 14, RETINAL DYSTROPHY, RETINITIS PIGMENTOSA
LRBA	Common variable immunodeficiency 8, with autoimmunity
LRIT3	Congenital stationary night blindness, type 1F
LRP4	Cenani-Lenz syndactyly syndrome
LRP5	Exudative vitreoretinopathy 4, Familial exudative vitreoretinopathy, autosomal dominant
LRP6	7, Tooth agenesis, selective

LRPAP1	Myopia 23, Rare isolated myopia, autosomal recessive
LRPPRC	Congenital lactic acidosis, Saguenay-Lac-Saint-Jean type
LRSAM1	Charcot-Marie-Tooth disease type 2P
LRTOMT	Deafness, Rare genetic deafness, autosomal recessive 63
LTBP2	Congenital glaucoma, Microspherophakia
LTBP3	Dental anomalies and short stature
LTBP4	Cutis laxa with severe pulmonary, and urinary abnormalities, gastrointestinal
LYRM7	Mitochondrial complex III deficiency, nuclear type 8
LZTFL1	Bardet-Biedl syndrome 17
LZTR1	Noonan syndrome 2, Schwannomatosis 2
MAB21L1, NBEA	AND GENITAL SYNDROME, CEREBELLAR, CRANIOFACIAL, OCULAR
MAFB	Duane retraction syndrome 2, Duane retraction syndrome 3 with or without deafness, Duane syndrome type 1, Duane syndrome type 3
MAGED2	Bartter syndrome, antenatal, transient, type 5
MAGEL2	Inborn genetic diseases, Schaaf-Yang syndrome
MAGT1	Epstein-Barr virus infection, Immunodeficiency, X-Linked, and neoplasia, with magnesium defect
MAK	Retinal dystrophy
MAN2B1	Deficiency of alpha-mannosidase
MANBA	Beta-D-mannosidosis
MAP2K2	Rasopathy
MAPRE2	2, Skin creases, congenital symmetric circumferential
MARVELD2	Deafness, Rare genetic deafness, autosomal recessive 49, neurosensory
MAX	Hereditary cancer-predisposing syndrome
MBD5	Mental retardation, autosomal dominant 1
MC2R	ACTH resistance
MC4R	Monogenic diabetes, Obesity, Schizophrenia
MCCC1	3 Methylcrotonyl-CoA carboxylase 1 deficiency
MCCC2	3-methylcrotonyl CoA carboxylase 2 deficiency
MCM5	MEIER-GORLIN SYNDROME 8
MCM8	Premature ovarian failure 10
MCOLN1	Mucolipidosis type IV
MCPH1	Abnormality of brain morphology, Primary autosomal recessive microcephaly 1
MECP2	Angelman syndrome, Atypical Rett syndrome, Autism, Delayed gross motor development, Delayed speech and language development, Developmental regression, Encephalopathy, Global developmental delay, History of neurodevelopmental disorder, Inborn genetic diseases, Intellectual disability, Loss of ability to walk, Mental retardation, Rett syndrome, Severe neonatal-onset encephalopathy with microcephaly, Smith-Magenis Syndrome-like, Syndromic X-linked intellectual disability Lubs type, X-linked, X-linked 3, neonatal severeMental retardation, susceptibility to, syndromic 13, syndromic 13Rett syndrome
MED12	Cardiovascular phenotype, FG syndrome 1, History of neurodevelopmental disorder

MED13L	Mental retardation and distinctive facial features with or without cardiac defects
MED25	Broad-based gait, Charcot-Marie-Tooth disease, Decreased body weight, Failure to thrive, Generalized hypotonia, Impaired distal proprioception, Sensory ataxia, Sensory ataxic neuropathy, Sensory neuropathy, type 2
MEF2C	MEF2C-Related Disorder, Mental retardation, and/or cerebral malformations, epilepsy, stereotypic movements
MEFV	Familial Mediterranean fever
MEN1	Hereditary cancer-predisposing syndrome, Lipoma, Multiple endocrine neoplasia, somatic, type 1
MERTK	Retinitis pigmentosa 38
MESD	OSTEOGENESIS IMPERFECTA, TYPE XX
METTL23	Inborn genetic diseases, Mental retardation, autosomal recessive 44
MFN2	Charcot-Marie-Tooth disease, type 2
MFRP, C1QTNF5	Microphthalmia, Nanophthalmos 2, isolated 5
MFSD8	Neuronal ceroid lipofuscinosis 7
MIP	Cataract 15, multiple types
MIR6886, LDLR	Familial hypercholesterolemia, Familial hypercholesterolemia 1, Homozygous familial hypercholesterolemia
MITF	Coloboma, Rare genetic deafness, Waardenburg syndrome type 2A, albinism, and deafness, macrocephaly, microphthalmia, osteopetrosis
MKRN3	2, Precocious puberty, central
MKS1	Joubert syndrome, Joubert syndrome 28, Meckel syndrome type 1, Meckel-Gruber syndrome
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts 1
MLH1	Carcinoma of colon, Colon cancer, Hereditary cancer-predisposing syndrome, Hereditary nonpolyposis colon cancer, Lynch syndrome, Lynch syndrome I, Lynch syndrome II, Muir-TorrÃ© syndrome, Turcot syndrome
MLH3	Hereditary nonpolyposis colorectal cancer type 7
MLYCD	Deficiency of malonyl-CoA decarboxylase
MMAA	Methylmalonic acidemia, Vitamin B12-responsive methylmalonic acidemia type cblA
MMAB	Methylmalonic acidemia, Vitamin B12-responsive methylmalonic acidemia type cblB
MMACHC	DIGENIC, Disorders of Intracellular Cobalamin Metabolism, METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, Methylmalonic acidemia with homocystinuria, Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency, cblC TYPE
MME	Charcot-Marie-Tooth disease, Congenital membranous nephropathy due to fetomaternal anti-neutral endopeptidase alloimmunization, axonal, type 2T
MMUT	Methylmalonic acidemia, Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency
MOCS2	Molybdenum cofactor deficiency, complementation group B
MPDZ	2, Congenital hydrocephalus, Hydrocephalus, congenital, with or without brain or eye anomalies
MPL	Congenital amegakaryocytic thrombocytopenia, essential thrombocytemia
MPLKIP	Trichothiodystrophy, nonphotosensitive 1

MPO	Myeloperoxidase deficiency
MPV17	Navajo neurohepatopathy
MPZ	Charcot-Marie-Tooth disease
MPZL2	AUTOSOMAL RECESSIVE 111, DEAFNESS
MRE11	Hereditary cancer-predisposing syndrome
MSH2	Carcinoma of colon, Colon cancer, Glioblastoma, Hereditary cancer-predisposing syndrome, Hereditary nonpolyposis colon cancer, Lynch syndrome, Lynch syndrome I, Malignant tumor of ascending colon, Malignant tumor of sigmoid colon, Muir-TorrÃ© syndrome, Ovarian Neoplasms, Turcot syndrome
MSH6	Endometrial carcinoma, Hereditary cancer-predisposing syndrome, Hereditary nonpolyposis colon cancer, Hereditary nonpolyposis colorectal cancer type 5, Hereditary nonpolyposis colorectal carcinoma, Lynch syndrome, Lynch syndrome I, Turcot syndrome
MSTO1	Mitochondrial myopathy-cerebellar ataxia-pigmentary retinopathy syndrome
MSX2	Parietal foramina 1
MTFMT	Abnormal facial shape, Combined oxidative phosphorylation deficiency 15, Cytochrome C oxidase-negative muscle fibers, Decreased activity of mitochondrial complex I, Inability to walk by childhood/adolescence, Leigh syndrome, MITOCHONDRIAL COMPLEX I DEFICIENCY, Mitochondrial oxidative phosphorylation disorder, NUCLEAR TYPE 27, Poor speech, Short stature
MTHFD1	COMBINED IMMUNODEFICIENCY AND MEGALOBLASTIC ANEMIA WITH OR WITHOUT HYPERHOMOCYSTEINEMIA
MTM1	Severe X-linked myotubular myopathy
MTRR	Disorders of Intracellular Cobalamin Metabolism, Homocystinuria without methylmalonic aciduria, Homocystinuria-Megaloblastic anemia due to defect in cobalamin metabolism, cblE complementation type
MTTP	Abetalipoproteinaemia
MUTYH	Carcinoma of colon, Colon cancer, Familial colorectal cancer, Hereditary cancer-predisposing syndrome, MUTYH-associated polyposis, MYH-associated polyposis, Neoplasm of stomach, Pilomatrixoma
MVK	Hyperimmunoglobulin D with periodic fever, Mevalonic aciduria, Porokeratosis 3, disseminated superficial actinic type
MYBPC3	Asymmetric septal hypertrophy, Cardiomyopathy, Cardiovascular phenotype, Dyspnea, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy 1, Familial hypertrophic cardiomyopathy 4, Heart block, Hypertrophic cardiomyopathy, Inborn genetic diseases, Left ventricular hypertrophy, Left ventricular noncompaction, Left ventricular noncompaction 10, Long QT syndrome, MYBPC3-Related Disorders, Noncompaction cardiomyopathy, Primary dilated cardiomyopathy, Primary familial hypertrophic cardiomyopathy, Tachycardia, Ventricular extrasystoles
MYCN	Inborn genetic diseases
MYEF2, SLC24A5	Albinism, oculocutaneous, type VI
MYF5	Abnormality of the ribs, EXTERNAL, External ophthalmoplegia, OPHTHALMOPLEGIA, Scoliosis, WITH RIB AND VERTEBRAL ANOMALIES
MYH11, NDE1	Familial aortopathy
MYH2, MYHAS	Myopathy, and ophthalmoplegia, proximal

MYH3	Contractures, Spondylocarpotarsal synostosis syndrome, and variable skeletal fusions syndrome 1A, pterygia
MYH6	Familial hypertrophic cardiomyopathy 1
MYH7	Hypertrophic cardiomyopathy, Primary dilated cardiomyopathy
MYH7, MHRT	Cardiomyopathy, Cardiovascular phenotype, Hypertrophic cardiomyopathy, MYH7-Related Disorders
MYL2, LOC114827850	Familial hypertrophic cardiomyopathy 10
MYLK	Visceral myopathy
MYO15A	Congenital sensorineural hearing impairment, Deafness, Nonsyndromic hearing loss and deafness, Rare genetic deafness, autosomal recessive 3
MYO3A	Deafness, autosomal recessive 30
MYO5B	Congenital microvillous atrophy
MYO6	Deafness, Nonsyndromic hearing loss and deafness, Rare genetic deafness, autosomal dominant 22
MYO7A	Deafness, MYO7A-Related Disorders, Rare genetic deafness, Retinal dystrophy, Retinitis pigmentosa, Usher syndrome, Usher syndrome type 1, autosomal dominant 11, autosomal recessive 2, type 1B
MYOCD	CONGENITAL, MEGABLADDER, Prune belly syndrome
MYRF	CARDIAC-UROGENITAL SYNDROME
NADSYN1	AND LIMB DEFECTS SYNDROME 3, CARDIAC, Congenital NAD deficiency disorder, RENAL, VERTEBRAL
NAGLU	Charcot-Marie-Tooth disease, MPS-III-B, Mucopolysaccharidosis, Sanfilippo syndrome, axonal type 2V
NALCN	Hypotonia, infantile, with psychomotor retardation and characteristic facies 1
NBAS	Fever-associated acute infantile liver failure syndrome, Infantile liver failure syndrome 2
NBN	Acute lymphoid leukemia, Aplastic anemia, Breast-ovarian cancer, Familial cancer of breast, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Lissencephaly, Microcephaly, Ovarian Neoplasms, familial 1, normal intelligence and immunodeficiency
NCF1, LOC106029312	Chronic granulomatous disease, Chronic granulomatous disease due to deficiency of NCF-1, Granulomatous disease, autosomal recessive, autosomal recessive cytochrome b-positive, chronic, cytochrome b-positive, type 1, type III
NCR1, NLRP7	1, Hydatidiform mole, recurrent
NCSTN	Familial acne inversa 1
NDE1	Lissencephaly 4
NDNF	HYPOGONADOTROPIC HYPOGONADISM 25 WITH ANOSMIA
NDUFA12	Leigh syndrome
NDUFAF2	Inborn genetic diseases, Leigh syndrome, MITOCHONDRIAL COMPLEX I DEFICIENCY, Mitochondrial complex I deficiency, NDUFAF2-Related Disorders, NUCLEAR TYPE 10, nuclear type 1
NDUFAF3	Mitochondrial complex I deficiency
NDUFB11	Linear skin defects with multiple congenital anomalies 3
NDUFS4	Leigh syndrome, Mitochondrial complex I deficiency, nuclear type 1
NDUFS6	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 9

NDUFV1	MITOCHONDRIAL COMPLEX I DEFICIENCY, Mitochondrial complex I deficiency, NUCLEAR TYPE 4, nuclear type 1
NEB	Inborn genetic diseases, Nemaline myopathy, Nemaline myopathy 2, Non-immune hydrops fetalis
NEB, RIF1	Nemaline myopathy, Nemaline myopathy 2
NEBL	Hypertrophic cardiomyopathy, Long QT syndrome, Primary dilated cardiomyopathy, Primary familial hypertrophic cardiomyopathy, Sudden unexplained death
NEFL	Charcot-Marie-Tooth disease type 2E
NEK1	24, AMYOTROPHIC LATERAL SCLEROSIS, Majewski type, SUSCEPTIBILITY TO, Short rib-polydactyly syndrome, Short-rib thoracic dysplasia 3 with or without polydactyly
NEUROD1	Maturity-onset diabetes of the young type 6
NEXN	Dilated cardiomyopathy 1CC, Familial hypertrophic cardiomyopathy 20
NF1	Axillary freckling, CafÃ©-au-lait macules with pulmonary stenosis, Focal T2 hyperintense basal ganglia lesion, Ganglioglioma, Hereditary cancer-predisposing syndrome, Inborn genetic diseases, Juvenile myelomonocytic leukemia, Multiple cafe-au-lait spots, Neurofibroma, Neurofibromas, Neurofibromatosis, Neurofibromatosis-Noonan syndrome, Optic nerve glioma, Pilocytic astrocytoma, Tibial pseudoarthrosis, familial spinal, type 1
NF1, LOC111811965	Hereditary cancer-predisposing syndrome, Neurofibromatosis, type 1
NF2	Meningioma, Neurofibromatosis, type 2
NFIB	ACQUIRED, Intellectual disability, MACROCEPHALY, Macrocephalus, WITH IMPAIRED INTELLECTUAL DEVELOPMENT
NFIX	Marshall-Smith syndrome
NGLY1	Congenital disorder of deglycosylation, Intellectual disability, Neuromotor delay, Peripheral neuropathy
NHLRC1	Epilepsy, Lafora disease, progressive myoclonic 2b
NHLRC2	AND CEREBRAL ANGIOMATOSIS, FIBROSIS, NEURODEGENERATION
NHS	Nance-Horan syndrome
NIPAL4	Autosomal recessive congenital ichthyosis 6
NIPBL	Cornelia de Lange syndrome 1
NKX2-5	Abnormality of cardiovascular system morphology, Atrial septal defect 7 with or without atrioventricular conduction defects
NKX3-2	Spondylo-megaepiphyseal-metaphyseal dysplasia
NKX6-2	AUTOSOMAL RECESSIVE, SPASTIC ATAXIA 8, WITH HYPOMYELINATING LEUKODYSTROPHY
NLGN4X	Autism, Non-syndromic X-linked intellectual disability, X-linked 2, susceptibility to
NLRP7	1, Hydatidiform mole, recurrent
NOTCH1	Adams-Oliver syndrome 5, Aortic valve disorder, congenital heart defect
NPC1	Niemann-Pick disease, Niemann-Pick disease type C1, type C
NPHP1	Nephronophthisis, Nephronophthisis 1
NPHP3, NPHP3-ACAD11	Meckel syndrome type 7

NPHS1	Finnish congenital nephrotic syndrome
NPHS2	Idiopathic nephrotic syndrome, Nephrotic syndrome, idiopathic, steroid-resistant
NPHS2, AXDND1	Idiopathic nephrotic syndrome, Nephrotic range proteinuria, Nephrotic syndrome, idiopathic, steroid-resistant
NPRL3, HBA-LCR	Epilepsy, familial focal, with variable foci 3
NR0B1	Congenital adrenal hypoplasia, X-linked
NR2E3	Abnormality of color vision, Cone-rod dystrophy, Enhanced s-cone syndrome, Horizontal nystagmus, NR2E3-Related Disorders, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 37, Visual impairment
NR3C2	Autosomal dominant pseudohypoaldosteronism type 1
NSD1	Beckwith-Wiedemann syndrome, Inborn genetic diseases, Sotos syndrome 1
NSD2	4p partial monosomy syndrome, Wolf-Hirschhorn like syndrome
NSMCE2	Seckel syndrome 10
NSMF	Hypogonadotropic hypogonadism 9 with or without anosmia
NSUN2	Mental retardation, autosomal recessive 5
NT5E	Calcification of joints and arteries
NTHL1	Familial adenomatous polyposis 3, Hereditary cancer-predisposing syndrome
NTRK1	Hereditary insensitivity to pain with anhidrosis
OAT	Ornithine aminotransferase deficiency
OBSL1	Three M syndrome 2
OCA2	1, Skin/hair/eye pigmentation, Tyrosinase-positive oculocutaneous albinism, variation in
OCLN	Pseudo-TORCH syndrome 1
OFD1	Joubert syndrome, Orofaciodigital syndrome I, Simpson-Golabi-Behmel syndrome, type 2
OPA1	Abortive cerebellar ataxia, Dominant hereditary optic atrophy, Inborn genetic diseases, Mitochondrial diseases, Retinal dystrophy
OPHN1	Mental retardation X-linked with cerebellar hypoplasia and distinctive facial appearance
OPN1LW	Cone monochromatism
ORC6	Meier-Gorlin syndrome 3
OSGIN2, NBN	Hereditary cancer-predisposing syndrome, Microcephaly, normal intelligence and immunodeficiency
OTC	Abnormality of ornithine metabolism, Hyperammonemia, Ornithine carbamoyltransferase deficiency, Protein avoidance
OTOA	Deafness, Rare genetic deafness, autosomal recessive 22
OTOF	Deafness, Rare genetic deafness, autosomal recessive 9
OTOG	Deafness, Intellectual disability, Rare genetic deafness, Seizures, autosomal recessive 18b
OTOGL	Rare genetic deafness
OTUD6B	Dysmorphic features, Epilepsy, Intellectual developmental disorder with dysmorphic facies, Intellectual disability, and distal limb anomalies, seizures
OTX2	Syndromic microphthalmia type 5

P2RY12, MED12L	Platelet-type bleeding disorder 8
P3H1	Osteogenesis imperfecta type 8
P3H2	Myopia, high, with cataract and vitreoretinal degeneration
P4HA2	Myopia 25, autosomal dominant
PAFAH1B1	Inborn genetic diseases, Lissencephaly due to LIS1 mutation
PAH	Phenylketonuria
PALB2	Basal cell carcinoma, Breast cancer, Cancer of the pancreas, Familial cancer of breast, Fanconi anemia, Generalized hypopigmentation, Hereditary breast and ovarian cancer syndrome, Hereditary cancer, Hereditary cancer-predisposing syndrome, Neoplasm of the breast, Ovarian Neoplasms, PALB2-Related Disorders, Pancreatic cancer 3, Pre-B-cell acute lymphoblastic leukemia, Tracheoesophageal fistula, Tumor susceptibility linked to germline BAP1 mutations, complementation group N, susceptibility to
PANK2	Pigmentary pallidal degeneration
PAPSS2	Spondyloepimetaphyseal dysplasia, pakistani type
PARN	Dyskeratosis congenita, autosomal recessive 6
PATL2	OOCYTE MATURATION DEFECT 4
PAX2	Focal segmental glomerulosclerosis 7, Renal coloboma syndrome
PAX3	Rare genetic deafness, Waardenburg syndrome, Waardenburg syndrome type 1
PAX6	Aniridia 1, Keratitis, autosomal dominant
PAX9	3, Tooth agenesis, selective
PC	Pyruvate carboxylase deficiency
PCCA	Propionic acidemia
PCCB	Propionic acidemia
PCDH15	DIGENIC, Deafness, Nonsyndromic Deafness, Rare genetic deafness, Retinal dystrophy, TYPE ID/F, USHER SYNDROME, Usher syndrome, Usher syndrome type 1, Usher syndrome type 1D, Usher syndrome type 1F, autosomal recessive 23, type 1G
PCDH19	Absence seizures, Delayed speech and language development, Early infantile epileptic encephalopathy 9, Frontal cortical atrophy, Generalized seizures, Generalized tonic-clonic seizures, Global developmental delay, Hand tremor, Long palpebral fissure, Prominent fingertip pads, Strabismus, Temporal cortical atrophy
PCLO	Pontocerebellar hypoplasia type 3
PCNT	Microcephalic osteodysplastic primordial dwarfism type II
PCSK1, LOC101929710	Proprotein convertase 1/3 deficiency
PCSK9	Familial hypercholesterolemia, Familial hypercholesterolemia 1, Low density lipoprotein cholesterol level quantitative trait locus 1
PCYT1A	Spondylometaphyseal dysplasia-cone-rod dystrophy syndrome
PDE11A	2, Pigmented nodular adrenocortical disease, primary
PDE6B	Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 40
PDE6C	Achromatopsia 5
PDE8B	Striatal degeneration, autosomal dominant 1
PDHA1	Inborn genetic diseases, Pyruvate dehydrogenase E1-alpha deficiency

PDX1	DIABETES MELLITUS, Maturity-onset diabetes of the young type 4, PERMANENT NEONATAL 1, Pancreatic agenesis 1
PDZD7	AUTOSOMAL RECESSIVE 57, DEAFNESS, Rare genetic deafness, Usher syndrome, type 2A
PEPD	Prolidase deficiency
PEX1	Deafness enamel hypoplasia nail defects, Peroxisome biogenesis disorder 1A (Zellweger), Peroxisome biogenesis disorder 1B, Peroxisome biogenesis disorders, Retinal dystrophy, Zellweger syndrome spectrum
PEX1, GATAD1	Deafness enamel hypoplasia nail defects, Peroxisome biogenesis disorder 1A (Zellweger), Peroxisome biogenesis disorder 1B, Peroxisome biogenesis disorders, Zellweger syndrome spectrum
PEX10	Peroxisome biogenesis disorder, Peroxisome biogenesis disorder 6A, Peroxisome biogenesis disorder 6B, Peroxisome biogenesis disorders, Zellweger syndrome spectrum, complementation group 7
PEX10, PLCH2	Peroxisome biogenesis disorder 6B
PEX12	Infantile Refsum's disease, Peroxisome biogenesis disorder 3A, Peroxisome biogenesis disorders, Zellweger syndrome spectrum
PEX2	Peroxisome biogenesis disorder 5B, Peroxisome biogenesis disorder 5a (zellweger), Peroxisome biogenesis disorders, Zellweger syndrome spectrum
PEX26	Peroxisome biogenesis disorder 7A, Peroxisome biogenesis disorder 7B, Peroxisome biogenesis disorders, Zellweger syndrome spectrum
PEX6	Heimler syndrome 2, Peroxisome biogenesis disorder 4B, Peroxisome biogenesis disorder 4a (zellweger), Peroxisome biogenesis disorders, Retinal dystrophy, Zellweger syndrome spectrum
PEX7	PEX7-Related Disorders, Peroxisome biogenesis disorder 9B, Phytanic acid storage disease, Rhizomelic chondrodysplasia punctata type 1
PGAM2, DBNL	Glycogen storage disease type X
PGAP1	Mental retardation, autosomal recessive 42
PGAP3	Hyperphosphatasia with mental retardation syndrome 4
PGM3, DOP1A	Immunodeficiency 23
PHEX	Familial X-linked hypophosphatemic vitamin D refractory rickets
PHEX, PTCHD1-AS	Familial X-linked hypophosphatemic vitamin D refractory rickets
PHF3, EYS	Retinal dystrophy, Retinitis pigmentosa 25
PHF6	Borjeson-Forssman-Lehmann syndrome
PHGDH	Phosphoglycerate dehydrogenase deficiency
PHIP	Developmental delay, and dysmorphic features, intellectual disability, obesity
PHYH	1, Phytanic acid storage disease, Refsum disease, adult
PI4KA	Polymicrogyria, perisylvian, with cerebellar hypoplasia and arthrogryposis
PIGA	Paroxysmal nocturnal hemoglobinuria 1
PIGN	Multiple congenital anomalies-hypotonia-seizures syndrome 1
PIGO	Hyperphosphatasia with mental retardation syndrome 2, Hyperphosphatasia-intellectual disability syndrome
PIGT	Multiple congenital anomalies-hypotonia-seizures syndrome 3, PIGT-related disorder
PIK3R1	SHORT syndrome

PINK1	Parkinson disease 6, autosomal recessive early-onset
PIRC66, MIR4713HG, CYP19A1	Aromatase deficiency
PITX3	Anterior segment mesenchymal dysgenesis, Cataract 11
PJVK	Deafness, Rare genetic deafness, autosomal recessive 59
PKD1	Autosomal recessive polycystic kidney disease, Polycystic kidney disease, adult type
PKD1, LOC105371049	Polycystic kidney disease, adult type
PKHD1	Autosomal recessive polycystic kidney disease, Polycystic kidney dysplasia, Polycystic liver disease
PKP1	Epidermolysis bullosa simplex due to plakophilin deficiency
PKP2	Arrhythmogenic right ventricular cardiomyopathy, Arrhythmogenic right ventricular dysplasia/cardiomyopathy, Arrhythmogenic ventricular cardiomyopathy, Cardiac arrhythmia, Cardiomyopathy, Cardiovascular phenotype, Sudden unexplained death, type 9
PLA2G5	Fleck retina, familial benign
PLA2G6	Infantile neuroaxonal dystrophy, Iron accumulation in brain, Neurodegeneration with brain iron accumulation 2b, PLA2G6-associated neurodegeneration
PLCB1	Early infantile epileptic encephalopathy 12
PLCB4	Auriculocondylar syndrome 2
PLCD1	Leukonychia totalis
PLD1	Cardiac valvular defect, developmental
PLD3, PRX	Charcot-Marie-Tooth disease, SPINOCEREBELLAR ATAXIA 46
PLEC	Epidermolysis bullosa simplex with muscular dystrophy
PLN, CEP85L	Cardiac arrest, Cardiomyopathy, Cardiovascular phenotype, Dilated cardiomyopathy 1P, Familial hypertrophic cardiomyopathy 18, Hypertrophic cardiomyopathy, Primary dilated cardiomyopathy, Sudden cardiac death
PLOD1	Cardiovascular phenotype, Ehlers-Danlos syndrome, hydroxylysine-deficient
PLOD2	Bruck syndrome 2
PLP1, RAB9B	Hereditary spastic paraplegia 2
PLS3	Bone mineral density quantitative trait locus 18
PMFBP1	SPERMATOGENIC FAILURE 31
PMM2	Congenital disorder of glycosylation, type Ia
PMP22	Charcot-Marie-Tooth disease
PMS2	Acute lymphoid leukemia, Burkitt lymphoma, Colorectal cancer, Glioblastoma, Hereditary cancer, Hereditary cancer-predisposing syndrome, Hereditary nonpolyposis colon cancer, Hereditary nonpolyposis colorectal cancer type 4, Lymphoma, Lynch syndrome, Lynch syndrome I, Pulmonary arterial hypertension, Pulmonary insufficiency, Respiratory insufficiency, Tumor susceptibility linked to germline BAP1 mutations, Turcot syndrome, non-polyposis
PNKD, CATIP-AS2	Paroxysmal nonkinesigenic dyskinesia 1
PNKP	Ataxia-oculomotor apraxia 4, Early infantile epileptic encephalopathy 10, Early infantile epileptic encephalopathy 12, History of neurodevelopmental disorder

PNPLA2	Neutral lipid storage myopathy
PNPLA6	Hereditary spastic paraplegia 39, Laurence-Moon syndrome, PNPLA6-related disorders, Trichomegaly-retina pigmentary degeneration-dwarfism syndrome
PNPLA8	Mitochondrial myopathy-lactic acidosis-deafness syndrome
PNPO	Pyridoxal phosphate-responsive seizures
POC5	Retinitis pigmentosa, Syndromic retinitis pigmentosa
POGLUT1	Dowling-degos disease 4
POGZ	Global developmental delay, Speech apraxia, White-sutton syndrome, dysmorphy, intellectual deficiency
POLA1	VAN ESCH-O''''DRISCOLL SYNDROME, Van Esch type, X-linked intellectual disability
POLD1	Colorectal cancer 10, Hereditary cancer-predisposing syndrome, Mandibular hypoplasia, and lipodystrophy syndrome, deafness, progeroid features
POLE	12, ADRENAL HYPOPLASIA CONGENITA, AND IMMUNODEFICIENCY, Colorectal cancer, GENITAL ANOMALIES, Hereditary cancer-predisposing syndrome, INTRAUTERINE GROWTH RETARDATION, METAPHYSEAL DYSPLASIA, susceptibility to
POLG	Generalized epilepsy, Global developmental delay, Obesity, Progressive sclerosing poliodystrophy, Seizures
POLH	Xeroderma pigmentosum variant type
POLR1A	Acrofacial dysostosis, Cincinnati type
POLR1C	Treacher Collins syndrome 3
POLR1D	Treacher Collins syndrome 2
POLR2F, SOX10	Rare genetic deafness, Waardenburg syndrome type 4C
POLR3A	Hypomyelinating leukodystrophy 7, Neonatal pseudo-hydrocephalic progeroid syndrome
POLR3B	Cerebellar hypoplasia with endosteal sclerosis, Hypogonadotropic hypogonadism 7 with or without anosmia, Hypomyelinating leukodystrophy 7, Hypomyelinating leukodystrophy 8, with or without oligodontia and/or hypogonadotropic hypogonadism
POMK	12, Muscular dystrophy-dystroglycanopathy (limb-girdle), type c
POMT1	1, Congenital muscular dystrophy-dystroglycanopathy with mental retardation, Limb-girdle muscular dystrophy-dystroglycanopathy, Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), POMT1-Related Disorders, Walker-Warburg congenital muscular dystrophy, type A, type B1, type C1
POMT2	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, Limb-girdle muscular dystrophy-dystroglycanopathy, type A2, type C2
POP1	Anauxetic dysplasia 2
POR	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis, Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency
PORCN	Focal dermal hypoplasia
POT1	10, Hereditary cancer-predisposing syndrome, Melanoma, cutaneous malignant, susceptibility to
POU3F4	Deafness, Rare genetic deafness, X-linked 2
POU4F3	Rare genetic deafness

PPARG	Diabetes Mellitus, Diabetes mellitus, Noninsulin-Dependent, digenic, type II, with Acanthosis Nigricans and Hypertension
PPIB	Osteogenesis imperfecta type 9
PPOX	Variegate porphyria
PPP1R12A	GENITOURINARY AND/OR BRAIN MALFORMATION SYNDROME
PPT1	History of neurodevelopmental disorder, Neuronal Ceroid-Lipofuscinosis, Neuronal ceroid lipofuscinosis, Neuronal ceroid lipofuscinosis 1, Recessive
PQBP1	Delayed speech and language development, Hyperactivity, Inborn genetic diseases, Intellectual disability, Microcephaly, Renpenning syndrome 1
PRB3	PRB3M(NULL)
PRDM16	Left ventricular noncompaction 8
PRDM5	Brittle cornea syndrome 2
PRDX1, MMACHC	DIGENIC, METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, cblC TYPE
PRF1	Familial hemophagocytic lymphohistiocytosis, Familial hemophagocytic lymphohistiocytosis 2
PRKAR1A	Carney complex, type 1
PRKAR1A, FAM20A	Amelogenesis imperfecta type 1G
PRKAR1B, DNAAF5	18, Ciliary dyskinesia, primary
PRKCSH	Polycystic liver disease 1
PRKN	Parkinson disease 2
PRMT7	Short stature, and seizures, brachydactyly, intellectual developmental disability
PROK2	Hypogonadotropic hypogonadism 4 with or without anosmia
PROKR2	Inborn genetic diseases, Kallmann syndrome 3
PROM1	Cone-rod dystrophy 12, PROM1-Related Disorders, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 41
PROP1	Pituitary hormone deficiency, combined, combined 2
PRPH2	Macular dystrophy, Retinal dystrophy, Retinitis pigmentosa 7, Retinitis punctata albescens, adult-onset, autosomal dominant, vitelliform
PRRT2	2, Episodic kinesigenic dyskinesia 1, History of neurodevelopmental disorder, Infantile convulsions and choreoathetosis, Paroxysmal kinesigenic dyskinesia, Paroxysmal nonkinesigenic dyskinesia 1, Seizures, benign familial infantile
PRSS12	Mental retardation, autosomal recessive 1
PRSS56	Microphthalmia, isolated 6
PRX	Charcot-Marie-Tooth disease, demyelinating, type 4F
PSAP	Combined saposin deficiency
PSEN1	3, Acne inversa, familial
PSENEN	2, Acne inversa, familial
PTCH1	Gorlin syndrome, Hereditary cancer-predisposing syndrome
PTCH2	Gorlin syndrome, Medulloblastoma

PTEN	Cowden syndrome, Cowden syndrome 1, Glioblastoma, Glioma susceptibility 2, Hemangioma, Hereditary cancer-predisposing syndrome, Inborn genetic diseases, Macrocephaly/autism syndrome, Malignant tumor of prostate, Meningioma, Neoplasm of brain, Neoplasm of the breast, Neoplasm of the large intestine, Non-small cell lung cancer, Ovarian Neoplasms, PTEN hamartoma tumor syndrome, PTEN-related disorder, Proteus-like syndrome, VACTERL association with hydrocephalus, familial
PTH1R	Chondrodysplasia Blomstrand type
PTPN11	Metachondromatosis
PTPRF	2, Breasts and/or nipples, aplasia or hypoplasia of
PTPRO	Nephrotic syndrome, type 6
PTS	BH4-deficient hyperphenylalaninemia A, Hyperphenylalaninemia, a, bh4-deficient, due to partial pts deficiency
PUF60	Verheij syndrome
PURA	Apnea, Generalized hypotonia, Intellectual disability, Limb dystonia, Mental retardation, PURA Syndrome, PURA-related severe neonatal hypotonia-seizures-encephalopathy syndrome due to a point mutation, autosomal dominant 31
PUS7	AND SHORT STATURE, INTELLECTUAL DEVELOPMENTAL DISORDER WITH ABNORMAL BEHAVIOR, MICROCEPHALY
PXDN	Anterior segment dysgenesis 7
PYCR1	Autosomal recessive cutis laxa type 2B
PYGL	Glycogen storage disease, type VI
PYGM	Glycogen storage disease, type V
RAB23	Carpenter syndrome, Carpenter syndrome 1
RAB27A	Griscelli syndrome, Griscelli syndrome type 2
RAB33B	Smith-McCort dysplasia 2
RAB3GAP1	Warburg micro syndrome 1
RABL3	5, PANCREATIC CANCER, SUSCEPTIBILITY TO
RAD50	Hereditary cancer-predisposing syndrome, Nijmegen breakage syndrome-like disorder
RAD51C	Breast-ovarian cancer, Fanconi anemia, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms, RAD51C-Related Disorders, complementation group O, familial 3
RAD51D, RAD51L3-RFFL	Breast-ovarian cancer, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms, familial 4
RAD51L3-RFFL, RAD51D	Breast-ovarian cancer, Hereditary cancer-predisposing syndrome, familial 4
RAI1	Smith-Magenis syndrome
RAPSN	11, Myasthenic syndrome, associated with acetylcholine receptor deficiency, congenital
RARS1	9, Leukodystrophy, hypomyelinating
RASA1	Capillary malformation-arteriovenous malformation, Capillary malformation-arteriovenous malformation 1
RB1	Hereditary cancer-predisposing syndrome, Neoplasm, Osteosarcoma, Retinoblastoma, Small cell lung cancer, Urinary bladder cancer, trilateral
RBBP8	Microcephaly with mental retardation and digital anomalies

RBM20	Cardiovascular phenotype, Dilated cardiomyopathy 1DD, Primary dilated cardiomyopathy
RBP3	Retinitis pigmentosa 66
RD3	Leber congenital amaurosis 12
RDH12	Retinitis pigmentosa 53
RDH5, BLOC1S1-RDH5	Fundus albipunctatus, Pigmentary retinal dystrophy, autosomal recessive
RECQL	Hereditary cancer-predisposing syndrome
RECQL, PYROXD1	Hereditary cancer-predisposing syndrome
RECQL4	B lymphoblastic leukemia lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1), Baller-Gerold syndrome, High Grade Surface Osteosarcoma, Rapadilino syndrome, Rothmund-Thomson syndrome, Rothmund-Thomson syndrome type 2
REEP6	Retinitis pigmentosa 77
RELT	AMELOGENESIS IMPERFECTA, TYPE IIIC
REN	Hyperproreninemia, familial
RET	Hirschsprung disease 1, Sensorineural hearing loss
RFX5	Bare lymphocyte syndrome, complementation group c, type II
RFXANK	Bare lymphocyte syndrome, complementation group B, type II
RFXAP	Bare Lymphocyte Syndrome, Bare lymphocyte syndrome 2, Complementation Group D, Type II
RHAG	Rh-null, regulator type
RHCE	AMORPH TYPE, RH-NULL
RHO	Autosomal dominant retinitis pigmentosa
RIF1, NEB	Nemaline myopathy, Nemaline myopathy 2
RIN2	Macrocephaly, alopecia, and scoliosis, cutis laxa
RIPK1	IMMUNODEFICIENCY 57 WITH AUTOINFLAMMATION
RIPK4	Bartsocas-Papas syndrome
RNASEH2A	Aicardi Goutieres syndrome 4
RNASEH2B	Aicardi Goutieres syndrome 2
RNF113A	Trichothiodystrophy 5, nonphotosensitive
RNF216	Gordon Holmes syndrome
ROBO3	Gaze palsy, familial horizontal, with progressive scoliosis 1
RORA, RORA-AS1	INTELLECTUAL DEVELOPMENTAL DISORDER WITH OR WITHOUT EPILEPSY OR CEREBELLAR ATAXIA
RP1	Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 1
RP1L1	RETINITIS PIGMENTOSA 88
RPE65	Leber congenital amaurosis 2, RETINITIS PIGMENTOSA 87 WITH CHOROIDAL INVOLVEMENT, RPE65-Related Disorders, Retinal dystrophy, Retinitis pigmentosa 20
RPGR	Inborn genetic diseases, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 15, X-linked, and sinorespiratory infections, with deafness
RPGRIP1	Leber congenital amaurosis 6
RPGRIP1L	Joubert syndrome, Joubert syndrome 7

RPL36A-HNRNPH2, GLA	Fabry disease
RPL5, DIPK1A	Diamond-Blackfan anemia, Diamond-Blackfan anemia 1
RPS10, RPS10-NUDT3	Diamond-Blackfan anemia 9
RPS27	Diamond-Blackfan anemia 17
RPS6KA3	Coffin-Lowry syndrome, Mental retardation, X-linked 19
RSPH1	Kartagener syndrome, Primary ciliary dyskinesia, Primary ciliary dyskinesia 24
RSPH4A	11, Ciliary dyskinesia, Kartagener syndrome, Primary ciliary dyskinesia, primary
RSPO2	TETRAAMELIA SYNDROME 2
RTEL1, RTEL1-TNFRSF6B	3, 4, 5, Dyskeratosis congenita, Idiopathic fibrosing alveolitis, Pulmonary fibrosis and/or bone marrow failure, autosomal dominant, autosomal recessive, chronic form, telomere-related
RTN2	Hereditary spastic paraplegia 12
RTTN	Congenital microcephaly, Microcephaly, and polymicrogyria with or without seizures, short stature
RUNX1	Acute myeloid leukemia, Familial platelet disorder with associated myeloid malignancy
RYR1	1, Central core myopathy, Malignant hyperthermia, Minicore myopathy, Multi-minicore disease and atypical periodic paralysis, Neuromuscular disease, RYR1-Related Disorders, susceptibility to
SACS	Autosomal recessive spastic ataxia, Charlevoix-Saguenay spastic ataxia, Spastic paraplegia
SAG	Oguchi's disease, Retinitis pigmentosa 47, SAG-Related Disorders
SALL1	Townes syndrome
SAMD9L	Ataxia-pancytopenia syndrome
SAMHD1	Aicardi Goutieres syndrome 5
SASH1	Dyschromatosis universalis hereditaria 1
SATB2	SATB2-Related Disorder
SBDS	Inborn genetic diseases, Shwachman-Diamond syndrome 1
SBF1	Charcot-Marie-Tooth disease type 4
SCAPER	Attention deficit hyperactivity disorder, INTELLECTUAL DEVELOPMENTAL DISORDER AND RETINITIS PIGMENTOSA, Intellectual disability, Rod-cone dystrophy, moderate
SCARB2	Epilepsy, progressive myoclonic 4, with or without renal failure
SCARF2	Van den Ende-Gupta syndrome
SCN1A	Autosomal dominant epilepsy, Early infantile epileptic encephalopathy, Familial hemiplegic migraine type 3, Generalized epilepsy with febrile seizures plus, History of neurodevelopmental disorder, Severe myoclonic epilepsy in infancy, type 2, Dravet
SCN1A, LOC102724058	Autosomal dominant epilepsy, Early infantile epileptic encephalopathy, Epileptic encephalopathy, Generalized epilepsy with febrile seizures plus, Seizures, Severe myoclonic epilepsy in infancy, type 2
SCN2A	SCN2A-related disorder
SCN5A	Brugada syndrome, Brugada syndrome (shorter-than-normal QT interval), Brugada syndrome 1, Cardiovascular phenotype, Dilated cardiomyopathy 1E, Heart block, Long QT syndrome 1, nonprogressive

SCN5A, LOC110121269	Brugada syndrome, Brugada syndrome (shorter-than-normal QT interval)
SCN9A, SCN1A-AS1	Generalized epilepsy with febrile seizures plus, Hereditary sensory and autonomic neuropathy type IIA, Indifference to pain, autosomal recessive, congenital, type 7
SCNN1A	Autosomal recessive pseudohypoaldosteronism type 1, Idiopathic bronchiectasis
SCNN1B	Liddle syndrome 1
SCNN1G	Autosomal recessive pseudohypoaldosteronism type 1, LIDDLE SYNDROME 2
SCO1	Mitochondrial complex IV deficiency
SCP2	Leukoencephalopathy with dystonia and motor neuropathy
SDCCAG8	Bardet-Biedl syndrome, Bardet-Biedl syndrome 16, Senior-Loken syndrome 7
SDHA	Carney triad, Dilated cardiomyopathy 1GG, Hereditary cancer-predisposing syndrome, Leigh syndrome, Mitochondrial complex II deficiency, Paragangliomas 5, Pilocytic astrocytoma
SDHAF2	Hereditary Paraganglioma-Pheochromocytoma Syndromes
SDHB	Carney-Stratakis syndrome, Gastrointestinal stromal tumor, Hereditary Paraganglioma-Pheochromocytoma Syndromes, Hereditary cancer-predisposing syndrome, Paragangliomas 4, Pheochromocytoma
SDHC	Gastrointestinal stromal tumor, Hereditary Paraganglioma-Pheochromocytoma Syndromes, Hereditary cancer-predisposing syndrome, Paragangliomas 3
SDHD	Carney-Stratakis syndrome, Cowden syndrome 3, Hereditary Paraganglioma-Pheochromocytoma Syndromes, Hereditary cancer-predisposing syndrome, Paragangliomas 1, Paragangliomas 1 with sensorineural hearing loss, Pheochromocytoma
SDR9C7	AUTOSOMAL RECESSIVE 13, CONGENITAL, ICHTHYOSIS
SEC23B	Congenital dyserythropoietic anemia
SEC24D	Cole-Carpenter syndrome 2
SECISBP2	Thyroid hormone metabolism, abnormal
SELENBP1	EXTRAORAL HALITOSIS DUE TO METHANETHIOL OXIDASE DEFICIENCY, Extra oral halitosis
SELENON	Eichsfeld type congenital muscular dystrophy
SEMA3A	Hypogonadotropic hypogonadism 16 with or without anosmia
SEPSECS	Pontocerebellar hypoplasia type 2D
SEPTIN12	Spermatogenic failure 10
SERAC1	3-methylglutaconic aciduria with deafness, Mitochondrial oxidative phosphorylation disorder, and Leigh-like syndrome, encephalopathy
SERPINA6	Corticosteroid-binding globulin deficiency
SERPINA7	Thyroxine-binding globulin quantitative trait locus
SERPINB6	Rare genetic deafness
SERPINB7	Palmoplantar keratoderma, nagashima type
SERPINC1	Antithrombin III deficiency
SERPINF1	Osteogenesis imperfecta, type VI
SERPING1	Hereditary angioedema type 1
SERPINH1	Osteogenesis imperfecta type 10
SETBP1	SETBP1-Related Disorder
SETD5	Inborn genetic diseases, Mental retardation, autosomal dominant 23

SF3B4	Hereditary hearing loss and deafness, Inborn genetic diseases, Nager syndrome
SFRP4	Pyle metaphyseal dysplasia
SFTPA1	Respiratory distress associated with prematurity
SFTPB	1, Surfactant metabolism dysfunction, pulmonary
SGCA	Autosomal recessive limb-girdle muscular dystrophy type 2D
SGCD	Neuromuscular disease
SGCE, CASD1	Myoclonic dystonia
SGCG	Severe autosomal recessive muscular dystrophy of childhood - North African type
SGSH	Developmental regression, Diarrhea, Gastrointestinal dysmotility, Global developmental delay, MPS-III-A, Mucopolysaccharidosis, Nystagmus, Retinal dystrophy, Sanfilippo syndrome, Severe visual impairment
SH2D1A	Lymphoproliferative syndrome 1, X-Linked Lymphoproliferative Syndrome, X-linked
SH3PXD2B	Frank-Ter Haar syndrome
SH3TC2	Charcot-Marie-Tooth disease, Charcot-Marie-Tooth disease type 4, Inborn genetic diseases, Mononeuropathy of the median nerve, SH3TC2-Related Disorders, mild, type 4C
SHANK3	22q13.3 deletion syndrome, Autism spectrum disorder, History of neurodevelopmental disorder, Inborn genetic diseases, SHANK3-Related Disorder
SHOX	Leri-Weill dyschondrosteosis
SI	Sucrase-isomaltase deficiency
SIX6	Colobomatous optic disc-macular atrophy-chorioretinopathy syndrome
SKIV2L	Trichohepatoenteric syndrome 2
SLC10A7	AMELOGENESIS IMPERFECTA, AND SKELETAL DYSPLASIA WITH SCOLIOSIS, SHORT STATURE
SLC12A1	Bartter syndrome, antenatal, type 1
SLC12A3	Familial hypokalemia-hypomagnesemia
SLC12A6	Agenesis of the corpus callosum with peripheral neuropathy, Charcot-Marie-Tooth disease
SLC17A5	Salla disease, Sialic acid storage disease, severe infantile type
SLC19A1, COL18A1	Knobloch syndrome 1
SLC19A2	Megaloblastic anemia, thiamine-responsive, with diabetes mellitus and sensorineural deafness
SLC19A3	Biotin-responsive basal ganglia disease
SLC22A5	Renal carnitine transport defect
SLC25A20	Carnitine acylcarnitine translocase deficiency
SLC26A2	3MC syndrome 2, Achondrogenesis, Atelosteogenesis type II, Diastrophic dysplasia, Multiple epiphyseal dysplasia type 4, Osteochondrodysplasia, SLC26A2-Related Disorders, type IB
SLC26A3	Congenital secretory diarrhea, chloride type
SLC26A4	Enlarged vestibular aqueduct, Pendred syndrome, Rare genetic deafness
SLC2A10	Arterial tortuosity syndrome, Cardiovascular phenotype
SLC2A2	Fanconi-Bickel syndrome
SLC30A8	Diabetes mellitus type 2

SLC33A1	Spastic paraplegia, Spastic paraplegia 42, autosomal dominant
SLC34A3	Autosomal recessive hypophosphatemic bone disease
SLC35A2	SLC35A2-CDG
SLC35D1	Schneckenbecken dysplasia
SLC37A4	Glucose-6-phosphate transport defect, Glycogen storage disease, Inborn genetic diseases, Phosphate transport defect
SLC38A8	FOVEAL HYPOPLASIA 2 WITH OPTIC NERVE MISROUTING AND ANTERIOR SEGMENT DYSGENESIS
SLC39A4	Hereditary acrodermatitis enteropathica
SLC45A2	Oculocutaneous albinism type 4
SLC4A1	Autosomal dominant distal renal tubular acidosis
SLC4A11	4, Corneal dystrophy, Corneal endothelial dystrophy, Fuchs endothelial
SLC52A3	Brown-Vialetto-Van Laere syndrome 1
SLC6A1	Myoclonic-atonic epilepsy, SLC6A1-Related Disorder
SLC9A3	Diarrhea 8, congenital, secretory sodium
SLC9A3, SLC9A3-AS1	Diarrhea 8, congenital, secretory sodium
SLC9A6	Gastrostomy tube feeding in infancy, Global developmental delay, Recurrent respiratory infections, Scoliosis, Seizures, Sleep disturbance
SLCO2A1	Primary hypertrophic osteoarthropathy, autosomal recessive 2
SLITRK1	Tourette Syndrome, Trichotillomania
SLURP1	Acroerythrokeratoderma
SMAD3	Familial thoracic aortic aneurysm and aortic dissection
SMAD4	Carcinoma of pancreas, Hereditary cancer-predisposing syndrome, Juvenile polyposis syndrome, Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Myhre syndrome
SMAD6	Aortic valve disease 2, Aortic valve disorder, CRANIOSYNOSTOSIS 7, SUSCEPTIBILITY TO
SMARCA4	Neuroblastoma
SMARCAL1	Schimke immuno-osseous dysplasia
SMARCB1	Teratoid tumor, atypical
SMARCE1	Meningioma, familial
SMC1A	85, Congenital muscular hypertrophy-cerebral syndrome, EARLY INFANTILE, EPILEPTIC ENCEPHALOPATHY, WITH OR WITHOUT MIDLINE BRAIN DEFECTS
SMN1	Werdnig-Hoffmann disease
SMPD1	Niemann-Pick disease, Sphingomyelin/cholesterol lipidosis, type A, type B
SNAP29	2, CEDNIK syndrome, Leukodystrophy, hypomyelinating
SNRPB	Cerebro-costo-mandibular syndrome
SOHLH1	Nonsyndromic hypergonadotropic hypogonadism, OVARIAN DYSGENESIS 5
SON	Inborn genetic diseases, ZTTK syndrome
SOS1	Gingival fibromatosis 1
SOX2, SOX2-OT	Anophthalmia/microphthalmia-esophageal atresia syndrome
SOX9	Campomelic dysplasia with autosomal sex reversal, Camptomelic dysplasia

SOX9, LOC108021846	Campomelic dysplasia with autosomal sex reversal
SP110, SP140	Hepatic veno-occlusive disease-immunodeficiency syndrome
SP7	Osteogenesis imperfecta type 12
SPART	Troyer syndrome
SPAST	Spastic paraplegia 4, autosomal dominant
SPEF2	Primary ciliary dyskinesia, SPERMATOGENIC FAILURE 43
SPEG	5, Myopathy, centronuclear
SPEG, ASIC4-AS1	5, Myopathy, centronuclear
SPG11	Amyotrophic lateral sclerosis type 5, Hereditary spastic paraplegia, Spastic paraplegia 11, autosomal recessive
SPG7	Hereditary spastic paraplegia, Hereditary spastic paraplegia 7, Mitochondrial diseases
SPINK2	Spermatogenic failure 29
SPINK5	Netherton syndrome
SPNS2	AUTOSOMAL RECESSIVE 115, DEAFNESS, Inborn genetic diseases
SPRTN	Ruijs-Aalfs syndrome
SPTA1	Elliptocytosis 2, Hereditary pyropoikilocytosis
SPTB	Hereditary spherocytosis, Spherocytosis type 2
SQSTM1	Amyotrophic lateral sclerosis and/or frontotemporal dementia 1, Paget disease of bone 2, SQSTM1-related disorder, early-onset
SRCAP	Floating-Harbor syndrome
SRPK2, KMT2E	See cases
SRY	46, XY sex reversal, type 1
ST14	Ichthyosis, autosomal recessive 11, congenital
STAG1	AUTOSOMAL DOMINANT 47, MENTAL RETARDATION
STAG3	Abnormality of the ovary, Female infertility, Premature ovarian failure 8, Premature ovarian insufficiency
STAT1	Mycobacterial and viral infections, autosomal recessive, susceptibility to
STIM1	1, Combined immunodeficiency due to STIM1 deficiency, Myopathy, Stormorken syndrome, tubular aggregate
STK11	Hereditary cancer-predisposing syndrome, Peutz-Jeghers syndrome
STRA6	Microphthalmia syndromic 9
STRC	Deafness, Rare genetic deafness, autosomal recessive 16
STXBP1	Early infantile epileptic encephalopathy, Early infantile epileptic encephalopathy 4, Epileptic encephalopathy
STXBP2	5, Hemophagocytic lymphohistiocytosis, familial
SUCLG1	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic with methylmalonic aciduria)
SUFU	Gorlin syndrome, Medulloblastoma, Medulloblastoma with extensive nodularity, desmoplastic
SULT2B1	AUTOSOMAL RECESSIVE 14, Autosomal recessive congenital ichthyosis 2, CONGENITAL, ICHTHYOSIS
SUMF1	Multiple sulfatase deficiency
SUN5	Spermatogenic failure 16

SURF1	Abnormal pyramidal signs, Cerebellar ataxia, Charcot-Marie-Tooth disease, Dysarthria, Inborn genetic diseases, Leigh syndrome, Leigh syndrome due to COX IV deficiency, Leigh syndrome due to mitochondrial complex IV deficiency, Mitochondrial complex IV deficiency, Muscle weakness, type 4k
SUZ12	IMAGAWA-MATSUMOTO SYNDROME
SYCP2	Cryptozoospermia, Early spermatogenesis maturation arrest, Oligosynaptic infertility
SYCP3	Spermatogenic failure 4
SYNE1	ARTHROGRYPOSIS MULTIPLEX CONGENITA, Cerebellar ataxia, Emery-Dreifuss muscular dystrophy 4, MYOGENIC TYPE, Spinocerebellar ataxia, autosomal dominant, autosomal recessive 8
SYNE4	Rare genetic deafness
SYNGAP1	Inborn genetic diseases, Mental retardation, autosomal dominant 5
SZT2	Early infantile epileptic encephalopathy 18
TAC3	Hypogonadotropic hypogonadism 10 with or without anosmia
TACO1	Mitochondrial complex IV deficiency
TALDO1	Deficiency of transaldolase
TANGO2	AND NEURODEGENERATION, Acute rhabdomyolysis, CARDIAC ARRHYTHMIAS, Cardiac arrhythmia, Episodic flaccid weakness, Intellectual functioning disability, METABOLIC CRISES, RECURRENT, Seizures, WITH RHABDOMYOLYSIS
TAP1	Bare lymphocyte syndrome type 1
TAP2	Bare lymphocyte syndrome type 1, PEPTIDE TRANSPORTER PSF2 POLYMORPHISM
TAZ	3-Methylglutaconic aciduria type 2
TBC1D20	Warburg micro syndrome 4
TBC1D24	1, Caused by mutation in the TBC1 domain family, DOORS syndrome, Deafness, Epileptic encephalopathy, Inborn genetic diseases, autosomal dominant 65, early infantile, member 24
TBCK	Hypotonia, Inborn genetic diseases, Syndromic Infantile Encephalopathy, infantile, with psychomotor retardation and characteristic facies 3
TBR1	Autism 5, Autistic behavior, Intellectual disability, Moderate global developmental delay, Neurodevelopmental disorder, Severe global developmental delay
TBX19	Adrenocorticotropic hormone deficiency
TBX22	Cleft palate with ankyloglossia
TBX3	Ulnar-mammary syndrome
TBX4	Coxopodopatellar syndrome
TBX5	Congenital heart disease (variable), Holt-Oram syndrome
TBXAS1	Ghosal hematodiaphyseal dysplasia, Thromboxane synthetase deficiency
TCAP	Autosomal recessive limb-girdle muscular dystrophy type 2G, Dilated cardiomyopathy 1N, Primary familial hypertrophic cardiomyopathy
TCF12	Craniosynostosis 3
TCF20	Neurodevelopmental abnormality
TCF4	Intellectual disability, Pitt-Hopkins syndrome
TCN2	Inborn genetic diseases, Transcobalamin II deficiency

TCOF1	Treacher Collins syndrome 1
TCTEX1D2	Short-rib thoracic dysplasia 17 with or without polydactyly
TCTEX1D2, TM4SF19-TCTEX1D2	Short-rib thoracic dysplasia 17 with or without polydactyly
TCTN2	Joubert syndrome, Meckel syndrome type 8
TCTN3	Orofacial-digital syndrome IV
TDO2	Hypertryptophanemia, familial
TDRD7	Cataract, autosomal recessive congenital 4
TDRD9	SPERMATOGENIC FAILURE 30
TECPR2	Spastic paraplegia 49, autosomal recessive
TECTA	Deafness, Nonsyndromic hearing loss and deafness, Rare genetic deafness, autosomal dominant 12, autosomal recessive 21, neurosensory autosomal recessive 21
TENM3	MICROPHTHALMIA, SYNDROMIC 15
TENT5A	Osteogenesis imperfecta, type 18
TEX14	SPERMATOGENIC FAILURE 23
TEX15	SPERMATOGENIC FAILURE 25
TFAP2B	Patent ductus arteriosus 2
TFR2	Hemochromatosis type 3
TG	Iodotyrosyl coupling defect
TGFB2	Cardiovascular phenotype, Holt-Oram syndrome, Loeys-Dietz syndrome 4
TGFB3	Cardiovascular phenotype, Loeys-Dietz syndrome 5
TGFBR1	Familial thoracic aortic aneurysm and aortic dissection
TGFBR2	Familial thoracic aortic aneurysm and aortic dissection, Hereditary nonpolyposis colorectal cancer type 6, Loeys-Dietz syndrome, Loeys-Dietz syndrome 2, Malignant tumor of esophagus
TGM1	Autosomal recessive congenital ichthyosis 1, Ichthyosis (disease)
TGM5	Peeling skin syndrome 2
TH	Segawa syndrome, autosomal recessive
THRB	Thyroid hormone resistance, autosomal dominant, generalized
TICAM1	4, Herpes simplex encephalitis, susceptibility to
TIMM8A	Deafness dystonia syndrome
TIMMDC1	Leigh syndrome
TJP2	Progressive familial intrahepatic cholestasis 4
TK2	Mitochondrial DNA depletion syndrome 2
TLR5	1, Legionellosis, Melioidosis, Systemic lupus erythematosus, resistance to
TM4SF20	Specific language impairment 5
TMC1	Deafness, Dominant, Nonsyndromic Hearing Loss, Rare genetic deafness, autosomal recessive 7
TMCO1	Craniofacial dysmorphism, and mental retardation syndrome, skeletal anomalies
TMCO6, NDUFA2	Cystic Leukoencephalopathy
TMEM127	Hereditary Paraganglioma-Pheochromocytoma Syndromes, Hereditary cancer-predisposing syndrome, Pheochromocytoma

TMEM216	Joubert syndrome, Joubert syndrome 2, Meckel syndrome, TMEM216-Related Disorders, type 2
TMEM237	Joubert syndrome
TMEM260	Structural heart defects and renal anomalies syndrome
TMEM67	Cerebellar vermis hypoplasia, Generalized hypotonia, Iris coloboma, Joubert syndrome, Joubert syndrome 6, Meckel syndrome, Meckel-Gruber syndrome, Nystagmus, TMEM67-Related Disorders, type 3
TMEM70	Mitochondrial proton-transporting ATP synthase complex deficiency, Nuclearly-encoded mitochondrial complex V (ATP synthase) deficiency 2
TMEM94	Intellectual developmental disorder with cardiac defects and dysmorphic facies
TMEM99, KRT10	Bullous ichthyosiform erythroderma
TMPRSS3	Deafness, Inborn genetic diseases, Rare genetic deafness, autosomal recessive 8
TNFRSF10B	Squamous cell carcinoma of the head and neck
TNFRSF11B	Hyperphosphatasemia with bone disease
TNFRSF13B	Absent epiphyses, Chronic lung disease, Cleft palate, Clubfoot, Coat hanger sign of ribs, Common Variable Immune Deficiency, Common variable immunodeficiency 2, Dominant, Hemivertebrae, Immunoglobulin A deficiency 2, Interstitial pulmonary abnormality, Micrognathia, Patent ductus arteriosus, Preaxial foot polydactyly, Pseudoarthrosis, Respiratory failure, Short femur, Skeletal dysplasia, Vertebral hypoplasia, Vertebral segmentation defect
TNFRSF1A	5, Familial Periodic Fever, Multiple sclerosis, susceptibility to
TNFSF11	Autosomal recessive osteopetrosis 2
TNNI3	Cardiovascular phenotype
TNNI3K, FPGT-TNNI3K	Cardiac conduction disease with or without dilated cardiomyopathy
TNNT2	Cardiomyopathy, Cardiovascular phenotype, Familial hypertrophic cardiomyopathy 2, Familial restrictive cardiomyopathy 3, Hypertrophic cardiomyopathy, Left ventricular noncompaction 6, Primary familial hypertrophic cardiomyopathy
TNPO3	Limb-girdle muscular dystrophy, type 1F
TNXB	1, Ehlers-Danlos syndrome, Ehlers-Danlos syndrome due to tenascin-X deficiency, classic-like
TONSL	Sponastrime dysplasia
TONSL, TONSL-AS1	Sponastrime dysplasia
TOP3A	AND INCREASED SISTER CHROMATID EXCHANGE 2, GROWTH RESTRICTION, MICROCEPHALY
TOPORS	Retinal dystrophy, Retinitis pigmentosa
TP53	Head and Neck Neoplasms, Hereditary cancer-predisposing syndrome, Li-Fraumeni syndrome, Li-Fraumeni syndrome 1, Li-Fraumeni-like syndrome, Multiple myeloma, Neoplasm of the large intestine, Ovarian Neoplasms
TP63	Ectrodactyly, Orofacial cleft 8, and cleft lip/palate syndrome 3, ectodermal dysplasia
TPI1	Triosephosphate isomerase deficiency
TPM2	ARTHROGRYPOSIS, DISTAL, TYPE 2B4
TPO	Deficiency of iodide peroxidase

TPP1	Ceroid lipofuscinosis neuronal 2, Childhood-onset autosomal recessive slowly progressive spinocerebellar ataxia, Inborn genetic diseases, Neuronal ceroid lipofuscinosis
TPRN	Deafness, autosomal recessive 79
TRAPPC11	Limb-girdle muscular dystrophy, type 2S
TRAPPC2	Spondyloepiphyseal dysplasia tarda
TRDN	5, Catecholaminergic polymorphic ventricular tachycardia, Ventricular tachycardia, catecholaminergic polymorphic, with or without muscle weakness
TREX1, ATRIP, ATRIP-TREX1	Aicardi Goutieres syndrome 1, Chilblain Lupus, Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations, TREX1-Related Disorders
TRIM14, NANS	Genevieve type, Spondyloepimetaphyseal dysplasia
TRIM32, ASTN2	Limb-girdle muscular dystrophy
TRIOBP	Nonsyndromic hearing loss and deafness
TRIP11	Achondrogenesis, Goldblatt hypertension, Osteochondrodysplasia, type IA
TRMU	Acute infantile liver failure due to synthesis defect of mtDNA-encoded proteins
TRNT1	Retinitis pigmentosa and erythrocytic microcytosis, Sideroblastic anemia with B-cell immunodeficiency, and developmental delay, periodic fevers
TRPM4	Cardiomyopathy, Progressive familial heart block type IB, TRPM4-Related Disorders
TRPS1	Trichorhinophalangeal dysplasia type I
TRPV4	Charcot-Marie-Tooth disease axonal type 2C
TRPV6	HYPERPARATHYROIDISM, TRANSIENT NEONATAL
TSC1	Cortical dysplasia, Cortical tubers, Focal cortical dysplasia type II, Hereditary cancer-predisposing syndrome, Lymphangiomyomatosis, Multiple renal cysts, Renal cortical cysts, Renal insufficiency, Seizures, Tuberous sclerosis 1, Tuberous sclerosis syndrome, Urinary bladder cancer
TSC2	Focal cortical dysplasia type II, Lymphangiomyomatosis, Tuberous sclerosis 2, Tuberous sclerosis syndrome
TSFM	Combined oxidative phosphorylation deficiency 3, Primary dilated cardiomyopathy
TSHB	Secondary hypothyroidism
TSHR	1, Hypothyroidism, congenital, nongoitrous
TSHZ1	Aural atresia, congenital
TSPAN1, POMGNT1	Congenital muscular alpha-dystroglycanopathy with brain and eye anomalies, Congenital muscular dystrophy-dystroglycanopathy with mental retardation, Limb-girdle muscular dystrophy-dystroglycanopathy, Muscle eye brain disease, POMGNT1-Related Disorders, Retinitis pigmentosa 76, type B3, type C3
TSPAN12	Exudative vitreoretinopathy 5
TSPAN7	Mental retardation 58, X-linked
TSPEAR	ECTODERMAL DYSPLASIA 14, HAIR/TOOTH TYPE WITH HYPOHIDROSIS
TSPEAR-AS1, TSPEAR	Deafness, ECTODERMAL DYSPLASIA 14, HAIR/TOOTH TYPE WITH HYPOHIDROSIS, autosomal recessive 98
TTC19	Mitochondrial complex III deficiency, nuclear type 2
TTC21A	SPERMATOGENIC FAILURE 37

TTC21B, TTC21B-AS1	SHORT-RIB THORACIC DYSPLASIA 4 WITH POLYDACTYLY
TTC29	SPERMATOGENIC FAILURE 42
TTC37	Trichohepatoenteric syndrome, Trichohepatoenteric syndrome 1
TTC7A	Multiple gastrointestinal atresias
TTLL5	Cone-rod dystrophy 19
TTN	Cardiomyopathy, Cardiovascular phenotype, Dilated cardiomyopathy 1G, Limb-girdle muscular dystrophy, Myotubular myopathy, Primary dilated cardiomyopathy, Tibial muscular dystrophy, type 2J
TTN-AS1, TTN	Cardiovascular phenotype, Dilated cardiomyopathy 1G, Limb-girdle muscular dystrophy, Primary dilated cardiomyopathy, TTN-Related Disorders, type 2J
TTN, LOC101927055	Primary dilated cardiomyopathy
TTN, TTN-AS1	9, Broad-based gait, Cardiomyopathy, Cardiovascular phenotype, Congenital muscular dystrophy, Decreased patellar reflex, Delayed gross motor development, Dilated cardiomyopathy 1G, Dilated cardiomyopathy 1S, Distal muscle weakness, Familial dilated cardiomyopathy, Familial hypertrophic cardiomyopathy 9, Gowers sign, Heart murmur, Limb-girdle muscular dystrophy, Muscular dystrophy, Myopathy, Primary dilated cardiomyopathy, Proximal lower limb amyotrophy, Scoliosis, Severe muscular hypotonia, TTN-Related disorder, Tibial muscular dystrophy, Waddling gait, early-onset, myofibrillar, type 2J, with early respiratory failure, with fatal cardiomyopathy
TTPA	Ataxia, Familial isolated deficiency of vitamin E, Friedreich-like, with isolated vitamin E deficiency
TUB, RIC3	Retinal dystrophy and obesity
TUBA3D, MZT2A	KERATOCONUS 9
TUBB8	Oocyte maturation defect 2
TULP1	Leber congenital amaurosis, Retinitis pigmentosa
TWIST1	Craniosynostosis 1, Robinow-Sorauf syndrome, Saethre-Chotzen syndrome
TXNL4A	Burn-McKeown syndrome
TYK2	Tyrosine kinase 2 deficiency
TYR	3, Albinism, Inborn genetic diseases, Myopia (disease), Nonsyndromic Oculocutaneous Albinism, Nystagmus, Oculocutaneous albinism, Oculocutaneous albinism type 1B, Skin/hair/eye pigmentation, Tyrosinase-negative oculocutaneous albinism, ocular, variation in, with sensorineural deafness
TYRP1, LURAP1L-AS1	Oculocutaneous albinism type 3
UBAP1	AUTOSOMAL DOMINANT, SPASTIC PARAPLEGIA 80
UBE3A, SNHG14	Angelman syndrome, History of neurodevelopmental disorder, Inborn genetic diseases
UBE3B	Kaufman oculocerebrofacial syndrome
UBR1	Johanson-Blizzard syndrome
UCP3	Obesity, and type II diabetes, severe
UGT1A, UGT1A10, UGT1A8,	Crigler-Najjar syndrome, Crigler-Najjar syndrome type 1, type II

UGT1A7, UGT1A6, UGT1A5, UGT1A9, UGT1A4, UGT1A1, UGT1A3	
UNC13D	Familial hemophagocytic lymphohistiocytosis 3
UNC80	Hypotonia, Hypotonia-speech impairment-severe cognitive delay syndrome, infantile, with psychomotor retardation and characteristic facies 2
UNG	Hyper-IgM syndrome type 5
UPF3B	Mental retardation, X-linked, syndromic 14
USH1C	Deafness, Rare genetic deafness, Retinal dystrophy, Retinitis pigmentosa, Usher syndrome, Usher syndrome type 1, autosomal recessive 18, type 1C
USH2A	Abnormality of the upper limb, Abnormality of upper limb bone, Abnormality of upper limb joint, Anxiety, Brisk reflexes, Chronic pain, Cognitive impairment, Cone-rod dystrophy, Congenital sensorineural hearing impairment, Congenital stationary night blindness, Dislocated radial head, Distal arthrogryposis, Dysautonomia, Hearing impairment, High palate, Inborn genetic diseases, Macular dystrophy, Multiple joint contractures, Rare genetic deafness, Retinal dystrophy, Retinitis pigmentosa, Retinitis pigmentosa 39, Short stature, USH2A-Related Disorders, Usher syndrome, Usher syndrome type 2, type 2A
USH2A, USH2A-AS1	Rare genetic deafness, Retinal dystrophy, Retinitis pigmentosa 39, USH2A-Related Disorders, Usher syndrome, type 2A
USH2A, USH2A-AS2	Rare genetic deafness, Retinitis pigmentosa 39, Usher syndrome, type 2A
USP18	Pseudo-TORCH syndrome 2
USP27X	Mental retardation, X-linked 105
USP9X	Mental retardation, USP9X related disorders, X-linked 99, female-restricted, syndromic
VCL	Dilated cardiomyopathy 1W, Familial hypertrophic cardiomyopathy 15, Primary dilated cardiomyopathy
VHL	2, Erythrocytosis, Hereditary cancer-predisposing syndrome, Von Hippel-Lindau syndrome, familial
VHL, LOC107303340	1, 2, Erythrocytosis, Hereditary cancer-predisposing syndrome, Renal cell carcinoma, Von Hippel-Lindau syndrome, familial, papillary
VIM, VIM-AS1	Cataract 30, Congenital cataract
VIPAS39	Arthrogryposis, and cholestasis 2, renal dysfunction
VPS13A	Choreoacanthocytosis
VPS13B	Abnormality of the eye, Cohen syndrome, Inborn genetic diseases, Intellectual disability, Microcephaly, Neutropenia, Progressive visual loss, Recurrent aphthous stomatitis, Retinal dystrophy, Short foot, Short stature, Small hand
VPS33B	Arthrogryposis, Inborn genetic diseases, and cholestasis 1, renal dysfunction
VRK2, FANCL	Fanconi anemia, complementation group A, complementation group L
VWF	von Willebrand disorder
WAC	Desanto-shinawi syndrome

WAS	Wiskott-Aldrich syndrome, X-linked severe congenital neutropenia, X-linked thrombocytopenia with normal platelets
WDR35	Cranioectodermal dysplasia, Cranioectodermal dysplasia 2, Jeune thoracic dystrophy, SHORT-RIB THORACIC DYSPLASIA 7 WITHOUT POLYDACTYLY, Short Rib Polydactyly Syndrome, Short rib polydactyly syndrome 5, Short-rib thoracic dysplasia 7/20 with polydactyly, WDR35-Related Disorders, digenic
WDR45	Neurodegeneration with brain iron accumulation, Neurodegeneration with brain iron accumulation 5
WDR72	Amelogenesis imperfecta
WDR73	Galloway-Mowat syndrome 1
WEE2-AS1, WEE2	OOCYTE MATURATION DEFECT 5
WFS1	Autosomal dominant nonsyndromic deafness 6, Diabetes mellitus AND insipidus with optic atrophy AND deafness, WFS1-Related Spectrum Disorders, Wolfram-like syndrome, autosomal dominant
WHRN	Deafness, Rare genetic deafness, Usher syndrome, autosomal recessive 31, type 2D
WRN	Medulloblastoma, Werner syndrome
WT1	Drash syndrome, Frasier syndrome, Wilms tumor, Wilms tumor 1, and mental retardation syndrome, aniridia, genitourinary anomalies
WT1, LOC107982234	Drash syndrome, Frasier syndrome, Pre-B-cell acute lymphoblastic leukemia, Wilms tumor, Wilms tumor 1, and mental retardation syndrome, aniridia, genitourinary anomalies
XDH	Deficiency of xanthine oxidase
XIAP	Lymphoproliferative syndrome 2, X-linked
XK	McLeod neuroacanthocytosis syndrome
XPA	Xeroderma pigmentosum, Xeroderma pigmentosum group A
XPC	Xeroderma pigmentosum, group C
XRCC2	Fanconi anemia, Hereditary Cancer Syndrome, Hereditary breast and ovarian cancer syndrome, Hereditary cancer-predisposing syndrome, Ovarian Neoplasms, complementation group U
XRCC4	Short stature, and endocrine dysfunction, microcephaly
XYLT1	Desbuquois dysplasia 2
XYLT1, LOC102723692	Desbuquois dysplasia 2
XYLT2	Inborn genetic diseases, Spondyloocular syndrome, autosomal recessive
YY1AP1	Grange syndrome
ZBTB18	Mental retardation, autosomal dominant 22
ZDBF2	Nasopalpebral lipoma-coloboma syndrome
ZEB2	Mowat-Wilson syndrome
ZFYVE26	Hereditary spastic paraplegia 15, Spastic paraplegia
ZFYVE26, RDH12	Abnormality of the eye, Leber congenital amaurosis 13, RDH12-Related Disorders, Retinal dystrophy, Retinitis pigmentosa
ZMPSTE24	Lethal tight skin contracture syndrome, Mandibuloacral dysplasia with type B lipodystrophy, ZMPSTE24-Related Disorders

ZNF408	Retinitis pigmentosa 72
ZNF462	Craniosynostosis, Mental retardation, WEISS-KRUSZKA SYNDROME, autosomal dominant
ZNF711	ZNF711-Related X-linked Mental Retardation
ZP1	Oocyte maturation defect 1
ZP2	OOCYTE MATURATION DEFECT 6

In an embodiment, the disease or disorder associated with a PTC is a lysosomal storage disease (e.g., Fabry disease, Gaucher disease,or Niemann-Pick disease). In some embodiments, the disease or disorder associated with a PTC is Fabry disease. In an embodiment, upon administration of a TREM (e.g., a TREM described herein) to a cell or subject, the level of a GLA protein in the cell or subject is modulated, e.g., increased, by about 0.1%, 0.5%, 1%, 2%, 3%, 4% 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., compared with a reference value (e.g., level of a GLA protein in a healthy, non-Fabry disease fibroblast).

In some embodiments, the disease or disorder associated with a PTC is a blood clotting disorder, e.g., Hemophilia B. In an embodiment, upon administration of a TREM (e.g., a TREM described herein) to a cell or subject, the level of a Factor IX (FIX) protein in the cell or subject is modulated, e.g., increased, by about 0.1%, 0.5%, 1%, 2%, 3%, 4% 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., compared with a reference value (e.g., level of a FIX protein in a healthy, non-disease cell).

In some embodiments, the disease or disorder associated with a PTC is an autosomal recessive disorder, such as neuronal ceroid lipofuscinosis type 2 (CNL2). In an embodiment, upon administration of a TREM (e.g., a TREM described herein) to a cell or subject, the level of a tripeptidyl peptidase 1 (TPP1) protein in the cell or subject is modulated, e.g., increased, by about 0.1%, 0.5%, 1%, 2%, 3%, 4% 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., compared with a reference value (e.g., level of a TPP1 protein in a healthy, non-disease cell).

In some embodiments, the disease or disorder associated with a PTC is a disease or disorder associated with hearing loss, such as Usher syndrome (e.g., Usher syndrome type 1F). In an embodiment, upon administration of a TREM (e.g., a TREM described herein) to a cell or subject, the level of a protocadherin 15 precursor (PCDH15) protein in the cell or subject is

modulated, e.g., increased, by about 0.1%, 0.5%, 1%, 2%, 3%, 4% 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., compared with a reference value (e.g., level of a PCDH15 protein in a healthy, non-disease cell).

In an embodiment, the disease or disorder associated with a PTC is a proliferative disease, such as a benign neoplasm or a cancer. In an embodiment, the proliferative disease is associated with a benign neoplasm. For example, a benign neoplasm may include adenoma, fibroma, hemangioma, tuberous sclerosis, and lipoma. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In an embodiment, the proliferative disease is a cancer. As used herein, the term "cancer" refers to a malignant neoplasm (Stedman's Medical Dictionary, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the disclosure. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (e.g., cholangiocarcinoma); bladder cancer; breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (e.g., meningioma, glioblastomas, glioma (e.g., astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (e.g., cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (e.g., uterine cancer, uterine sarcoma); esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; eye cancer (e.g., intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (e.g., stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma), throat cancer (e.g., laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer), e.g., adenoid cystic carcinoma (ACC)); hematopoietic cancers (e.g., leukemia such as acute lymphocytic leukemia (ALL) (e.g., B-cell

ALL, T-cell ALL), acute myelocytic leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (e.g., B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (e.g., B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (e.g., B-cell NHL such as diffuse large cell lymphoma (DLCL) (e.g., diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (e.g., mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (i.e., Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (e.g., cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma); liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma); lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (e.g., systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (e.g., polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (e.g., gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (e.g., bone cancer); ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (e.g., pancreatic adenocarcinoma, intraductal

papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (e.g., Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (e.g., prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (e.g., appendix cancer); soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (e.g., seminoma, testicular embryonal carcinoma); thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (e.g., Paget's disease of the vulva). In some embodiments, the cancer is a solid tumor, such as a sarcoma or a carcinoma (e.g., lung cancer, brain cancer, breast cancer, bladder cancer, prostate cancer, colon cancer, rectal cancer).

In another aspect, the present disclosure features methods of treating a disease or disorder in a cell or subject by administration of a TREM (e.g., a TREM described herein) to the cell or subject. Exemplary diseases or disorders include hemophilias, aminoacidopathies, metal storage disorders, peroxisome biogenesis disorder, progressive rare lung disease, diseases related to lipid metabolism, diseases related to galactose metabolism, systemic organic acidemias, urea cycle disorders, cholestastis disorders, bilirubin metabolism disorders, lysososomal storage disorders, glycogen storage diseases, and oxalate metabolism disorders. In an embodiment, the disease or disorder is a hemophilia, e.g., hemophilia A or hemophilia B. In an embodiment, the disease or disorder is an aminoacidopathy, e.g., tyrosinemia type 1, tyrosinemia type 2, tyrosinemia type 3, maple syrup urine disease, alkaptonuria, or phenylketonuria. In an embodiment, the disease or disorder is a systemic organic acidemia, e.g., methylmalonic acidemia (MMUT), methylmalonic acidemia (non-MMUT), propionic acidemia type A, propionic acidemia type B, or isovaleric acidemia. In an embodiment, the disease or disorder is a urea cycle disorder, e.g, argininosuccinate lyase deficiency, argininosuccinate lyase deficiency-D, citrullinemia type 1, citrullinemia type 2, carbamoyl phosphate synthetase-D, ornithine transcarbamylase, arginemia, or hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome. In an embodiment, the disease or disorder is lysosomal storage disorder, e.g., mucopolysaccharidosis 1,

mucopolysaccharidosis 2, Fabry disease, lysosomal acid lipas deficiency, Pompe disease, Gaucher disease, Niemann Pick A, or Niemann Pick B. In an embodiment, the disease or disorder is a bilirubin metabolism disorder, e.g., Crigler-Najjar syndrome. In an embodiment, the disease or disorder is a cholestastis disorder, e.g., progressive familial intrahepatic cholestasis (PFIC) type 1, PFIC type 2, or PFIC type 3. In an embodiment, the disease or disorder is a disease related to lipid metabolism, e.g., sitosterolemia (ABCG5) or sitosterolemia (ABCG8). In an embodiment, the disease or disorder is a glycogen storage disease, e.g., glycogen storage disease 1a, glycogen storage disease 1b, or glycogen storage disease 3a. In an embodiment, the disease or disorder is a metal storage disorder, e.g., Wilson disease or hereditary hemochromatosis. In an embodiment, the disease or disorder is a progressive rare lung disease, e.g., alpha-1 antitrypsin deficiency. In an embodiment, the disease or disorder is a peroxisome biogenesis disorder, e.g., PBD RCDP1. In an embodiment, the disease or disorder is an oxalate metabolism disorder, e.g, primary hyperoxaluria type 1, primary hyperoxaluria type 2, or primary hyperoxaluria type 3. In an embodiment, the disease or disorder is a congenital disorder related to Notch signaling, e.g., Alagille syndrome. In an embodiment, the disease or disorder is an amyloidosis, e.g., familial amyloid polyneuropathy.

In one aspect, the present disclosure features a method of treating a disease or disorder in a subject, the method comprising administering to the subject a TREM comprising the nucleotide sequence of any one of the TREMS listed in FIG. 2. In an embodiment, the disease or disorder is selected from a hemophilia, aminoacidopathy, metal storage disorder, peroxisome biogenesis disorder, progressive rare lung disease, disease related to lipid metabolism, disease related to galactose metabolism, systemic organic acidemia, urea cycle disorder, cholestastis disorder, bilirubin metabolism disorder, lysososomal storage disorder, glycogen storage disease, and oxalate metabolism disorder. In an embodiment, the TREM comprises the sequence of any one of SEQ ID NO: 622, 623, 624, 4249, 4386, 4834, 5630, 6707, 6749, 6947, or 8051, or a fragment or variant thereof. [WILL EXPAND HERE A BIT]

Method of making TREMs, TREM core fragments, and TREM fragments

In vitro methods for synthesizing oligonucleotides are known in the art and can be used to make a TREM, a TREM core fragment or a TREM fragment disclosed herein. For example, a

TREM, TREM core fragment or TREM fragment can be synthesized using solid state synthesis or liquid phase synthesis.

In an embodiment, a TREM, a TREM core fragment or a TREM fragment made according to an in vitro synthesis method disclosed herein has a different modification profile compared to a TREM expressed and isolated from a cell, or compared to a naturally occurring tRNA.

An exemplary method for making a modified TREM is provided in Example 1. The method provided in Example 1 can also be used to make a synthetic TREM core fragment or synthetic TREM fragment. Additional synthetic methods are disclosed in Hartsel SA et al., (2005) *Oligonucleotide Synthesis*, 033–050, the entire contents of which are hereby incorporated by reference.

TREM composition

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises a pharmaceutically acceptable excipient. Exemplary excipients include those provided in the FDA Inactive Ingredient Database (https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm).

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 150 grams of TREM, TREM core fragment or TREM fragment. In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50 or 100 milligrams of TREM, TREM core fragment or TREM fragment.

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 or 99% dry weight TREMs, TREM core fragments or TREM fragments.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM molecules, at least 1 x 10^7 TREM molecules, at least 1 x 10^8 TREM molecules or at least 1 x 10^9 TREM molecules.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM core fragment molecules, at least 1 x 10^7 TREM core fragment molecules, at least 1 x 10^8 TREM core fragment molecules or at least 1 x 10^9 TREM core fragment molecules.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM fragment molecules, at least 1 x 10^7 TREM fragment molecules, at least 1 x 10^8 TREM fragment molecules or at least 1 x 10^9 TREM fragment molecules.

In an embodiment, a TREM composition produced by any of the methods of making disclosed herein can be charged with an amino acid using an in vitro charging reaction as known in the art.

In an embodiment, a TREM composition comprise one or more species of TREMs, TREM core fragments, or TREM fragments. In an embodiment, a TREM composition comprises a single species of TREM, TREM core fragment, or TREM fragment. In an embodiment, a TREM composition comprises a first TREM, TREM core fragment, or TREM fragment species and a second TREM, TREM core fragment, or TREM fragment species. In an embodiment, the TREM composition comprises X TREM, TREM core fragment, or TREM fragment species, wherein X=2, 3, 4, 5, 6, 7, 8, 9, or 10.

In an embodiment, the TREM, TREM core fragment, or TREM fragment has at least 70, 75, 80, 85, 90, or 95, or has 100%, identity with a sequence encoded by a nucleic acid in Table 1.

In an embodiment, the TREM comprises a consensus sequence provided herein.

A TREM composition can be formulated as a liquid composition, as a lyophilized composition or as a frozen composition.

In some embodiments, a TREM composition can be formulated to be suitable for pharmaceutical use, e.g., a pharmaceutical TREM composition. In an embodiment, a pharmaceutical TREM composition is substantially free of materials and/or reagents used to separate and/or purify a TREM, TREM core fragment, or TREM fragment.

In some embodiments, a TREM composition can be formulated with water for injection. In some embodiments, a TREM composition formulated with water for injection is suitable for pharmaceutical use, e.g., comprises a pharmaceutical TREM composition.

TREM characterization

A TREM, TREM core fragment, or TREM fragment, or a TREM composition, *e.g.*, a pharmaceutical TREM composition, produced by any of the methods disclosed herein can be assessed for a characteristic associated with the TREM, TREM core fragment, or TREM fragment or the TREM composition, such as purity, sterility, concentration, structure, or

functional activity of the TREM, TREM core fragment, or TREM fragment. Any of the above-mentioned characteristics can be evaluated by providing a value for the characteristic, *e.g.*, by evaluating or testing the TREM, TREM core fragment, or TREM fragment, or the TREM composition, or an intermediate in the production of the TREM composition. The value can also be compared with a standard or a reference value. Responsive to the evaluation, the TREM composition can be classified, *e.g.*, as ready for release, meets production standard for human trials, complies with ISO standards, complies with cGMP standards, or complies with other pharmaceutical standards. Responsive to the evaluation, the TREM composition can be subjected to further processing, *e.g.*, it can be divided into aliquots, *e.g.*, into single or multi-dosage amounts, disposed in a container, *e.g.*, an end-use vial, packaged, shipped, or put into commerce. In embodiments, in response to the evaluation, one or more of the characteristics can be modulated, processed or re-processed to optimize the TREM composition. For example, the TREM composition can be modulated, processed or re-processed to (i) increase the purity of the TREM composition; (ii) decrease the amount of fragments in the composition; (iii) decrease the amount of endotoxins in the composition; (iv) increase the in vitro translation activity of the composition; (v) increase the TREM concentration of the composition; or (vi) inactivate or remove any viral contaminants present in the composition, *e.g.*, by reducing the pH of the composition or by filtration.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has a purity of at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, i.e., by mass.

In an embodiment, the TREM (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has less than 0.1%, 0,5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% TREM fragments relative to full length TREMs.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has low levels or absence of endotoxins, *e.g.*, a negative result as measured by the Limulus amebocyte lysate (LAL) test.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has in-vitro translation activity, *e.g.*, as measured by an assay described in Examples 12-13.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has a TREM concentration of at least 0.1 ng/mL, 0.5 ng/mL, 1 ng/mL, 5 ng/mL, 10 ng/mL, 50 ng/mL, 0.1 ug/mL, 0.5 ug/mL,1 ug/mL, 2 ug/mL, 5 ug/mL, 10 ug/mL, 20 ug/mL, 30 ug/mL, 40 ug/mL, 50 ug/mL, 60 ug/mL, 70 ug/mL, 80 ug/mL, 100 ug/mL, 200 ug/mL, 300 ug/mL, 500 ug/mL, 1000 ug/mL, 5000 ug/mL, 10,000 ug/mL, or 100,000 ug/mL.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) is sterile, *e.g.*, the composition or preparation supports the growth of fewer than 100 viable microorganisms as tested under aseptic conditions, the composition or preparation meets the standard of USP <71>, and/or the composition or preparation meets the standard of USP <85>.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has an undetectable level of viral contaminants, *e.g.*, no viral contaminants. In an embodiment, any viral contaminant, *e.g.*, residual virus, present in the composition is inactivated or removed. In an embodiment, any viral contaminant, *e.g.*, residual virus, is inactivated, *e.g.*, by reducing the pH of the composition. In an embodiment, any viral contaminant, *e.g.*, residual virus, is removed, *e.g.*, by filtration or other methods known in the field.

TREM administration

Any TREM composition or pharmaceutical composition described herein can be administered to a cell, tissue or subject, *e.g.*, by direct administration to a cell, tissue and/or an organ in vitro, ex-vivo or in vivo. In-vivo administration may be via, *e.g.*, by local, systemic and/or parenteral routes, for example intravenous, subcutaneous, intraperitoneal, intrathecal, intramuscular, ocular, nasal, urogenital, intradermal, dermal, enteral, intravitreal, intracerebral, intrathecal, or epidural.

Vectors and Carriers

In some embodiments the TREM, TREM core fragment, or TREM fragment or TREM composition described herein, is delivered to cells, *e.g.* mammalian cells or human cells, using a vector. The vector may be, *e.g.*, a plasmid or a virus. In some embodiments, delivery is *in vivo, in vitro*, *ex vivo*, or *in situ*. In some embodiments, the virus is an adeno associated virus (AAV), a lentivirus, or an adenovirus. In some embodiments, the system or components of the system are delivered to cells with a viral-like particle or a virosome. In some embodiments, the delivery uses more than one virus, viral-like particle or virosome.

Carriers

A TREM, a TREM composition or a pharmaceutical TREM composition described herein may comprise, may be formulated with, or may be delivered in, a carrier.

Viral vectors

The carrier may be a viral vector (*e.g.*, a viral vector comprising a sequence encoding a TREM, a TREM core fragment or a TREM fragment). The viral vector may be administered to a cell or to a subject (*e.g.*, a human subject or animal model) to deliver a TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition.

A viral vector may be systemically or locally administered (*e.g.*, injected). Viral genomes provide a rich source of vectors that can be used for the efficient delivery of exogenous genes into a mammalian cell. Viral genomes are known in the art as useful vectors for delivery because the polynucleotides contained within such genomes are typically incorporated into the nuclear genome of a mammalian cell by generalized or specialized transduction. These processes occur as part of the natural viral replication cycle, and do not require added proteins or reagents in order to induce gene integration. Examples of viral vectors include a retrovirus (*e.g.*, Retroviridae family viral vector), adenovirus (*e.g.*, Ad5, Ad26, Ad34, Ad35, and Ad48), parvovirus (*e.g.*, adeno-associated viruses), coronavirus, negative strand RNA viruses such as orthomyxovirus (*e.g.*, influenza virus), rhabdovirus (*e.g.*, rabies and vesicular stomatitis virus), paramyxovirus (*e.g.*, measles and Sendai), positive strand RNA viruses, such as picornavirus and alphavirus, and double stranded DNA viruses including adenovirus, herpesvirus (*e.g.*, Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus, replication deficient herpes virus), and poxvirus (*e.g.*, vaccinia, modified vaccinia Ankara (MVA), fowlpox and canarypox). Other viruses include Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus,

hepadnavirus, human papilloma virus, human foamy virus, and hepatitis virus, for example. Examples of retroviruses include: avian leukosis-sarcoma, avian C-type viruses, mammalian C-type, B-type viruses, D-type viruses, oncoretroviruses, HTLV-BLV group, lentivirus, alpharetrovirus, gammaretrovirus, spumavirus (Coffin, J. M., Retroviridae: The viruses and their replication, Virology (Third Edition) Lippincott-Raven, Philadelphia, 1996). Other examples include murine leukemia viruses, murine sarcoma viruses, mouse mammary tumor virus, bovine leukemia virus, feline leukemia virus, feline sarcoma virus, avian leukemia virus, human T-cell leukemia virus, baboon endogenous virus, Gibbon ape leukemia virus, Mason Pfizer monkey virus, simian immunodeficiency virus, simian sarcoma virus, Rous sarcoma virus and lentiviruses. Other examples of vectors are described, for example, in US Patent No. 5,801,030, the teachings of which are incorporated herein by reference. In some embodiments the system or components of the system are delivered to cells with a viral-like particle or a virosome.

Cell and vesicle-based carriers

A TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition described herein can be administered to a cell in a vesicle or other membrane-based carrier.

In embodiments, a TREM, a TREM core fragment or a TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein is administered in or via a cell, vesicle or other membrane-based carrier. In one embodiment, the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition can be formulated in liposomes or other similar vesicles. Liposomes are spherical vesicle structures composed of a uni- or multilamellar lipid bilayer surrounding internal aqueous compartments and a relatively impermeable outer lipophilic phospholipid bilayer. Liposomes may be anionic, neutral or cationic. Liposomes are biocompatible, nontoxic, can deliver both hydrophilic and lipophilic drug molecules, protect their cargo from degradation by plasma enzymes, and transport their load across biological membranes and the blood brain barrier (BBB) (see, *e.g.*, Spuch and Navarro, Journal of Drug Delivery, vol. 2011, Article ID 469679, 12 pages, 2011. doi:10.1155/2011/469679 for review).

Vesicles can be made from several different types of lipids; however, phospholipids are most commonly used to generate liposomes as drug carriers. Methods for preparation of multilamellar vesicle lipids are known in the art (see for example U.S. Pat. No. 6,693,086, the

teachings of which relating to multilamellar vesicle lipid preparation are incorporated herein by reference). Although vesicle formation can be spontaneous when a lipid film is mixed with an aqueous solution, it can also be expedited by applying force in the form of shaking by using a homogenizer, sonicator, or an extrusion apparatus (see, *e.g.*, Spuch and Navarro, Journal of Drug Delivery, vol. 2011, Article ID 469679, 12 pages, 2011. doi:10.1155/2011/469679 for review). Extruded lipids can be prepared by extruding through filters of decreasing size, as described in Templeton et al., Nature Biotech, 15:647-652, 1997, the teachings of which relating to extruded lipid preparation are incorporated herein by reference.

Lipid nanoparticles are another example of a carrier that provides a biocompatible and biodegradable delivery system for the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein. Nanostructured lipid carriers (NLCs) are modified solid lipid nanoparticles (SLNs) that retain the characteristics of the SLN, improve drug stability and loading capacity, and prevent drug leakage. Polymer nanoparticles (PNPs) are an important component of drug delivery. These nanoparticles can effectively direct drug delivery to specific targets and improve drug stability and controlled drug release. Lipid–polymer nanoparticles (PLNs), a new type of carrier that combines liposomes and polymers, may also be employed. These nanoparticles possess the complementary advantages of PNPs and liposomes. A PLN is composed of a core–shell structure; the polymer core provides a stable structure, and the phospholipid shell offers good biocompatibility. As such, the two components increase the drug encapsulation efficiency rate, facilitate surface modification, and prevent leakage of water-soluble drugs. For a review, see, *e.g.*, Li et al. 2017, Nanomaterials 7, 122; doi:10.3390/nano7060122.

Exemplary lipid nanoparticles are disclosed in International Application PCT/US2014/053907, the entire contents of which are hereby incorporated by reference. For example, an LNP described in paragraphs [403-406] or [410-413] of PCT/US2014/053907 can be used as a carrier for the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein.

Additional exemplary lipid nanoparticles are disclosed in U.S. Patent 10,562,849 the entire contents of which are hereby incorporated by reference. For example, an LNP of formula (I) as described in columns 1-3 of U.S. Patent 10,562,849 can be used as a carrier for the TREM,

TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein.

Lipids that can be used in nanoparticle formations (e.g., lipid nanoparticles) include, for example those described in Table 4 of WO2019217941, which is incorporated by reference, e.g., a lipid-containing nanoparticle can comprise one or more of the lipids in Table 4 of WO2019217941. Lipid nanoparticles can include additional elements, such as polymers, such as the polymers described in Table 5 of WO2019217941, incorporated by reference.

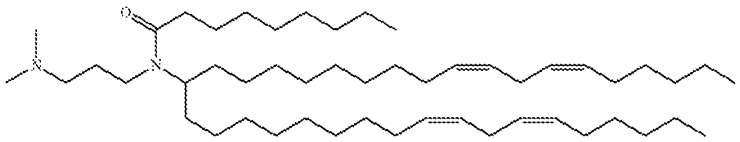
In some embodiments, conjugated lipids, when present, can include one or more of PEG-diacylglycerol (DAG) (such as l-(monomethoxy-polyethyleneglycol)-2,3- dimyristoylglycerol (PEG-DMG)), PEG-dialkyloxypropyl (DAA), PEG-phospholipid, PEG- ceramide (Cer), a pegylated phosphatidylethanoloamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-l-0-(w- methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypropylcarbam, N- (carbonyl-methoxypoly ethylene glycol 2000)-1 ,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, and those described in Table 2 of WO2019051289 (incorporated by reference), and combinations of the foregoing.

In some embodiments, sterols that can be incorporated into lipid nanoparticles include one or more of cholesterol or cholesterol derivatives, such as those in W02009/127060 or US2010/0130588, which are incorporated by reference. Additional exemplary sterols include phytosterols, including those described in Eygeris et al (2020), incorporated herein by reference.

In some embodiments, the lipid particle comprises an ionizable lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a sterol. The amounts of these components can be varied independently and to achieve desired properties. For example, in some embodiments, the lipid nanoparticle comprises an ionizable lipid is in an amount from about 20 mol % to about 90 mol % of the total lipids (in other embodiments it may be 20-70% (mol), 30-60% (mol) or 40-50% (mol); about 50 mol % to about 90 mol % of the total lipid present in the lipid nanoparticle), a non-cationic lipid in an amount from about 5 mol % to about 30 mol % of the total lipids, a conjugated lipid in an amount from about 0.5 mol % to about 20 mol % of the total lipids, and a sterol in an amount from about 20 mol % to about 50 mol % of the total lipids. The ratio of total lipid to nucleic acid can be varied as desired. For example, the total lipid to nucleic acid (mass or weight) ratio can be from about 10: 1 to about 30: 1.

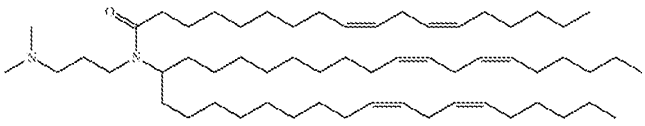
In some embodiments, the lipid to nucleic acid ratio (mass/mass ratio; w/w ratio) can be in the range of from about 1 : 1 to about 25: 1, from about 10: 1 to about 14: 1, from about 3 : 1 to about 15: 1, from about 4: 1 to about 10: 1, from about 5: 1 to about 9: 1, or about 6: 1 to about 9: 1. The amounts of lipids and nucleic acid can be adjusted to provide a desired N/P ratio, for example, N/P ratio of 3, 4, 5, 6, 7, 8, 9, 10 or higher. Generally, the lipid nanoparticle formulation's overall lipid content can range from about 5 mg/ml to about 30 mg/mL.

Some non-limiting example of lipid compounds that may be used (e.g., in combination with other lipid components) to form lipid nanoparticles for the delivery of compositions described herein, e.g., nucleic acid (e.g., RNA) described herein includes,



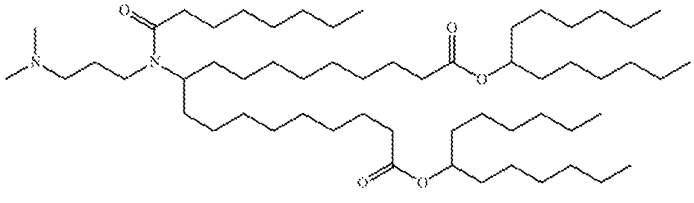
(i)

In some embodiments an LNP comprising Formula (i) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



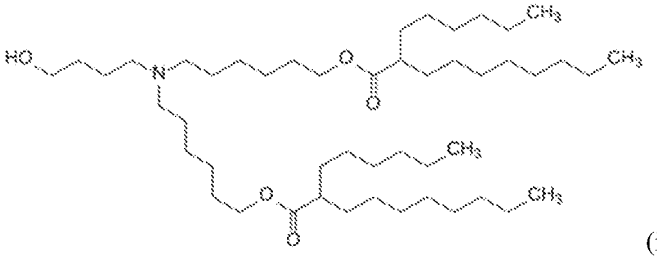
(ii)

In some embodiments an LNP comprising Formula (ii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

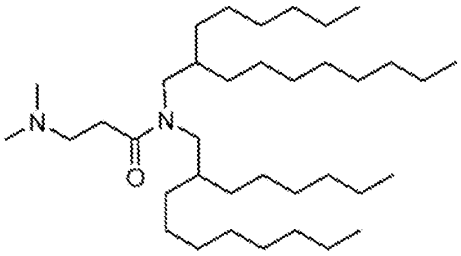


(iii)

In some embodiments an LNP comprising Formula (iii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

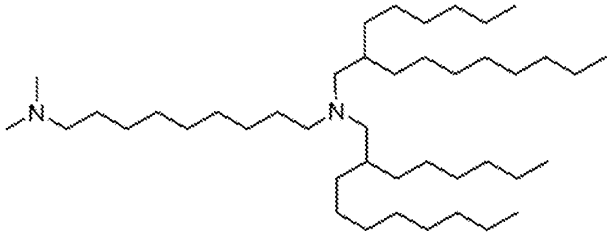


(iv)



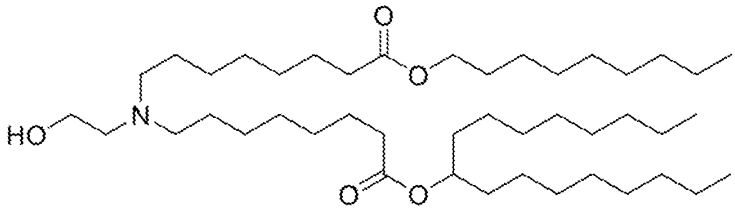
(v)

In some embodiments an LNP comprising Formula (v) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

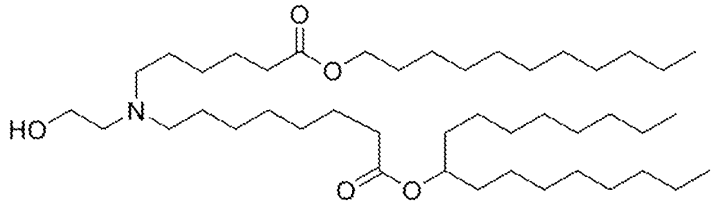


(vi)

In some embodiments an LNP comprising Formula (vi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

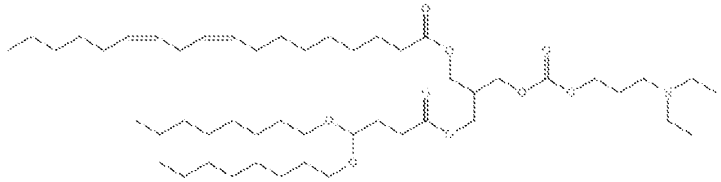


(vii)



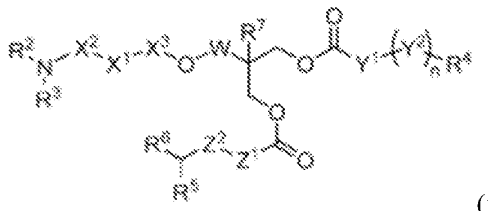
(viii)

In some embodiments an LNP comprising Formula (viii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



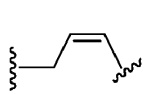
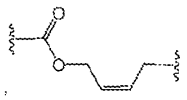
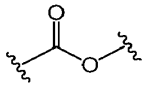
(ix)

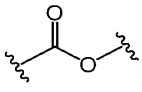
In some embodiments an LNP comprising Formula (ix) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

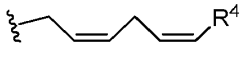


(x)

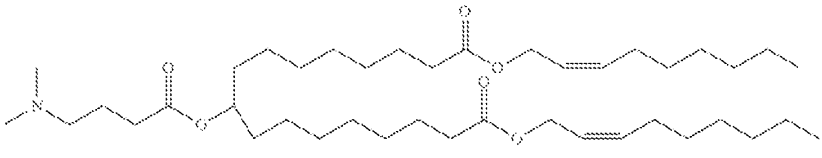
wherein X^1 is O, NR^1, or a direct bond, X^2 is C2-5 alkylene, X^3 is C(=O) or a direct bond, R^1 is H or Me, R^3 is Ci-3 alkyl, R^2 is Ci-3 alkyl, or R^2 taken together with the nitrogen atom to which it is attached and 1-3 carbon atoms of X^2 form a 4-, 5-, or 6-membered ring, or X^1 is NR^1, R^1 and R^2 taken together with the nitrogen atoms to which they are attached form a 5- or 6-membered ring, or R^2 taken together with R^3 and the nitrogen atom to which they are attached form a 5-, 6-, or 7-membered ring, Y^1 is C2-12 alkylene, Y^2 is selected from


(in either orientation),

(in either orientation),

(in either orientation),

n is 0 to 3, R^4 is Ci-15 alkyl, Z^1 is Ci-6 alkylene or a direct bond, Z^2 is  , (in either orientation) or absent, provided that if Z^1 is a direct bond, Z^2 is absent; R^5 is C5-9 alkyl or C6-10 alkoxy, R^6 is C5-9 alkyl or C6-10 alkoxy, W is methylene or a direct bond, and R^7 is H or Me, or a salt thereof, provided that if R^3 and R^2 are C2 alkyls, X^1 is O, X^2 is linear C3 alkylene, X^3 is

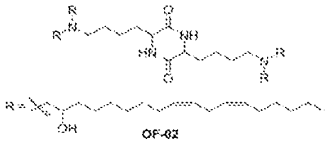
C(=0), Y^1 is linear Ce alkylene, (Y^2)n-R^4 is  , R^4 is linear C5 alkyl, Z^1 is C2 alkylene, Z^2 is absent, W is methylene, and R^7 is H, then R^5 and R^6 are not Cx alkoxy.

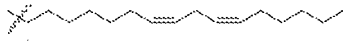
In some embodiments an LNP comprising Formula (xii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



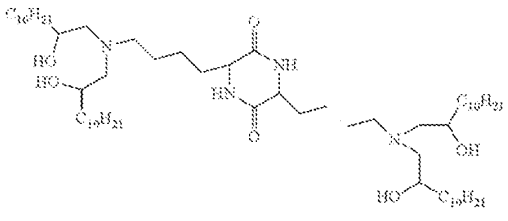
(xi)

In some embodiments an LNP comprising Formula (xi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

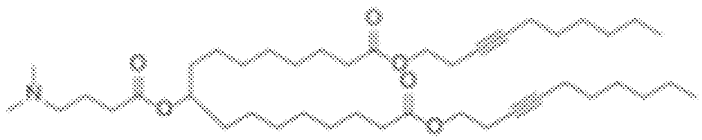


where R= 

(xii)

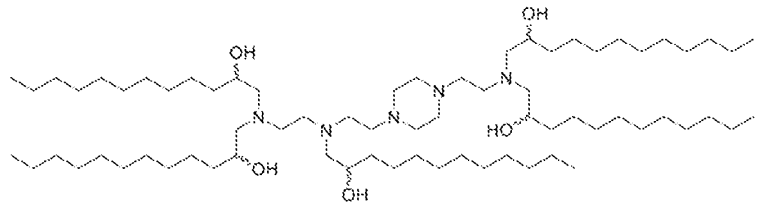


(xiii)



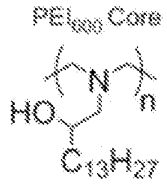
(xiv)

In some embodiments an LNP comprises a compound of Formula (xiii) and a compound of Formula (xiv).



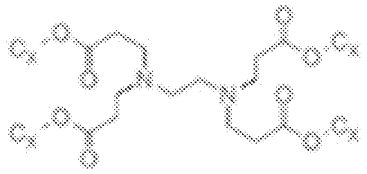
(xv)

In some embodiments, an LNP comprising Formula (xv) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

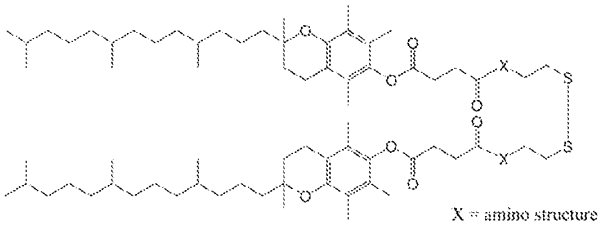


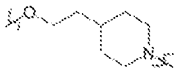
(xvi)

In some embodiments an LNP comprising a formulation of Formula (xvi) is used to deliver a TREM composition described herein to the lung endothelial cells.

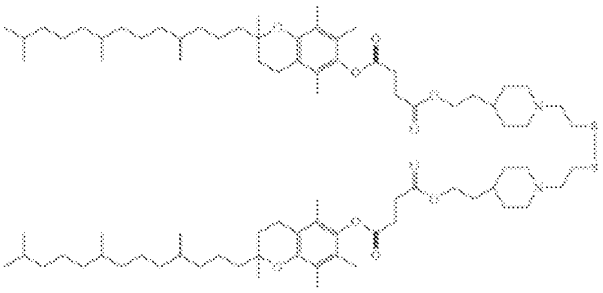


(xvii)

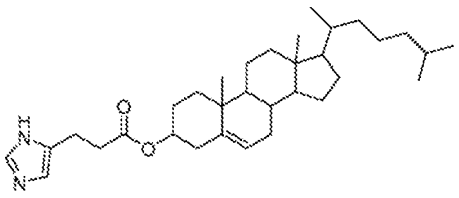


where X=  (xviii)

(a)

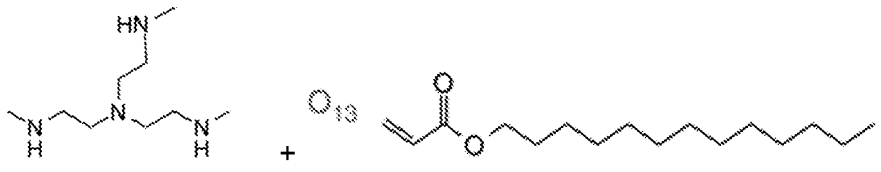


(xviii)(b)

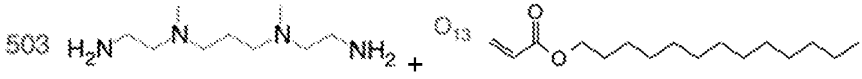


(xix)

In some embodiments, a lipid compound used to form lipid nanoparticles for the delivery of compositions described herein, e.g., a TREM described herein is made by one of the following reactions:



(xx) (a)



(xx)(b)

In some embodiments, a composition described herein (e.g., TREM composition) is provided in an LNP that comprises an ionizable lipid. In some embodiments, the ionizable lipid is heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102); e.g., as described in Example 1 of US9,867,888 (incorporated by reference herein in its entirety). In some embodiments, 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 (LP01), e.g., as synthesized in Example 13 of WO2015/095340 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Di((Z)-non-2-en-1-yl) 9-((4-dimethylamino)-butanoyl)oxy)heptadecanedioate (L319), e.g. as synthesized in Example 7, 8, or 9 of US2012/0027803 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is 1,1'-((2-(4-(2-((2-(Bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl) amino)ethyl)piperazin-1-yl)ethyl)azanediyl)bis(dodecan-2-ol) (C12-200), e.g., as synthesized in Examples 14 and 16 of WO2010/053572 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Imidazole cholesterol ester (ICE) lipid (3S, 10R, 13R, 17R)-10, 13-dimethyl-17- ((R)-6-methylheptan-2-yl)-2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-lH- cyclopenta[a]phenanthren-3-yl 3-(1H-imidazol-4-yl)propanoate, e.g., Structure (I) from WO2020/106946 (incorporated by reference herein in its entirety).

In some embodiments, an ionizable lipid may be a cationic lipid, an ionizable cationic lipid, e.g., a cationic lipid that can exist in a positively charged or neutral form depending on pH, or an amine-containing lipid that can be readily protonated. In some embodiments, the cationic lipid is a lipid capable of being positively charged, e.g., under physiological conditions. Exemplary cationic lipids include one or more amine group(s) which bear the positive charge. In

some embodiments, the lipid particle comprises a cationic lipid in formulation with one or more of neutral lipids, ionizable amine-containing lipids, biodegradable alkyne lipids, steroids, phospholipids including polyunsaturated lipids, structural lipids (e.g., sterols), PEG, cholesterol and polymer conjugated lipids. In some embodiments, the cationic lipid may be an ionizable cationic lipid. An exemplary cationic lipid as disclosed herein may have an effective pKa over 6.0. In embodiments, a lipid nanoparticle may comprise a second cationic lipid having a different effective pKa (e.g., greater than the first effective pKa), than the first cationic lipid. A lipid nanoparticle may comprise between 40 and 60 mol percent of a cationic lipid, a neutral lipid, a steroid, a polymer conjugated lipid, and a therapeutic agent, e.g., a TREM described herein, encapsulated within or associated with the lipid nanoparticle. In some embodiments, the TREM is co-formulated with the cationic lipid. The TREM may be adsorbed to the surface of an LNP, e.g., an LNP comprising a cationic lipid. In some embodiments, the TREM may be encapsulated in an LNP, e.g., an LNP comprising a cationic lipid. In some embodiments, the lipid nanoparticle may comprise a targeting moiety, e.g., coated with a targeting agent. In embodiments, the LNP formulation is biodegradable. In some embodiments, a lipid nanoparticle comprising one or more lipid described herein, e.g., Formula (i), (ii), (ii), (vii) and/or (ix) encapsulates at least 1%, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98% or 100% of a TREM.

Exemplary ionizable lipids that can be used in lipid nanoparticle formulations include, without limitation, those listed in Table 1 of WO2019051289, incorporated herein by reference. Additional exemplary lipids include, without limitation, one or more of the following formulae: X of US2016/0311759; I of US20150376115 or in US2016/0376224; I, II or III of US20160151284; I, IA, II, or IIA of US20170210967; I-c of US20150140070; A of US2013/0178541; I of US2013/0303587 or US2013/0123338; I of US2015/0141678; II, III, IV, or V of US2015/0239926; I of US2017/0119904; I or II of WO2017/117528; A of US2012/0149894; A of US2015/0057373; A of WO2013/116126; A of US2013/0090372; A of US2013/0274523; A of US2013/0274504; A of US2013/0053572; A of W02013/016058; A of W02012/162210; I of US2008/042973; I, II, III, or IV of US2012/01287670; I or II of US2014/0200257; I, II, or III of US2015/0203446; I or III of US2015/0005363; I, IA, IB, IC, ID, II, IIA, IIB, IIC, IID, or III-XXIV of US2014/0308304; of US2013/0338210; I, II, III, or IV of

W02009/132131; A of US2012/01011478; I or XXXV of US2012/0027796; XIV or XVII of US2012/0058144; of US2013/0323269; I of US2011/0117125; I, II, or III of US2011/0256175; I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII of US2012/0202871; I, II, III, IV, V, VI, VII, VIII, X, XII, XIII, XIV, XV, or XVI of US2011/0076335; I or II of US2006/008378; I of US2013/0123338; I or X-A-Y-Z of US2015/0064242; XVI, XVII, or XVIII of US2013/0022649; I, II, or III of US2013/0116307; I, II, or III of US2013/0116307; I or II of US2010/0062967; I-X of US2013/0189351; I of US2014/0039032; V of US2018/0028664; I of US2016/0317458; I of US2013/0195920; 5, 6, or 10 of US10,221,127; III-3 of WO2018/081480; I-5 or I-8 of WO2020/081938; 18 or 25 of US9,867,888; A of US2019/0136231; II of WO2020/219876; 1 of US2012/0027803; OF-02 of US2019/0240349; 23 of US10,086,013; cKK-E12/A6 of Miao et al (2020); C12-200 of WO2010/053572; 7C1 of Dahlman et al (2017); 304-O13 or 503-O13 of Whitehead et al; TS-P4C2 of US9,708,628; I of WO2020/106946; I of WO2020/106946.

In some embodiments, the ionizable lipid is MC3 (6Z,9Z,28Z,3 lZ)-heptatriaconta-6,9,28,3 l-tetraen-l9-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA or MC3), e.g., as described in Example 9 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is the lipid ATX-002, e.g., as described in Example 10 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is (l3Z,l6Z)-A,A-dimethyl-3- nonyldocosa-l3, l6-dien-l-amine (Compound 32), e.g., as described in Example 11 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Compound 6 or Compound 22, e.g., as described in Example 12 of WO2019051289A9 (incorporated by reference herein in its entirety).

Exemplary non-cationic lipids include, but are not limited to, distearoyl-sn-glycero-phosphoethanolamine, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane- 1 - carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), monomethyl-phosphatidylethanolamine (such as 16-O-monomethyl PE), dimethyl- phosphatidylethanolamine (such as 16-O-dimethyl

PE), l8-l-trans PE, l-stearoyl-2-oleoyl- phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidicacid,cerebrosides, dicetylphosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, or mixtures thereof. It is understood that other diacylphosphatidylcholine and diacylphosphatidylethanolamine phospholipids can also be used. The acyl groups in these lipids are preferably acyl groups derived from fatty acids having C10-C24 carbon chains, e.g., lauroyl, myristoyl, paimitoyl, stearoyl, or oleoyl. Additional exemplary lipids, in certain embodiments, include, without limitation, those described in Kim et al. (2020) dx.doi.org/10.1021/acs.nanolett.0c01386, incorporated herein by reference. Such lipids include, in some embodiments, plant lipids found to improve liver transfection with mRNA (e.g., DGTS).

Other examples of non-cationic lipids suitable for use in the lipid nanoparticles include, without limitation, nonphosphorous lipids such as, e.g., stearylamine, dodeeylamine, hexadecylamine, acetyl palmitate, glycerol ricinoleate, hexadecyl stereate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethyloxylated fatty acid amides, dioctadecyl dimethyl ammonium bromide, ceramide, sphingomyelin, and the like. Other non-cationic lipids are described in WO2017/099823 or US patent publication US2018/0028664, the contents of which is incorporated herein by reference in their entirety.

In some embodiments, the non-cationic lipid is oleic acid or a compound of Formula I, II, or IV of US2018/0028664, incorporated herein by reference in its entirety. The non-cationic lipid can comprise, for example, 0-30% (mol) of the total lipid present in the lipid nanoparticle. In some embodiments, the non-cationic lipid content is 5-20% (mol) or 10-15% (mol) of the total lipid present in the lipid nanoparticle. In embodiments, the molar ratio of ionizable lipid to the neutral lipid ranges from about 2:1 to about 8:1 (e.g., about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, or 8:1).

In some embodiments, the lipid nanoparticles do not comprise any phospholipids.

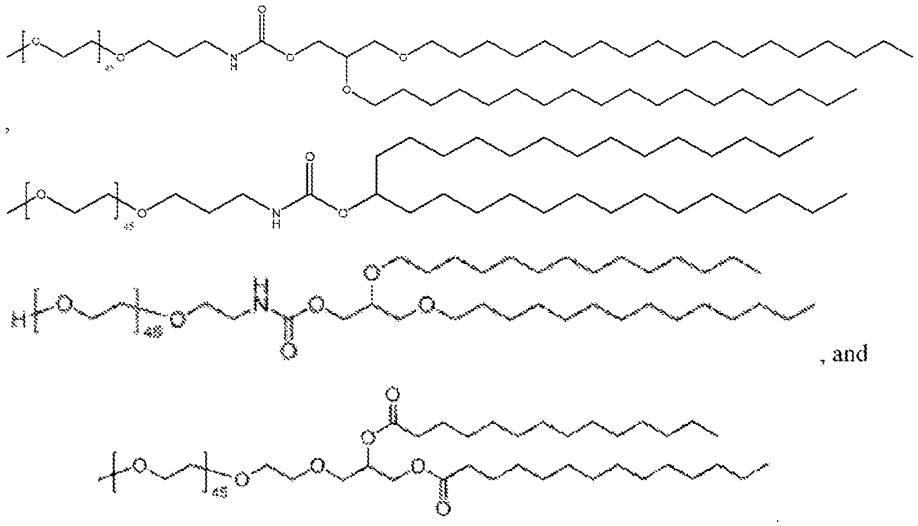
In some aspects, the lipid nanoparticle can further comprise a component, such as a sterol, to provide membrane integrity. One exemplary sterol that can be used in the lipid nanoparticle is cholesterol and derivatives thereof. Non-limiting examples of cholesterol derivatives include polar analogues such as 5a-choiestanol, 53-coprostanol, choiesteryl-(2'-hydroxy)-ethyl ether, choiesteryl-(4'- hydroxy)-butyl ether, and 6-ketocholestanol; non-polar analogues such as 5a-cholestane, cholestenone, 5a-cholestanone, 5p-cholestanone, and cholesteryl decanoate; and mixtures thereof. In some embodiments, the cholesterol derivative is a polar analogue, e.g., choiesteryl-(4 '-hydroxy)-buty1 ether. Exemplary cholesterol derivatives are described in PCT publication W02009/127060 and US patent publication US2010/0130588, each of which is incorporated herein by reference in its entirety.

In some embodiments, the component providing membrane integrity, such as a sterol, can comprise 0-50% (mol) (e.g., 0-10%, 10-20%, 20-30%, 30-40%, or 40-50%) of the total lipid present in the lipid nanoparticle. In some embodiments, such a component is 20-50% (mol) 30-40% (mol) of the total lipid content of the lipid nanoparticle.

In some embodiments, the lipid nanoparticle can comprise a polyethylene glycol (PEG) or a conjugated lipid molecule. Generally, these are used to inhibit aggregation of lipid nanoparticles and/or provide steric stabilization. Exemplary conjugated lipids include, but are not limited to, PEG-lipid conjugates, polyoxazoline (POZ)-lipid conjugates, polyamide-lipid conjugates (such as ATTA-lipid conjugates), cationic-polymer lipid (CPL) conjugates, and mixtures thereof. In some embodiments, the conjugated lipid molecule is a PEG-lipid conjugate, for example, a (methoxy polyethylene glycol)-conjugated lipid.

Exemplary PEG-lipid conjugates include, but are not limited to, PEG-diacylglycerol (DAG) (such as l-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (PEG-DMG)), PEG-dialkyloxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanoloamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-l-0-(w-methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypropylcarbam, N-(carbonyl-methoxypolyethylene glycol 2000)-l,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, or a mixture thereof. Additional exemplary PEG-lipid conjugates are described, for example, in US5,885,613, US6,287,591, US2003/0077829, US2003/0077829, US2005/0175682, US2008/0020058, US2011/0117125, US2010/0130588, US2016/0376224, US2017/0119904, and US/099823, the contents of all of

which are incorporated herein by reference in their entirety. In some embodiments, a PEG-lipid is a compound of Formula III, III-a-I, III-a-2, III-b-1, III-b-2, or V of US2018/0028664, the content of which is incorporated herein by reference in its entirety. In some embodiments, a PEG-lipid is of Formula II of US20150376115 or US2016/0376224, the content of both of which is incorporated herein by reference in its entirety. In some embodiments, the PEG-DAA conjugate can be, for example, PEG-dilauryloxypropyl, PEG- dimyristyloxypropyl, PEG-dipalmityloxypropyl, or PEG-distearyloxypropyl. The PEG-lipid can be one or more of PEG-DMG, PEG-dilaurylglycerol, PEG-dipalmitoylglycerol, PEG- disterylglycerol, PEG-dilaurylglycamide, PEG-dimyristylglycamide, PEG- dipalmitoylglycamide, PEG-disterylglycamide, PEG-cholesterol (l-[8'-(Cholest-5-en-3[beta]- oxy)carboxamido-3',6'-dioxaoctanyl] carbamoyl-[omega]-methyl-poly(ethylene glycol), PEG- DMB (3,4-Ditetradecoxylbenzyl- [omega]-methyl-poly(ethylene glycol) ether), and 1,2- dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]. In some embodiments, the PEG-lipid comprises PEG-DMG, 1,2- dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]. In some embodiments, the PEG-lipid comprises a structure selected from:



, and

In some embodiments, lipids conjugated with a molecule other than a PEG can also be used in place of PEG-lipid. For example, polyoxazoline (POZ)-lipid conjugates, polyamide-lipid conjugates (such as ATTA-lipid conjugates), and cationic-polymer lipid (GPL) conjugates can be used in place of or in addition to the PEG-lipid.

Exemplary conjugated lipids, i.e., PEG-lipids, (POZ)-lipid conjugates, ATTA-lipid conjugates and cationic polymer-lipids are described in the PCT and LIS patent applications listed in Table 2 of WO2019051289A9, the contents of all of which are incorporated herein by reference in their entirety.

In some embodiments, the PEG or the conjugated lipid can comprise 0-20% (mol) of the total lipid present in the lipid nanoparticle. In some embodiments, PEG or the conjugated lipid content is 0.5- 10% or 2-5% (mol) of the total lipid present in the lipid nanoparticle. Molar ratios of the ionizable lipid, non-cationic-lipid, sterol, and PEG/conjugated lipid can be varied as needed. For example, the lipid particle can comprise 30-70% ionizable lipid by mole or by total weight of the composition, 0-60% cholesterol by mole or by total weight of the composition, 0-30% non-cationic-lipid by mole or by total weight of the composition and 1-10% conjugated lipid by mole or by total weight of the composition. Preferably, the composition comprises 30-40% ionizable lipid by mole or by total weight of the composition, 40-50% cholesterol by mole or by total weight of the composition, and 10- 20% non-cationic-lipid by mole or by total weight of the composition. In some other embodiments, the composition is 50-75% ionizable lipid by mole or by total weight of the composition, 20-40% cholesterol by mole or by total weight of the composition, and 5 to 10% non-cationic-lipid, by mole or by total weight of the composition and 1-10% conjugated lipid by mole or by total weight of the composition. The composition may contain 60-70% ionizable lipid by mole or by total weight of the composition, 25-35% cholesterol by mole or by total weight of the composition, and 5-10% non-cationic-lipid by mole or by total weight of the composition. The composition may also contain up to 90% ionizable lipid by mole or by total weight of the composition and 2 to 15% non-cationic lipid by mole or by total weight of the composition. The formulation may also be a lipid nanoparticle formulation, for example comprising 8-30% ionizable lipid by mole or by total weight of the composition, 5-30% non- cationic lipid by mole or by total weight of the composition, and 0-20% cholesterol by mole or by total weight of the composition; 4-25% ionizable lipid by mole or by total weight of the composition, 4-25% non-cationic lipid by mole or by total weight of the composition, 2 to 25% cholesterol by mole or by total weight of the composition, 10 to 35% conjugate lipid by mole or by total weight of the composition, and 5% cholesterol by mole or by total weight of the composition; or 2-30% ionizable lipid by mole or by total weight of the composition, 2-30% non-cationic lipid by mole or by total weight of the composition, 1 to 15% cholesterol by mole or

by total weight of the composition, 2 to 35% conjugate lipid by mole or by total weight of the composition, and 1-20% cholesterol by mole or by total weight of the composition; or even up to 90% ionizable lipid by mole or by total weight of the composition and 2-10% non-cationic lipids by mole or by total weight of the composition, or even 100% cationic lipid by mole or by total weight of the composition. In some embodiments, the lipid particle formulation comprises ionizable lipid, phospholipid, cholesterol and a PEG-ylated lipid in a molar ratio of 50: 10:38.5: 1.5. In some other embodiments, the lipid particle formulation comprises ionizable lipid, cholesterol and a PEG-ylated lipid in a molar ratio of 60:38.5: 1.5.

In some embodiments, the lipid particle comprises ionizable lipid, non-cationic lipid (e.g. phospholipid), a sterol (e.g., cholesterol) and a PEG-ylated lipid, where the molar ratio of lipids ranges from 20 to 70 mole percent for the ionizable lipid, with a target of 40-60, the mole percent of non-cationic lipid ranges from 0 to 30, with a target of 0 to 15, the mole percent of sterol ranges from 20 to 70, with a target of 30 to 50, and the mole percent of PEG-ylated lipid ranges from 1 to 6, with a target of 2 to 5.

In some embodiments, the lipid particle comprises ionizable lipid / non-cationic- lipid / sterol / conjugated lipid at a molar ratio of 50: 10:38.5: 1.5.

In an aspect, the disclosure provides a lipid nanoparticle formulation comprising phospholipids, lecithin, phosphatidylcholine and phosphatidylethanolamine.

In some embodiments, one or more additional compounds can also be included. Those compounds can be administered separately, or the additional compounds can be included in the lipid nanoparticles of the invention. In other words, the lipid nanoparticles can contain other compounds in addition to the nucleic acid or at least a second nucleic acid, different than the first. Without limitations, other additional compounds can be selected from the group consisting of small or large organic or inorganic molecules, monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides, peptides, proteins, peptide analogs and derivatives thereof, peptidomimetics, nucleic acids, nucleic acid analogs and derivatives, an extract made from biological materials, or any combinations thereof.

In some embodiments, LNPs are directed to specific tissues by the addition of targeting domains. For example, biological ligands may be displayed on the surface of LNPs to enhance interaction with cells displaying cognate receptors, thus driving association with and cargo delivery to tissues wherein cells express the receptor. In some embodiments, the biological

ligand may be a ligand that drives delivery to the liver, e.g., LNPs that display GalNAc result in delivery of nucleic acid cargo to hepatocytes that display asialoglycoprotein receptor (ASGPR). The work of Akinc et al. *Mol Ther* 18(7):1357-1364 (2010) teaches the conjugation of a trivalent GalNAc ligand to a PEG-lipid (GalNAc-PEG-DSG) to yield LNPs dependent on ASGPR for observable LNP cargo effect (see, e.g., FIG. 6 of Akinc et al. 2010, *supra*). Other ligand-displaying LNP formulations, e.g., incorporating folate, transferrin, or antibodies, are discussed in WO2017223135, which is incorporated herein by reference in its entirety, in addition to the references used therein, namely Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61 ; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; and Peer and Lieberman, Gene Ther. 2011 18:1127-1133.

In some embodiments, LNPs are selected for tissue-specific activity by the addition of a Selective ORgan Targeting (SORT) molecule to a formulation comprising traditional components, such as ionizable cationic lipids, amphipathic phospholipids, cholesterol and poly(ethylene glycol) (PEG) lipids. The teachings of Cheng et al. Nat Nanotechnol 15(4):313-320 (2020) demonstrate that the addition of a supplemental "SORT" component precisely alters the in vivo RNA delivery profile and mediates tissue-specific (e.g., lungs, liver, spleen) gene delivery and editing as a function of the percentage and biophysical property of the SORT molecule.

In some embodiments, the LNPs comprise biodegradable, ionizable lipids. In some embodiments, the LNPs comprise (9Z,l2Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,l2-dienoate, also called 3- ((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,l2Z)-octadeca-9,l2-dienoate) or another ionizable lipid. See, e.g, lipids of WO2019/067992, WO/2017/173054, WO2015/095340, and WO2014/136086, as well as references provided

therein. In some embodiments, the term cationic and ionizable in the context of LNP lipids is interchangeable, e.g., wherein ionizable lipids are cationic depending on the pH.

In some embodiments, the average LNP diameter of the LNP formulation may be between 10s of nm and 100s of nm, e.g., measured by dynamic light scattering (DLS). In some embodiments, the average LNP diameter of the LNP formulation may be from about 40 nm to about 150 nm, such as about 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm. In some embodiments, the average LNP diameter of the LNP formulation may be from about 50 nm to about 100 nm, from about 50 nm to about 90 nm, from about 50 nm to about 80 nm, from about 50 nm to about 70 nm, from about 50 nm to about 60 nm, from about 60 nm to about 100 nm, from about 60 nm to about 90 nm, from about 60 nm to about 80 nm, from about 60 nm to about 70 nm, from about 70 nm to about 100 nm, from about 70 nm to about 90 nm, from about 70 nm to about 80 nm, from about 80 nm to about 100 nm, from about 80 nm to about 90 nm, or from about 90 nm to about 100 nm. In some embodiments, the average LNP diameter of the LNP formulation may be from about 70 nm to about 100 nm. In a particular embodiment, the average LNP diameter of the LNP formulation may be about 80 nm. In some embodiments, the average LNP diameter of the LNP formulation may be about 100 nm. In some embodiments, the average LNP diameter of the LNP formulation ranges from about l mm to about 500 mm, from about 5 mm to about 200 mm, from about 10 mm to about 100 mm, from about 20 mm to about 80 mm, from about 25 mm to about 60 mm, from about 30 mm to about 55 mm, from about 35 mm to about 50 mm, or from about 38 mm to about 42 mm.

A LNP may, in some instances, be relatively homogenous. A polydispersity index may be used to indicate the homogeneity of a LNP, e.g., the particle size distribution of the lipid nanoparticles. A small (e.g., less than 0.3) polydispersity index generally indicates a narrow particle size distribution. A LNP may have a polydispersity index from about 0 to about 0.25, such as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, or 0.25. In some embodiments, the polydispersity index of a LNP may be from about 0.10 to about 0.20.

The zeta potential of a LNP may be used to indicate the electrokinetic potential of the composition. In some embodiments, the zeta potential may describe the surface charge of an LNP. Lipid nanoparticles with relatively low charges, positive or negative, are generally

desirable, as more highly charged species may interact undesirably with cells, tissues, and other elements in the body. In some embodiments, the zeta potential of a LNP may be from about -10 mV to about +20 mV, from about -10 mV to about +15 mV, from about -10 mV to about +10 mV, from about -10 mV to about +5 mV, from about -10 mV to about 0 mV, from about -10 mV to about -5 mV, from about -5 mV to about +20 mV, from about -5 mV to about +15 mV, from about -5 mV to about +10 mV, from about -5 mV to about +5 mV, from about -5 mV to about 0 mV, from about 0 mV to about +20 mV, from about 0 mV to about +15 mV, from about 0 mV to about +10 mV, from about 0 mV to about +5 mV, from about +5 mV to about +20 mV, from about +5 mV to about +15 mV, or from about +5 mV to about +10 mV.

The efficiency of encapsulation of a TREM describes the amount of TREM that is encapsulated or otherwise associated with a LNP after preparation, relative to the initial amount provided. The encapsulation efficiency is desirably high (e.g., close to 100%). The encapsulation efficiency may be measured, for example, by comparing the amount of TREM in a solution containing the lipid nanoparticle before and after breaking up the lipid nanoparticle with one or more organic solvents or detergents. An anion exchange resin may be used to measure the amount of free protein or nucleic acid (e.g., RNA) in a solution. Fluorescence may be used to measure the amount of free TREM in a solution. For the lipid nanoparticles described herein, the encapsulation efficiency of a TREM may be at least 50%, for example 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the encapsulation efficiency may be at least 80%. In some embodiments, the encapsulation efficiency may be at least 90%. In some embodiments, the encapsulation efficiency may be at least 95%.

A LNP may optionally comprise one or more coatings. In some embodiments, a LNP may be formulated in a capsule, film, or table having a coating. A capsule, film, or tablet including a composition described herein may have any useful size, tensile strength, hardness or density.

Additional exemplary lipids, formulations, methods, and characterization of LNPs are taught by WO2020061457, which is incorporated herein by reference in its entirety.

In some embodiments, in vitro or ex vivo cell lipofections are performed using Lipofectamine MessengerMax (Thermo Fisher) or TransIT-mRNA Transfection Reagent (Mirus Bio). In certain embodiments, LNPs are formulated using the GenVoy_ILM ionizable lipid mix

(Precision NanoSystems). In certain embodiments, LNPs are formulated using 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA) or dilinoleylmethyl-4-dimethylaminobutyrate (DLin-MC3-DMA or MC3), the formulation and in vivo use of which are taught in Jayaraman et al. Angew Chem Int Ed Engl 51(34):8529-8533 (2012), incorporated herein by reference in its entirety.

LNP formulations optimized for the delivery of CRISPR-Cas systems, e.g., Cas9-gRNA RNP, gRNA, Cas9 mRNA, are described in WO2019067992 and WO2019067910, both incorporated by reference.

Additional specific LNP formulations useful for delivery of nucleic acids are described in US8158601 and US8168775, both incorporated by reference, which include formulations used in patisiran, sold under the name ONPATTRO.

Exosomes can also be used as drug delivery vehicles for the TREM, TREM core fragment, TREM fragment, or TREM compositions or pharmaceutical TREM composition described herein. For a review, see Ha et al. July 2016. Acta Pharmaceutica Sinica B. Volume 6, Issue 4, Pages 287-296; https://doi.org/10.1016/j.apsb.2016.02.001.

Ex vivo differentiated red blood cells can also be used as a carrier for a TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein. See, *e.g.*, WO2015073587; WO2017123646; WO2017123644; WO2018102740; wO2016183482; WO2015153102; WO2018151829; WO2018009838; Shi et al. 2014. Proc Natl Acad Sci USA. 111(28): 10131–10136; US Patent 9,644,180; Huang et al. 2017. Nature Communications 8: 423; Shi et al. 2014. Proc Natl Acad Sci USA. 111(28): 10131–10136.

Fusosome compositions, *e.g.*, as described in WO2018208728, can also be used as carriers to deliver the TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein.

Virosomes and virus-like particles (VLPs) can also be used as carriers to deliver a TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein to targeted cells.

Plant nanovesicles, e.g., as described in WO2011097480A1, WO2013070324A1, or WO2017004526A1 can also be used as carriers to deliver the TREM, TREM core fragment,

TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein.

Delivery without a carrier

A TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition described herein can be administered to a cell without a carrier, e.g., via naked delivery of the TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition.

In some embodiments, naked delivery as used herein refers to delivery without a carrier. In some embodiments, delivery without a carrier, e.g., naked delivery, comprises delivery with a moiety, e.g., a targeting peptide.

In some embodiments, a TREM, a TREM core fragment or a TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein is delivered to a cell without a carrier, e.g., via naked delivery. In some embodiments, the delivery without a carrier, e.g., naked delivery, comprises delivery with a moiety, e.g., a targeting peptide.

Use of TREMs

A TREM composition (*e.g.*, a pharmaceutical TREM composition described herein) can modulate a function in a cell, tissue or subject. In embodiments, a TREM composition (*e.g.*, a pharmaceutical TREM composition) described herein is contacted with a cell or tissue, or administered to a subject in need thereof, in an amount and for a time sufficient to modulate (increase or decrease) one or more of the following parameters: adaptor function (*e.g.*, cognate or non-cognate adaptor function), *e.g.*, the rate, efficiency, robustness, and/or specificity of initiation or elongation of a polypeptide chain; ribosome binding and/or occupancy; regulatory function (*e.g.*, gene silencing or signaling); cell fate; mRNA stability; protein stability; protein transduction; protein compartmentalization. A parameter may be modulated, *e.g.*, by at least 5% (*e.g.*, at least 10%, 15%, 20%, 25%, 30%, 40%. 50%. 60%. 70%, 80%, 90%, 100%, 150%, 200% or more) compared to a reference tissue, cell or subject (*e.g.*, a healthy, wild-type or control cell, tissue or subject).

All references and publications cited herein are hereby incorporated by reference.

The following examples are provided to further illustrate some embodiments of the present invention, but are not intended to limit the scope of the invention; it will be understood

by their exemplary nature that other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

EXAMPLES

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Example 1: Synthesis of modified TREMs

Generally, TREM molecules (e.g., modified TREMs) may be chemically synthesized and purified by HPLC according to standard solid phase synthesis methods using phosphoramidite chemistry. (see, e.g., Scaringe S. et al. (2004) *Curr Protoc Nucleic Acid Chem*, 2.10.1-2.10.16; Usman N. et al. (1987) *J. Am. Chem. Soc*, 109, 7845-7854). Individually modified TREM molecules containing one or more 2'-methoxy (2'OMe), 2'fluoro (2'F), 2'-methoxyethyl (2'-

MOE), or phosphorothioate (PS) modifications were prepared using either TREM-Arg-TGA, TREM-Ser-TAG, or TREM-Gln-TAA sequences as a framework according to phosphoramidite technology on solid phase used in oligonucleotide synthesis. For clarity, the arginine non-cognate TREM molecule named TREM-Arg-TGA contains the sequence of ARG-UCU-TREM body but with the anticodon sequence corresponding to UCA instead of UCU (i.e., SEQ ID NO: 622). Simlarly, a serine non-cognate TREM molecule named TREM-Ser-TAG contains the sequence of SER-GCU-TREM body but with the anticodon sequence corresponding to CUA instead of GCU (i.e., SEQ ID NO: 623). A glutamine non-cognate TREM molecule named TREM-Gln-TAA contains the sequence of GLN-CUG-TREM body but with the anticodon sequence corresponding to UUA instead of CUG (i.e., SEQ ID NO: 624).

To make the 2'OMe modified TREMs, the following 2'-O-methyl phosphoramidites were used: (5'-O-dimethoxytrityl-N6-(benzoyl)-2'-O-methyl-adenosine-3'-O-(2-cyanoethyl-N,N-diisopropy-lamino) phosphoramidite, 5'-O-dimethoxy-trityl-N4-(acetyl)-2'-O-methyl-cytidine-3'-O-(2-cyanoethyl-N,N-diisopropyl-amino) phosphoramidite, (5'- O -dimethoxytrityl-N2-(isobutyryl)-2'-O-methyl-guanosine-3'-O-(2-cyano-ethyl-N,N-diisopropylamino)-phosphoramidite, and 5'-O-dimethoxy-trityl-2'-O-methyluridine-3'- O -(2-cyanoethyl-N,N-diisopropylamino)phosphoramidite. To make the 2'-deoxy and 2'-F modified TREMs, analogous 2'-deoxy and 2'-fluoro-phosphoramidites with the same protecting groups as the 2'-O-methyl RNA amidites were used. To make the 2'-MOE modified TREMs, the following 2'-MOE-phosphoramidites were used: 5'-O-(4,4'-Dimethoxytrityl)-2'-O-methoxyethyl-N6-benzoyl-adenosine -3'-O-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-O-(4,4'-Dimethoxytrityl)-2'-O-methoxyethyl-5-methyl-N4-benzoyl- cytidine-3'-O-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-O-(4,4'-Dimethoxytrityl)-2'-O-methoxyethyl-N2-isobutyryl- guanosine-3'-O-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite, 5'-O-(4,4'-Dimethoxytrityl)-2'-O-methoxyethyl-5-methyl-uridine-3'-O-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite.

During the oligonucleotide synthesis via this phosphoramidites approach, the phosphorothioate was introduced by oxidizing the phosphite triester using a sulfur transfer reagent, such as tetraethylthiuram disulfide (TETD), bis(O,O-diisopropoxy phosphinothioyl) disulfide (Stec's reagent), 3H-1,2-benzodithiol-3-one-1,1,-dioxide (Beaucage reagent), phenylacetyl disulfide (PADS), 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH), 1,2-dithiazole-5-

thione (xanthane hydride or ADTT), 3-((dimethylamino-methylidene)amino)-3H-1,2,4-dithiazole-3-thione (DDTT), dimethylthiuram disulfide (DTD), 3-phenyl-1,2,4-dithiazoline-5-one (PolyOrg Sulfa or POS).

FIG. 2 describes a series of singly and multiply modified TREMs synthesized according to this procedure. The sequences of each of these TREMs are provided in the table, wherein r: ribonucleotide; m: 2'-OMe; *: PS linkage; f: 2'-fluoro; moe: 2'-moe; d: deoxyribonucleotide; 5MeC: 5-methylcytosine. Thus, for example, mA represents 2'-O-methyl adenosine, moe5MeC represents 2'-MOE nucleotide with 5-methylcytosine nucleobase, and dA represents an adenosine deoxyribonucleotide.

Example 2: HPLC and MS analysis of modified TREMs

Chemically modified TREM molecules may be analyzed by HPLC, for example, to evaluate the purity and homogeneity of the compositions. A Waters Aquity UPLC system using a Waters BEH C18 column (2.1 mm x 50 mm x 1.7 μm) may be used for this analysis. Samples may be prepared by dissolving 0.5 nmol of the TREM in 75 μL of water and injecting 2 μL of the solution. The buffers used may be 50 mM dimethylhexylammonium acetate with 10% CH_3CN (acetonitrile) as buffer A and 50 mM dimethylhexylammonium acetate with 75% CH_3CN as buffer B (gradient 25-75% buffer B over 5 mins), with a flow rate of 0.5 mL/min at 60 °C. ESI-LCMS data for the chemically modified TREMs may be acquired on a Thermo Ultimate 3000-LTQ-XL mass spectrometer.

FIG. 2 describe a series of singly and multiply modified TREMs synthesized according to the protocol outlined in Example 1. The calculated and detected molecular weights for each sequence were determined as outlined herein.

Example 3: Analysis of modified TREMs via anion-exchange HPLC

This example describes the quality control of a synthesized TREM via anion-exchange HPLC. Using the Dionex DNA-Pac–PA-100 column, a gradient is employed using HPLC buffer A and HPLC buffer B. 0.5 ODUs of a sample that has been dissolved in H2O or Tris buffer, pH 7.5 is injected onto the gradient. The gradient employed is based on oligonucleotide length and can be applied according to Table 13. The parameters provided in Table 14 can be used to program a linear gradient on the HPLC analyzer.

Table 13: Oligonucleotide length and gradient percentages

Length (bases)	Gradient (%B)
0–5	0–30
6–10	10–40
11–16	20–50
17–32	30–60
33–50	40–70
>50	50–80

Table 14: Parameters for a linear gradient on HPLC analyzer

Time (min)	Flow (mL/min)	% Buffer A	% Buffer B
0	1.5	100	0
1	1.5	100	0
3	1.5	70a	30a
15	1.5	40a	60a
15.5	2.5	0	100
17	2.5	0	100
17.25	2.5	100	0
23	2.5	100	0
s23.1	1.5	100	0
24	1.5	100	0
25	0.1	100	0

Example 4: Analysis of TREMs via PAGE Purification and Analysis

This example describes the quality control of a synthesized TREM via PAGE Purification and Analysis. Gel purification and analysis of 2'-ACE protected RNA follows standard protocols for denaturing PAGE (Ellington and Pollard (1998) *In Current Protocols in Molecular Biology*, Chanda, V). Briefly, the 2'-ACE protected oligo is resuspended in 200 mL of gel loading buffer. Invitrogen™ NuPAGE™ 4-12% Bis-Tris Gels or similar gel is prepared in gel apparatus. Samples are loaded and gel ran at 50-120 W, maintaining the apparatus at 40°C. When complete,

the gel is exposed to ultraviolet (UV) light at 254 nm to visualize the purity of the RNA using UV shadowing. If necessary, the desired gel band is excised with a clean razor blade. The gel slice is crushed and 0.3M NaOAc elution buffer is added to the gel particles, and soaked overnight. The mixture is decanted and filtered through a Sephadex column such as Nap-10 or Nap-25.

Example 5: Deprotection of synthesized TREM

This example describes the deprotection of a TREM made according to an in vitro synthesis method. The 2'-protecting groups are removed using 100 mM acetic acid, pH 3.8. The formic acid and ethylene glycol byproducts are removed by incubating at 60°C for 30 min followed by lyophilization or SpeedVac-ing to dryness. After this final deprotection step, the oligonucleotides are ready for use.

Example 6. Characterization of chemically modified TREMs for readthrough of a premature termination codon (PTC) in a reporter protein

This example describes an assay to test the ability of a non-cognate chemically modified TREM to readthrough a PTC in a cell line expressing a reporter protein having a PTC. This protocol describes analysis of chemically modified arginine, serine, and glutamine non-cognate TREM (i.e., Arg-TGA, Ser-TAG, Gln-TAA, Lys-TAA, Leu-TGA, Trp-TAG, Gln-TAG, Ser-TAA, Ser-TGA, Tyr-TAA, Tyr-TAG), though a non-cognate TREM specifying any one of the other amino acids can also be used.

A cell line engineered to stably express the NanoLuc reporter construct containing a premature termination codon (PTC) may be generated using the FlpIn and/or JumpIN cell system (ThermoFisher Scientific, USA) according to the manufacturer's instructions. The NanoLuc reporter can also be modified with a destabilizing PEST domain at its C-terminus to reduce the protein half-life. Delivery of the chemically modified TREMs into the NanoLuc reporter cells is carried out via a reverse transfection reaction using lipofectamine RNAiMAX (ThermoFisher Scientific, USA) according to manufacturer instructions. Briefly, 5 uL of a 2.5uM solution of chemically modified TREM sample are diluted in a 20uL RNAiMAX/OptiMEM mixture. After 30min gentle mixing at room temperature, the 25uL TREM/transfection mixture is added to a 96-well plate and kept still for 20-30min before adding the cells stably expressing the NanoLuc reporter construct containing a PTC. The NanoLuc reporter cells are harvested and diluted to 4×

10^5 cells/mL in complete growth medium, and 100uL of the diluted cell suspension is added and mixed to the plate containing the TREM.

To monitor the efficacy of the chemically modified TREM to read through the PTC in the reporter construct at 24 or 48 hours after TREM delivery into cells, a NanoGlo bioluminescent assay (Promega, USA) may be performed according to manufacturer instruction. Briefly, for cells that are to be assayed after 48 hours, 100uL complete growth medium is added to the 96-well plate 24 hours post-transfection to dilute the transfection reagent for cell health. At the time of harvest, either 24- or 48-hours post-transfection, cell media is replaced and allowed to equilibrate to room temperature. NanoGlo reagent is prepared by mixing the buffer with substrate in a 50:1 ratio. 50uL of mixed NanoGlo reagent is added to the 96-well plate and mixed on the shaker at 600rpm for 10min. Then the plate is centrifuged at 1000g for 2min, followed by a 5min incubation step at room temperature before measuring sample bioluminescence. As a positive control, a host cell expressing the NanoLuc reporter construct without a PTC is used. As a negative control, a host cell expressing the NanoLuc reporter construct with a PTC is used, but no TREM is transfected. The efficacyof the chemically modified TREMs is measured as a ratio of the NanoLuc luminescence in the experimental sample to the NanoLuc luminescence of the positive control or as a ratio of the NanoLuc luminescence in the experimental sample to the NanoLuc luminescence of the negative control. It is expected that if the sample TREM is functional, it may be able to read-through the stop mutation in the NanoLuc reporter and produce a luminescent reading higher than the luminescent reading measured in the negative control. If the sample TREM is not functional, the stop mutation is not rescued, and luminescence less or equal to the negative control is detected.

The impacts of chemical modifications were evaluated in singly and multiply modified TREM sequences and are summarized in FIG. 2. In this figure, the TREMs are annotated as follows: r: ribonucleotide; m: 2'-OMe; *: PS linkage; f: 2'-fluoro; moe: 2'-moe; d: deoxyribonucleotide; 5MeC: 5-methylcytosine. Thus, for example, mA represents 2'-O-methyl adenosine, moe5MeC represents 2'-MOE nucleotide with 5-methylcytosine nucleobase, and dA represents an adenosine deoxyribonucleotide.

FIG. 2 also summarizes the results of the activity screen in column "A" for measurements made using NanoLuc reporter cells at 48 hours post-transfection, which reported as log2 fold changes compared with the appropriate unmodified TREM, wherein "1" indicates less than a 1

log2 fold change; "2" indicates greater than or equal to 1 and less than 3.32 log2 fold change; and "3" indicates greater than or equal to 3.32 log2 fold change. The results show that certain modifications were tolerated at many positions, but particular sites were sensitive to modification or exhibited improved activity when modified

Example 7: Characterization of chemically modified TREMs for readthrough of a premature termination codon (PTC) in a disease reporter cell line

This example describes an assay to test the ability of an exemplary TREM to readthrough a PTC in a cell line expressing a disease reporter protein bearing the PTC.

Host cell modification

A cell line engineered to stably express a HaloTag and HiBiT-tagged disease reporter construct containing a premature termination codon (PTC), such as Factor IX at position 298 (FIX^{R298X}), Factor IX at position 29 (FIX^{R29X}), Factor IX at position 44 (FIX^{Q44X}), Tripeptidyl-peptidase 1 at position 208 ($TPP1^{R208X}$), Protocadherin Related 15 at position 245 ($PCDH15^{R245X}$), or Rhodopsin at position 334 (Rho^{S334X}) was generated using the Jump-In system according to manufacturer's instructions. Briefly, Jump-In GripTite HEK293 (Thermo Scientific A14150) cells were co-transfected with an expression vector containing the disease reporter, such as pJTI-R4-DEST-CMV-FIX-R298X-HaloTag-HiBiT-pA for FIX^{R298X} to make the Factor IX disease reporter expressing cell line, and a pJTI-R4-Int PhiC31 integrase expression vector using Lipofectamine2000 according to manufacturer's instructions. After 24 hours, the media was replaced with fresh media. The next day, the cells were re-seeded at 50% confluency and selected with 10ug/mL Blasticidin and 600ug/mL G418 for 7 days with media change every 2 days. The remaining cells were expanded and tested for reporter construct expression.

Translation suppression assay

Exemplary TREMs were synthesized and characterized as described herein, then transfected into cells. Forty-eight hours after TREM delivery into cells, conditioned media was collected, fresh media was added to the cells and allowed to equilibrate to room temperature. To measure the efficacy of arginine TREMs in PTC readthrough, full-length HiBiT-tagged disease reporter protein was assayed in both cells, and 48-hour conditioned media. Briefly, reconstituted Nano-Glo® HiBiT Lytic Reagent was added to both cells containing fresh media and 48-hour conditioned media at a 1:1 v/v ratio, mixed on an orbital shaker at 500rpm for 10 minutes, and incubated at room temperature for 10 minutes. The HiBiT-tagged disease reporter activity is

measured by reading the luminescence in a plate reader. The results of this experiment in the three HiBiT-tagged disease reporter constructs is shown below in Table 21. In this table, the results for each TREM tested are reported as log2 fold changes compared with the appropriate unmodified TREM (TREM NO. 2309), wherein "1" indicates less than a -0.05 log2 fold change; "2" indicates greater than or equal to -0.05 and less than 0.55 log2 fold change; and "3" indicates greater than or equal to 0.55 log2 fold change.

Table 21.

TREM NO.	SEQ ID NO.	TPP1 (R208X) 100 nM	PCDH15 (R245X) 100 nM	FIX (R298X) 100 nM
4	625	3	3	3
7	628	3	3	3
24	645	3	3	3
29	650	3	3	3
47	668	3	3	3
61	682	3	3	3
77	698	3	3	3
78	699	3	3	3
84	705	3	3	3
96	717	3	3	3
103	724	3	3	3
124	745	3	3	3
125	746	3	3	3
127	748	3	3	3
138	759	3	3	3
139	760	3	3	3
143	764	3	3	3
146	767	3	3	3
148	769	3	3	3
149	770	3	3	3
168	789	3	3	3
169	790	3	3	3
173	794	3	3	3
174	795	3	3	3
175	796	3	3	3
176	797	3	3	3
177	798	2	2	2
180	801	3	3	3
186	807	3	3	3
187	808	2	2	2
188	809	2	3	3
203	824	3	3	3

204	825	3	3	3
225	846	3	3	3
234	855	3	3	3
256	877	3	3	3
312	933	2	2	2
313	934	3	3	3
314	935	3	3	3
315	936	3	3	3
316	937	3	3	3
317	938	3	3	3
341	962	3	3	3
345	966	3	3	3
346	967	3	3	3
349	970	3	3	3
350	971	3	3	3
356	977	3	3	3
2309	2930	3	3	3
2355	2976	2	2	2
2359	2980	3	3	3
2368	2989	2	2	2
2370	2991	2	2	2
2377	2998	3	3	3
2381	3002	3	3	3
2393	3014	3	3	3
2396	3017	2	2	2
2397	3018	3	3	3
2407	3028	3	3	3
2410	3031	3	3	3
2411	3032	3	3	3
2412	3033	3	3	3
2413	3034	2	2	2
2417	3038	2	2	3
2419	3040	3	3	3
2421	3042	3	3	3
2429	3050	2	3	3
2442	3063	3	3	3
2422	3043	3	3	3
2476	3097	3	3	3
2524	3145	3	3	3
2536	3157	3	3	3
2538	3159	3	3	3
2540	3161	3	3	3
2541	3162	3	3	3
2565	3186	3	3	3
2566	3187	3	3	3

2585	3206	3	3	3
2592	3213	2	2	2
2594	3215	2	3	3
2596	3217	3	3	3
2621	3242	3	3	3
2630	3251	3	3	3
2632	3253	3	3	3
2637	3258	3	3	3
2642	3263	2	2	2
2650	3271	3	3	3
2657	3278	3	3	3
2664	3285	2	2	2

Additional testing was carried on a larger panel of TREMs with the results summarized in FIG. 2. Each TREM, TREM core fragment, and TREM fragment was screened against three disease reporter constructions, each of which contained a premature termination codon (PTC): Factor IX-R29TGA (B), Factor IX-Q44TAG (C), and RHO-S334TAA (D). The results from these screens are reported to the same scheme described above for Table 21, except only reporting results from the cell line corresponding to the type of stop codon designed to be recognized by the TREM.

Example 8: Correction of a missense mutation in an ORF with administration of a TREM

This example describes the administration of a TREM to correct a missense mutation. In this example, a TREM translates a reporter with a missense mutation into a wild type (WT) protein by incorporation of the WT amino acid (at the missense position) in the protein.

Host cell modification

A cell line stably expressing a GFP reporter construct containing a missense mutation, for example T203I or E222G, which prevent GFP excitation at the 470 nm and 390 nm wavelengths, is generated using the FlpIn system according to manufacturer's instructions. Briefly, HEK293T (293T ATCC ® CRL-3216) cells are co-transfected with an expression vector containing a GFP reporter with a missense mutation, such as pcDNA5/FRT-NanoLuc-TAA and a pOG44 Flp-Recombinase expression vector using Lipofectamine2000 according to manufacturer's instructions. After 24 hours, the media is replaced with fresh media. The next day, the cells are split 1:2 and selected with 100ug/mL Hygromycin for 5 days. The remaining cells are expanded and tested for reporter construct expression.

Synthesis and preparation of TREM

The TREM is synthesized as described in Example 1 and quality control methods as described in Examples 2-5 are performed. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Transfection of non-cognate TREM into host cells

To deliver the TREM to mammalian cells, 100 nM of TREM is transfected into cells expressing the ORF having a missense mutation using lipofectamine 2000 reagents according to the manufacturer's instructions. After 6-18 hours, the transfection media is removed and replaced with fresh complete media.

Missense mutation correction assay

To monitor the efficacy of the TREM to correct the missense mutation in the reporter construct, 24-48 hours after TREM transfection, cell media is replaced, and cell fluorescence is measured. As a negative control, no TREM is transfected in the cells and as a positive control, cells expressing WT GFP are used for this assay. If the TREM is functional, it is expected that the GFP protein produced fluoresces when illuminated with a 390 nm excitation wavelength using a fluorimeter, as observed in the positive control. If the TREM is not functional, the GFP protein produced fluoresces only when excited with a 470 nm wavelength, as is observed in the negative control.

Example 9: Evaluation of protein expression levels of SMC-containing ORF with administration of a TREM

This example describes administration of a TREM to alter expression levels of an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on protein expression levels of an SMC-containing protein, in this example, from the PNPL3A gene coding for adiponutrin, a plasmid containing the PNPL3A rs738408 ORF sequence is transfected in the normal human hepatocyte cell line THLE-3, edited by CRISPR/Cas to contain a frameshift mutation in a coding exon of PNPLA3 to knock out endogenous PNPLA3 (THLE-3_PNPLA3KO cells). As a control, an aliquot of THLE-3_PNPLA3KO cells are transfected with a plasmid containing the wildtype PNPL3A ORF sequence.

Synthesis and preparation of TREM

An arginine TREM is synthesized as described in Example 1 and quality control methods as described in Examples 2-5 are performed. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Evaluation of protein level of SMC-containing ORF

A TREM is delivered to the THLE-3_PNPLA3KO cells containing the rs738408 ORF sequence as well as to the THLE-3_PNPLA3KO cells containing the wildtype PNPLA3 ORF sequence. In this example, the TREM contains a proline isoacceptor containing an AGG anticodon, that base pairs to the CCT codon, i.e. with the sequence GGCUCGUUGGUCUAGGGGUAUGAUUCUCGCUUAGGGUGCGAGAGGUCCCGGGUU CAAAUCCCGGACGAGCCC. A time course is performed ranging from 30 minutes to 6 hours with hour-long interval time points. At each time point, cells are trypsinized, washed and lysed. Cell lysates are analyzed by Western blotting and blots are probed with antibodies against the adiponutrin protein. A total protein loading control, such as GAPDH, actin or tubulin, is also probed as a loading control.

The methods described in this example can be adopted for use to evaluate the expression levels of the adiponutrin protein in rs738408 ORF containing cells.

Example 10: Modulation of protein translation rate of SMC-containing ORF with TREM administration

This example describes administration of a TREM to alter the rate of protein translation of an SMC-containing ORF.

To monitor the effects of TREM addition on translation elongation rates, an in vitro translation system, in this example the RRL system from Promega, is used in which the fluorescence change over time of a reporter gene, in this example GFP, is a surrogate for translation rates.

Synthesis and preparation of TREM

An arginine TREM is synthesized as described in Example 1 and quality control methods as described in Examples 2-5 are performed. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Evaluation of protein translation rate of SMC-containing ORF

First, a rabbit reticulocyte lysate that is depleted of the endogenous tRNA using an antisense oligonucleotide targeting the sequence between the anticodon and variable loop is

generated (see, e.g., Cui et al. 2018. Nucleic Acids Res. 46(12):6387–6400). In this example, a TREM comprising an alanine isoacceptor containing an UGC anticodon, that base pairs to the GCA codon, i.e. with the sequence GGGGAUGUAGCUCAGUGGUAGAGCGCAUGCUUUGCAUGUAUGAGGUCCCGGGUU CGAUCCCCGGCAUCUCCA is added to the in vitro translation assay lysate in addition to 0.1-0.5 ug/uL of mRNA coding for the wildtype TERT ORF fused to the GFP ORF by a linker or an mRNA coding for the rs2736098 TERT ORF fused to the GFP ORF by a linker. The progress of GFP mRNA translation is monitored by fluorescence increase on a microplate reader at 37 °C using $\lambda_{ex}485/\lambda_{em}528$ with data points collected every 30 seconds over a period of 1hour. The amount of fluorescence change over time is plotted to determine the rate of translation elongation of the wildtype ORF compared to the rs2736098 ORF with and without TREM addition. The methods described in this example can be adopted for use to evaluate the translation rate of the rs2736098 ORF and the wildtype ORF in the presence or absence of TREM.

Example 11: Rescue of full-length GLA expression and activity in Fabry patient fibroblasts upon administration of an exemplary TREM

This example describes administration of exemplary TREMs to Fabry-patient derived fibroblasts (GLA R220X) to assess rescue of full-length GLA protein expression and activity. Fabry patient fibroblasts (Coriell, GM00881; GLA^{R220X}) and normal healthy fibroblasts (Coriell, GM03377) were transfected with 40 nM of either a chemically unmodified TREM (TREM NO. 2309) or an exemplary TREM comprising non-naturally occurring modifications (TREM NO. 78). GLA protein rescue was assessed by Western blotting 48 hours post-transfection in both cell lines. As shown in FIG. 4, administration of both TREMs induced rescue of full-length GLA protein, with the chemically modified TREM NO. 78 affording a considerable increase in the total GLA produced over the chemically unmodified TREM NO. 2309.

To expand on these findings, both time course and dose-response studies were carried out. In the time course study, patient fibroblasts were transiently transfected with the chemically modified TREM NO. 78 for 48 hours, 72 houts, and 96 hours, and full-length GLA protein rescue was assessed by Western blot. As shown in FIG. 5A, maximal protein rescue (approximately 50% versus normal healthy fibroblasts) across all time points was observed 96 hours post-transfection. In the dose-response study, TREM NO. 78 was provided to cells at doses of 2.6 nM, 16 nM, 40 nM, and 100 nM, and cells were harvested 96 hours post-transfection. As

shown in FIG. 5B & FIG. 5D, full-length GLA protein rescue levels rise until reaching a plateau at 40 nM. In addition, GLA transcript levels also increased in a concentration-dependent fashion as measured by qPCR, suggesting that TREM NO. 78 also rescues GLA mRNA nonsense mediated decay (NMD) in Fabry patient fibroblasts as shown in FIG. 5E.

Additional studies were carried out to assess whether administration of exemplary TREMs was sufficient to rescue GLA enzymatic activity. Fabry patient fibroblasts were treated with either TREM NO. 2309 or TREM NO. 78 at a dose of either 20 nM or 40 nM, and GLA activity was measured 96 hours post-transfection. An established GLA enzymatic activity was performed on cell extracts using a GLA-specific substrate that results in the generation of a fluorescent cleavage product (4-methylumbelliferone). As shown in FIG. 6, GLA activity increased following treatment with both TREMs, though administration of chemically modified TREM NO. 78 resulted in a profound rescue of GLA activity greater than or equal to GLA activity levels in normal healthy fibroblasts at both doses.

Example 12: *In Vivo* PTC Readthrough and Target Engagement of TREM by Hydrodynamic Gene Delivery

Hydrodynamic gene delivery (HGD) is a simple, fast, safe, and effective method for delivering transgenes in rodent models. A set of plasmids expressing both an eGFP-Luc-TGA reporter and and a TREM were designed. To evaluate tolerability and determine optimal plasmid concentration for maximum TREM delivery to the liver, the eGFP-WT Luc plasmid was administered to adult CD-1 mice via tail vein hydrodynamic injection at three doses: 10 µg, 30 µg, and 50 µg. As shown in FIG. 7A, plasmids in saline were successfully delivered to liver in a dose-dependent manner as shown by the luciferase readout signal. Next, 50 µg of DNA in saline (100 mg/kg) was administered to mice via tail vein hydrodynamic injuction to assess target engagement and PTC readthrough using either 1) eGFP -Nluc TGA reporter plasmid (PL-854), or 2) eGFP-Nluc WT reporter (PL1202), or 3) all-in-one plasmid eGFP-Nluc-TGA reporter with S-TAG (PL-1216), or 4) all-in-one plasmid eGFP-Nluc-TGA reporter with R-TGA (PL-1215). The Arg-TGA selectively rescued the TGA nonsense mutation in the reporter plasmid and showed a ~1000-fold increase in luciferase signal compared to controls (FIG. 7B).

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 (e.g., a backbone modification).

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 (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), or 2'deoxy modification.

4. The TREM of any one of the preceding claims, wherein the non-naturally occurring modification is a 2'OMe modification.

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

6. The TREM of any one of the preceding claims, wherein the non-naturally occurring modification is a 2'MOE modification.

7. The TREM of any one of the preceding claims, wherein the non-naturally occurring modification is a 2'-deoxy modification.

8. The TREM of any one of the preceding claims, 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 any one of the preceding claims, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

11. The TREM of any one of the preceding claims, wherein the TREM is a TREM provided in FIG. 2.

12. The TREM of any one of the preceding claims, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

13. The TREM of any one of the preceding claims, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

14. The TREM of any one of the preceding claims, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

15. The TREM of any one of the preceding claims, wherein the TREM is selected from TREM NOs. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2.

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16. 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.

17. 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 nucleotides.

18. 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 comprises the nucleotide sequence of SEQ ID NO: 622.

19. The TREM of any one of claims 1-17, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

20. The TREM of any one of claims 1-17, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

21. 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, according to the CtNS.

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

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a nucleotide within [DH Domain1], or [L3] 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 (e.g., a backbone modification).

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 (e.g., 2'F or 2'Cl), 2'-O-methoxyethyl (2'MOE), or 2'deoxy modification.

25. The TREM of any one of claims22-24, wherein the non-naturally occurring modification is a 2'OMe modification.

26. The TREM of any one of claims22-25 , wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

27. The TREM of any one of claims 22-26, wherein the non-naturally occurring modification is a 2'MOE modification.

28. The TREM of any one of claims 22-27, wherein the non-naturally occurring modification is a 2'-deoxy modification.

29. The TREM of any one of claims 22-28, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

30. The TREM of claim 29, wherein the non-naturally occurring modification is a phosphorothioate modification.

31. The TREM of any one of claims 22-30 , wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

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32. The TREM of any one of claims 22-31, wherein the TREM is a TREM provided in FIG. 2.

33. The TREM of any one of claims 22-32, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

34. The TREM of any one of claims 22-33, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

35. The TREM of any one of claims 22-34, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

36. The TREM of any one of claims 22-35, wherein the TREM is selected from TREM NO. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2in FIG. 2.

37. The TREM of any one of claims 22-3623-37, 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.

38. The TREM of any one of claims 22-37, 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 nucleotides.

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39. The TREM of any one of claims 22-38, 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 comprises the nucleotide sequence of SEQ ID NO: 622.

40. The TREM of any one of claims 22-38, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

41. The TREM of any one of claims 22-38, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

42. The TREM of any one of claims 22-41, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 10-26, according to the CtNS.

43. 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.

44. The TREM of claim 43, 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).

45. The TREM of any one of claims 43-44, 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.

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46. The TREM of any one of claims 43-45, wherein the non-naturally occurring modification is a 2'OMe modification.

47. The TREM of any one of claims 43-46, wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

48. The TREM of any one of claims 43-47, wherein the non-naturally occurring modification is a 2'MOE modification.

49. The TREM of any one of claims 43-48, wherein the non-naturally occurring modification is a 2'-deoxy modification.

50. The TREM of any one of claims 43-49, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

51. The TREM of claim 50, wherein the non-naturally occurring modification is a phosphorothioate modification.

52. The TREM of any one of claims 43-51, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

53. The TREM of any one of claims 43-52, wherein the TREM is a TREM provided in FIG. 2.

54. The TREM of any one of claims 43-53, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

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55. The TREM of any one of claims 43-54, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

56. The TREM of any one of claims 43-55, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

57. The TREM of any one of claims 43-56, wherein the TREM is selected from TREM NO. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2.

58. The TREM of any one of claims 43-57, 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.

59. The TREM of any one of claims 43-58, 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 nucleotides.

60. The TREM of any one of claims 43-59, 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 comprises the nucleotide sequence of SEQ ID NO: 622.

61. The TREM of any one of claims 43-59, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

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62. The TREM of any one of claims 43-59, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

63. The TREM of any one of claims 43-62, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 27-43, according to the CtNS.

64. 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.

65. The TREM of claim 64, 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).

66. The TREM of any one of claims 64-65, 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.

67. The TREM of any one of claims 64-66, wherein the non-naturally occurring modification is a 2'OMe modification.

68. The TREM of any one of claims 64-67, wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

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69. The TREM of any one of claims 64-68, wherein the non-naturally occurring modification is a 2'MOE modification.

70. The TREM of any one of claims 64-69, wherein the non-naturally occurring modification is a 2'-deoxy modification.

71. The TREM of any one of claims 64-70, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

72. The TREM of claim 71, wherein the non-naturally occurring modification is a phosphorothioate modification.

73. The TREM of any one of claims 64-72, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

74. The TREM of any one of claims 64-73, wherein the TREM is a TREM provided in FIG. 2.

75 The TREM of any one of claims 64-74, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

76. The TREM of any one of claims 64-75, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

77. The TREM of any one of claims 64-76, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

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78. The TREM of any one of claims 64-77, wherein the TREM is selected from TREM NO. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2.

79. The TREM of any one of claims 64-78, 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.

80. The TREM of any one of claims 64-79, 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 nucleotides.

81. The TREM of any one of claims 64-80, 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 comprises the nucleotide sequence of SEQ ID NO: 622.

82. The TREM of any one of claims 64-80, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

83. The TREM of any one of claims 64-80, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

84. The TREM of any one of claims 64-83, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 44-48, according to the CtNS.

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85. 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.

86. The TREM of claim 85, 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).

87 The TREM of any one of claims 85-86, 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.

88. The TREM of any one of claims 85-87, wherein the non-naturally occurring modification is a 2'OMe modification.

89. The TREM of any one of claims 85-88, wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

90. The TREM of any one of claims 85-89, wherein the non-naturally occurring modification is a 2'MOE modification.

91. The TREM of any one of claims 85-90, wherein the non-naturally occurring modification is a 2'-deoxy modification.

92. The TREM of any one of claims 85-91, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

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93. The TREM of claim 92 wherein the non-naturally occurring modification is a phosphorothioate modification.

94. The TREM of any one of claims 85-93, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

95. The TREM of any one of claims 85-94, wherein the TREM is a TREM provided in FIG. 2.

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

97. The TREM of any one of claims 85-96, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

98. The TREM of any one of claims 85-97, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

99. The TREM of any one of claims 85-98, wherein the TREM is selected from TREM NO. 1-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3000, 3001-3500, 3501-4000, 4001-4500, 4501-5000, 5001-5500, 5501-6000, 6001-6500, 6501-7000, 7001-7500, 7501-8000, 8001-8500, 8501-9000, and 9001-9136 in FIG. 2.

100. The TREM of any one of claims 85-99, 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.

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101. The TREM of any one of claims 85-100, 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 nucleotides.

102. The TREM of any one of claims 85-101, 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 comprises the nucleotide sequence of SEQ ID NO: 622.

103. The TREM of any one of claims 85-101, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

104. The TREM of any one of claims 85-101, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

105. The TREM of any one of claims 85-104, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 10-25, according to the CtNS.

106. 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.

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107. The TREM of claim 106, 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).

108. The TREM of any one of claims 106-107, 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.

109. The TREM of any one of claims 106-108, wherein the non-naturally occurring modification is a 2'OMe modification.

110. The TREM of any one of claims 106-109, wherein the non-naturally occurring modification is a 2'halo (e.g., 2'F or 2'Cl) modification.

111. The TREM of any one of claims 106-110, wherein the non-naturally occurring modification is a 2'MOE modification.

112. The TREM of any one of claims 106-111, wherein the non-naturally occurring modification is a 2'-deoxy modification.

113. The TREM of any one of claims 106-112, wherein the non-naturally occurring modification is present in the internucleotide region (e.g., a backbone modification).

114. The TREM of claim 113, wherein the non-naturally occurring modification is a phosphorothioate modification.

115. The TREM of any one of claims 106-114, wherein the TREM has a sequence selected from a sequence provided in FIG. 2.

116. The TREM of any one of claims 106-115, wherein the TREM is a TREM provided in FIG. 2.

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117. The TREM of any one of claims 106-116, wherein the TREM comprises a TREM having at least 70%, 75%, 80%, 85%, 90%, 95%, or 99% sequence identity with a TREM provided in FIG. 2.

118. The TREM of any one of claims 106-117, wherein the TREM comprises a sequence that differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from a TREM provided in FIG. 2.

119. The TREM of any one of claims 106-118, wherein the TREM comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional non-naturally occurring modifications compared with a TREM provided in FIG. 2 (e.g., 2'-ribose modifications or an internucleotide modification, e.g., 2'OMe, 2'-halo, 2'-MOE, 2'-deoxy, or phosphorothiorate modifications).

120. The TREM of any one of claims 106-119, wherein the TREM is selected from TREM NO. 1-100, 101-200, 201-300, 301-400, 401-500, 501-600, 601-700, 701-800, 801-900, 901-1000, 1001-1100, 1101-1200, 1201-1300, 1301-1400, 1401-1500, 1501-1600, 1601-1700, 1701-1800, 1801-1900, 1901-2000, 2001-2100, 2101-2200, 2201-2300, 2301-2400, 2401-2500, 2501-2600, and 2601-2663 in FIG. 2.

121. The TREM of any one of claims 106-120, 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.

122. The TREM of any one of claims 106-121, 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 nucleotides.

123. The TREM of any one of claims 106-122, wherein:

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(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 comprises the nucleotide sequence of SEQ ID NO: 622.

124. The TREM of any one of claims 106-122, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 623.

125. The TREM of any one of claims 106-122, wherein the TREM comprises the nucleotide sequence of SEQ ID NO: 624.

126. The TREM of any one of claims 106-125, wherein the non-naturally occurring modification is present at a nucleotide position which corresponds to one or more of nucleotides 66-76, according to the CtNS.

127. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 described herein.

128. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 2 described herein.

129. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 3 described herein.

130. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 4 described herein.

131. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 5 described herein.

132. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 6 described herein.

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133. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 and 2 described herein.

134. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 and 3 described herein.

135. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 and 4 described herein.

136. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 and 5 described herein.

137. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 1 and 6 described herein.

138. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 2 and 3 described herein.

139. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 2 and 4 described herein.

140. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 2 and 5 described herein.

141. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 2 and 6 described herein.

142. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 3 and 4 described herein.

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143. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 3 and 5 described herein.

144. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 3 and 6 described herein.

145. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 4 and 5 described herein.

146. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 4 and 6 described herein.

147. A TREM (e.g., a TREM provided in FIG. 2), according to Design Guidance 5 and 6 described herein.

148. A TREM (e.g., a TREM provided in FIG. 2), according to any three of Design Guidances 1, 2, 3, 4, 5, and 6 described herein.

149. A TREM (e.g., a TREM provided in FIG. 2), according to any four of Design Guidances 1, 2, 3, 4, 5, and 6 described herein.

150. A TREM (e.g., a TREM provided in FIG. 2), according to any five of Design Guidances 1, 2, 3, 4, 5, and 6 described herein.

151. A TREM (e.g., a TREM provided in FIG. 2), according to all of Design Guidances 1, 2, 3, 4, 5, and 6 described herein.

152. A pharmaceutical composition comprising a TREM of any one of the preceding claims.

153. The pharmaceutical composition of claim 152, further comprising a pharmaceutically acceptable component, e.g., an excipient.

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154. A lipid nanoparticle formulation comprising a TREM of any one of claims 1-153.

155. A lipid nanoparticle formulation comprising a pharmaceutical composition of claim 154.

156. A method of treating a subject having a disease or disorder associated with a PTC comprising administering to the subject a TREM, TREM core fragment, or TREM fragment described herein (e.g., a TREM of any one of claims 1-151), thereby treating the subject having the disease or disorder.

157. The method of claim 156, wherein the disease or disorder associated with a PTC comprises Hemophilia B, Fabry disease, Usher syndrome, or CLN2 disease.

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