

COMPOSITIONS OF MODIFIED TREMS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/130,373, U.S. Provisional Application No. 63/130,374, U.S. Provisional Application No. 63/130,375, U.S. Provisional Application No. 63/130,377, U.S. Provisional Application No. 63/130,381, and U.S. Provisional Application No. 63/130,387, each of which was filed on December 23, 2020. The entire contents of each of the foregoing applications is hereby incorporated by reference.

BACKGROUND

tRNAs are complex RNA molecules that possess a number of functions including the ability to initiate and elongate proteins.

SUMMARY

The present disclosure features, *inter alia*, a tRNA-based effector molecule (TREM) entity comprising an asialoglycoprotein receptor (ASGPR) binding moiety, as well as compositions and methods of use thereof. The ASGPR binding moiety may be conjugated to a nucleobase within the TREM entity, or within an internucleotide linkage of the TREM entity, or at a terminus (e.g., the 5' or 3' terminus) of the TREM entity. In an embodiment, the TREM entity comprises a TREM, a TREM Core Fragment, or a TREM Fragment. In an embodiment, the nucleobase comprises adenine, thymine, cytosine, guanosine, or uracil, or a variant or modified form thereof.

In one aspect, the TREM entity (e.g., TREM) described herein comprises the sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain]-[VL Domain]-[TH Domain]-[L4]-[ASt Domain2] (A), wherein, independently, the TREM comprises an ASGPR binding moiety. In an embodiment, the ASGPR binding moiety comprises an ASGPR carbohydrate and an ASGPR linker. In an embodiment, the ASGPR binding moiety comprises a galactose (Gal) and/or N-acetylgalactosamine (GalNAc) moiety. In an embodiment, the ASGPR binding moiety comprises a plurality of Gal and/or GalNAc moieties (e.g., 2, 3, 4, 5, 6, 7, 8, or more Gal and/or GalNAc moieties). In an embodiment, the ASGPR binding moiety comprises a

triantennary GalNAc moiety. In an embodiment, the TREM further comprises a chemical modification (e.g., a phosphothiorate internucleotide linkage, or a 2'-modification on a ribose moiety within the TREM).

In an embodiment, the ASGPR binding moiety is present on a nucleobase within a nucleotide in the TREM. In an embodiment, the ASGPR binding moiety is present on the 5' terminus of the TREM. In an embodiment, the ASGPR binding moiety is present on the 3' terminus of the TREM.

In an embodiment, the ASGPR binding moiety is present in a TREM domain selected from L1, ASt Domain1, L2, DH Domain, L3, ACH Domain, VL Domain, TH Domain, L4, and ASt Domain2. In an embodiment, the ASGPR binding moiety is present in the L1 region. In an embodiment, the ASGPR binding moiety is present in the AST Domain1. In an embodiment, the ASGPR binding moiety is present in the L2 region. In an embodiment, the ASGPR binding moiety is present in the DH Domain. In an embodiment, the ASGPR binding moiety is present in the L3 region. In an embodiment, the ASGPR binding moiety is present in the ACH Domain. In an embodiment, the ASGPR binding moiety is present in the VL Domain. In an embodiment, the ASGPR binding moiety is present in the TH Domain. In an embodiment, the ASGPR binding moiety is present in the L4 region. In an embodiment, the ASGPR binding moiety is present in the AST Domain2.

In an embodiment, the TREM comprising an ASGPR binding moiety retains the ability to support protein synthesis, be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, and/or support initiation. In an embodiment, the TREM comprising an ASGPR binding moiety comprises at least X contiguous nucleotides without a chemical modification, wherein X is greater than 10. In an embodiment, the TREM comprising an ASGPR binding moiety comprises no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) that do not comprise chemical modification. In an embodiment, the TREM comprising an ASGPR binding moiety 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 do not comprise a chemical modification. In an embodiment, the TREM comprising an ASGPR binding moiety comprises at least X contiguous nucleotides comprising a chemical modification, wherein X is greater than 10. In an embodiment, the TREM comprising an

ASGPR binding moiety comprises more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) that comprise a chemical modification. In an embodiment, the TREM comprising an ASGPR binding moiety comprises 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 chemical modification. In an embodiment, the chemical modification is a naturally occurring chemical modification or a non-naturally occurring chemical modification (e.g., a phosphothiorate internucleotide linkage or a 2'-modification on a ribose moiety within the TREM). In an embodiment, the chemical modification comprises a fluorophore.

In another aspect, a TREM comprising an ASGPR binding moiety, or a composition thereof, described herein may be used 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, a TREM comprising an ASGPR binding moiety, or a composition thereof, described herein may be used in 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 comprising an ASGPR binding moiety or a composition thereof in an amount and/or for a time sufficient to modulate the production parameter of the mRNA or polypeptide, wherein the TREM comprising an ASGPR binding moiety 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, a TREM comprising an ASGPR binding moiety, or a composition thereof, described herein may be used in a method of treating a subject having an endogenous open reading frame (ORF) which comprises a premature termination codon (PTC), comprising providing a TREM comprising an ASGPR binding moiety, or a composition thereof, wherein the TREM comprising an ASGPR binding moiety comprises an anticodon that pairs with the PTC in the ORF; contacting the subject with the TREM comprising an ASGPR binding moiety or a

composition thereof 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, a TREM comprising an ASGPR binding moiety, or a composition thereof, described herein may be used in a method of treating a subject having an disease or disorder associated with a premature termination codon (PTC), comprising providing a TREM comprising an ASGPR binding moiety or a composition described herein; contacting the subject with the TREM comprising an ASGPR binding moiety or a composition thereof 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 disorder described herein, e.g., a cancer or a monogenic disease.

Additional features of any of the aforesaid TREM entities (e.g., 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 following enumerated embodiments).

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.

BRIEF DESCRIPTIONS OF THE DRAWINGS

FIGS. 1A-1J are images that depict ASGPR-expressing U2OS cells transfected with exemplary TREMs comprising an ASGPR binding moiety described herein. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 650 backbone with ASGPR binding moieties at various positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy.

FIG. 2 is a graphical representation of the fluorescent microscopy results of FIGs. 1A-1J. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIGs. 3A-3H are images that depict ASGPR-expressing U2OS cells transfected with exemplary TREMs comprising an ASGPR binding moiety described herein. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 650 backbone with ASGPR binding moieties at

various positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy.

FIG. 4 is a graphical representation of the fluorescent microscopy results of FIGs. 3A-3H. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIGs. 5A-5J are images that depict ASGPR-expressing U2OS cells transfected with exemplary TREMs comprising an ASGPR binding moiety described herein. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 622 backbone with ASGPR binding moieties at various positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy.

FIG. 6 is a graphical representation of the fluorescent microscopy results of FIGs. 5A-5J. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIGs. 7A-7J are images depicting uptake of exemplary TREMs comprising an ASGPR binding moiety as described herein by primary human hepatocytes. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 650 backbone with ASGPR binding moieties at various positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy. FIG. 8 is a graphical representation of the fluorescent microscopy results of FIGs. 7A-7J. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIGs. 9A-9H are images depicting uptake of exemplary TREMs comprising an ASGPR binding moiety as described herein by primary human hepatocytes. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 653 backbone with ASGPR binding moieties at various positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy.

FIG. 10 is a graphical representation of the fluorescent microscopy results of FIGs. 9A-9H. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIGs. 11A-11J are images depicting uptake of exemplary TREMs comprising an ASGPR binding moiety as described herein by primary human hepatocytes. In this experiment, uptake of the TREMs comprising a SEQ ID NO. 622 backbone with ASGPR binding moieties at various

positions along the sequence and conjugated to Cy3 was monitored and visualized by fluorescent microscopy.

FIG. 12 is a graphical representation of the fluorescent microscopy results of FIGs. 11A-11J. The results are depicted as the average intensity over the concentration of oligo (nM) given to the cells.

FIG. 13 is a graph depicting the results of exemplary TREM uptake by ASGPR-expressing U2OS cells transfected with a nLUC-premature terminating codon (PTC) reporter. The exemplary TREMs comprising a SEQ ID NO. 650 backbone comprising an ASGPR-binding moiety at a position along the sequence were transfected using RNAiMAX transfection reagent. The results are shown as fold-change over the mock (no TREM) sample.

FIG. 14 is a graph depicting the results of exemplary TREM uptake by ASGPR-expressing U2OS cells transfected with a nLUC-premature terminating codon (PTC) reporter. The exemplary TREMs comprising a SEQ ID NO. 653 backbone comprising a ASGPR binding moiety at a position along the sequence were transfected using RNAiMAX transfection reagent. The results are shown as fold-change over the mock (no TREM) sample.

FIG. 15 is a graph depicting the results of exemplary TREM uptake by ASGPR-expressing U2OS cells transfected with a nLUC-premature terminating codon (PTC) reporter. The exemplary TREMs comprising a SEQ ID NO. 622 backbone comprising a ASGPR binding moiety at a position along the sequence were transfected using RNAiMAX transfection reagent. The results are shown as fold-change over the mock (no TREM) sample.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

The present disclosure features tRNA-based effector molecule (TREM) entities (e.g., TREMs, TREM Core Fragments, and TREM Fragments) comprising an asialoglycoprotein receptor (ASGPR) binding moiety, as well as compositions and related methods of use thereof. As disclosed herein, TREM entities (e.g., TREMs) are complex molecules which can mediate a variety of cellular processes. Pharmaceutical TREM compositions, e.g., TREMs comprising an ASGPR binding moiety, can be administered to a cell, a tissue, or to a subject to modulate these functions.

Definitions

An “acceptor stem domain (AStD),” as that term is used herein, refers to a domain that binds an amino acid. In an embodiment, an AStD comprises an ASt Domain1 and an ASt Domain 2. For example, the ASt Domain 1 is at or near the 5’ end of the TREM and the ASt Domain 2 is at or near the 3’ end of the TREM. 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 that has AStD activity and in other embodiments do 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. For example, 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 ASGPR binding moiety is present within the AStD. In an embodiment, the ASGPR binding moiety is bound to a nucleobase within a nucleotide in the AStD. In an embodiment, the ASGPR binding moiety is present within the internucleotide linkage in the AStD. In an embodiment, the ASGPR binding moiety is present on a terminus (*e.g.*, the 5’ or 3’ terminus) within the AStD.

In an embodiment, the ASt Domain 1 comprises positions 1-9 within the TREM sequence. In an embodiment, the ASGPR binding moiety is present within ASt Domain1 (*e.g.*, positions 1-9) within the TREM sequence. In an embodiment, the ASt Domain2 comprises positions 65-76 within the TREM sequence. In an embodiment, the ASPGR binding moiety is present within the ASt Domain 1 (*e.g.*, positions 65-76) within the TREM sequence.

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 ASPGR binding moiety is

present with the AStD which 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 R₁-R₂-R₃-R₄ -R₅-R₆-R₇ (an exemplary ASt Domian2) and residues R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁ (an exemplary ASt Domian2) of Formula I *zzz*, wherein *zzz* indicates any of the twenty amino acids. In some embodiments, Formula I *zzz* refers to all species.

In an embodiment, the AStD comprises residues R₁-R₂-R₃-R₄ -R₅-R₆-R₇ and residues R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁ of Formula II *zzz*, wherein *zzz* indicates any of the twenty amino acids. In some embodiments, Formula II *zzz* refers to mammals.

In an embodiment, the AStD comprises residues R₁-R₂-R₃-R₄ -R₅-R₆-R₇ and residues R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁ of Formula III *zzz*, wherein *zzz* indicates any of the twenty amino acids. In some embodiments, Formula III *zzz* refers to humans.

In an embodiment, *zzz* indicates any of the amino acids: Alanine, Arginine, Asparagine, Aspartate, Cysteine, Glutamine, Glutamate, Glycine, Histidine, Isoleucine, Methionine, Leucine, Lysine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, or Valine.

An “anticodon hairpin domain (ACHD)”, as that term is used herein, refers to a domain comprising an anticodon that binds a respective codon in an mRNA, and 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 ASGPR binding moiety is present within the ACHD. In an embodiment, the ASGPR binding moiety is bound to a nucleobase within a nucleotide in the ACHD.

In an embodiment, the ACHD comprises positions 27-43 within the TREM sequence. In an embodiment, the ASGPR binding moiety is present within the ACHD (*e.g.*, positions 27-43) within the TREM sequence.

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 ASGPR binding moiety is present within the corresponding sequence of a consensus sequence provided in the “Consensus Sequence” section or a sequence that differs from the consensus sequence by no more than 1, 2, 5, or 10 positions.

In an embodiment, the ACHD comprises residues -R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆ of Formula I *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula I *ZZZ* refers to all species.

In an embodiment, the ACHD comprises residues -R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆ of Formula II *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula II *ZZZ* refers to mammals.

In an embodiment, the ACHD comprises residues -R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆ of Formula III *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula III *ZZZ* refers to humans.

In an embodiment, *ZZZ* indicates any of the 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, the anticodon of a TREM entity comprises three nucleotide residues and pairs with a three nucleotide codon. In an embodiment, the anticodon of a TREM entity consists of three nucleotide residues and pairs with an anticodon which consists of three nucleotide residues. In an embodiment the anticodon of the TREM entity does not pair with a codon having four, five or a larger number of nucleotide residues but pairs only with three codon nucleotide residues.

In an embodiment, the TREM entity does not alter the reading frame of an mRNA. In an embodiment, the anti-codon of a TREM entity pairs with a triplet codon of an mRNA and does not pair with an adjacent nucleotide.

In an embodiment, use of the TREM entity does not alter the length of the polypeptide transcribed from the mRNA, e.g., it does not suppress a termination codon, e.g., a premature termination codon. In an embodiment, the TREM does not alter the length of the ORF of an mRNA.

An “asialoglycoprotein receptor (ASGPR) binding moiety,” as that term is used herein, refers to a moiety which binds an asialoglycoprotein receptor. In an embodiment, the ASGPR

binding moiety as described herein refers to structure comprising: (i) an ASGPR carbohydrate and (ii) a ASGPR linker (e.g., a linker connecting the carbohydrate to the TREM). Exemplary ASGPR moieties include galactose (Gal), galactosamine (GalNH₂), or an N-acetylgalactosamine (GalNAc) moiety, for example, a Gal, GalNH₂, or GalNAc, or an analog thereof. The ASGPR binding moieties may comprise functional groups (e.g., hydroxyl groups, carboxylate groups, amines) that may be protected by a chemical protecting group, e.g., an acetyl group or methyl group. In an embodiment, the ASGPR binding moiety comprises a triantennary GalNAc moiety. In an embodiment, the ASGPR binding moiety may ASGPR binding moieties are described in further detail herein.

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.

A dihydrouridine hairpin domain (DHD), as that term is used herein, refers to a domain which 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 ASGPR binding moiety is present within the DHD. In an embodiment, the ASGPR binding moiety is bound to a nucleobase within a nucleotide in the DHD.

In an embodiment, the DHD comprises positions 10-26 within the TREM sequence. In an embodiment, the ASGPR binding moiety is present within the DHD (*e.g.*, positions 10-26) within the TREM sequence.

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 ASGPR binding moiety is present within the corresponding sequence of a consensus sequence provided in the “Consensus Sequence” section or a sequence that differs from the consensus sequence by no more than 1, 2, 5, or 10 positions.

In an embodiment, the DHD comprises residues R₁₀-R₁₁-R₁₂-R₁₃-R₁₄ R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈ of Formula I *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula I *ZZZ* refers to all species.

In an embodiment, the DHD comprises residues R₁₀-R₁₁-R₁₂-R₁₃-R₁₄ R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈ of Formula II *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula II *ZZZ* refers to mammals.

In an embodiment, the DHD comprises residues R₁₀-R₁₁-R₁₂-R₁₃-R₁₄ R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈ of Formula III *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula III *ZZZ* refers to humans.

In an embodiment, *ZZZ* indicates any of the amino acids: Alanine, Arginine, Asparagine, Aspartate, Cysteine, Glutamine, Glutamate, Glycine, Histidine, Isoleucine, Methionine, Leucine, Lysine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, or Valine.

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 Linker 2 region (L2), as that term is used herein, refers to a linker comprising residues R₈-R₉ of a consensus sequence provided in the “Consensus Sequence” section.

A Linker 3 region (L3), that term is used herein, refers to a linker comprising residue R₂₉ of a consensus sequence provided in the “Consensus Sequence” section.

A “Linker 4 region (L4), as that term is used herein, refers to a domain comprising residue R₇₂ of a consensus sequence provided in the “Consensus Sequence” section.

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. In an embodiment, the modification is present within the nucleobase, nucleotide sugar, or internucleotide linkage of a nucleotide of the TREM. 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 “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 (e.g., internucleotide linkage). 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 “thymine hairpin domain (THD), as that term is used herein, refers to a domain which 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 ASPGR binding moiety is present within the THD. In an embodiment, the ASGPR binding moiety is bound to a nucleobase within a nucleotide in the THD.

In an embodiment, the THD comprises positions 50-64 within the TREM sequence. In an embodiment, the ASPGR binding moiety is present within the THD (e.g., positions 50-64) within the TREM sequence.

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 -R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄ of Formula I *zzz*, wherein *zzz* indicates any of the twenty amino acids. In some embodiments, Formula I *zzz* refers to all species.

In an embodiment, the THD comprises residues -R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄ of Formula II *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula II *ZZZ* refers to mammals.

In an embodiment, the THD comprises residues -R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄ of Formula II *ZZZ*, wherein *ZZZ* indicates any of the twenty amino acids. In some embodiments, Formula III *ZZZ* refers to humans.

In an embodiment, *ZZZ* indicates any of the amino acids: Alanine, Arginine, Asparagine, Aspartate, Cysteine, Glutamine, Glutamate, Glycine, Histidine, Isoleucine, Methionine, Leucine, Lysine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, or Valine.

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 acceptor stem domain (an AStD), which typically comprises an ASt Domain1 and an ASt Domain2;

(a'-1) a Linker 2 region (L2) a linker comprising residues R₈-R₉ of a consensus sequence provided in the “Consensus Sequence” section, *e.g.*, a Linker 2 region;

(b) a DHD or dihydrouridine hairpin domain (DHD);

(b'-1) a Linker 3 region, or L3;

(c) an ACHD or anticodon hairpin domain;

(d) a VLD, or variable loop domain (VLD);

- (e) a THD or thymine hairpin domain (THD);
- (e' 1) an L4 linker comprising residue R₇₂ of a consensus sequence provided in the “Consensus Sequence” section;
- (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-transcriptional 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 "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 “subject,” as this term is used herein, includes any organism, such as a human or other animal. In embodiments, the subject is a vertebrate animal (*e.g.*, mammal, bird, fish, reptile, or amphibian). In embodiments, the subject is a mammal, *e.g.*, a human. In embodiments, the method subject is a non-human mammal. In embodiments, the subject is a non-human mammal such as a non-human primate (*e.g.*, monkeys, apes), ungulate (*e.g.*, cattle, buffalo, sheep, goat, pig, camel, llama, alpaca, deer, horses, donkeys), carnivore (*e.g.*, dog, cat), rodent (*e.g.*, rat, mouse), or lagomorph (*e.g.*, rabbit). In embodiments, the subject is a bird, such as a member of the avian taxa Galliformes (*e.g.*, chickens, turkeys, pheasants, quail), Anseriformes (*e.g.*, ducks, geese), Paleognathae (*e.g.*, ostriches, emus), Columbiformes (*e.g.*, pigeons, doves), or Psittaciformes (*e.g.*, parrots). The subject may be a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)). A non-human subject may be a transgenic animal.

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 synthesized 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 comprises a chemical 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 comprises a chemical modification at a first position and a chemical 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 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.

In an embodiment, at least X% of the TREMs in a TREM composition comprises a chemical modification at a first position and less than Y% have a chemical 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.

A “variable loop domain (VLD),” as that term is used herein refers to a domain which 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 ASGPR binding moiety is present within the VLD. In an embodiment, the ASGPR binding moiety is bound to a nucleobase within a nucleotide in the VLD.

In an embodiment, the VLD comprises positions 44-49 within the TREM sequence. In an embodiment, the ASGPR binding moiety is present within the VLD (e.g., positions 44-49) within the TREM sequence.

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 $x=271$).

TREM Entities

Described herein are TREM entities, e.g., a TREM, a TREM Core Fragment, or a TREM Fragment, modified with an asialoglycoprotein receptor (ASGPR) binding moiety, as well as compositions and methods of use thereof. A TREM entity (e.g., a TREM) refers to an RNA molecule comprising one or more of the properties described herein. The ASGPR binding moiety may be conjugated to a nucleobase within the TREM entity, or within an internucleotide linkage of the TREM entity, or at a terminus (e.g., the 5' or 3' terminus) of the TREM entity. A TREM entity (e.g., a TREM) can comprise a chemical modification, e.g., as provided in Tables 4, 5, 6 or 7.

In an embodiment, a TREM entity 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], wherein the ASGPR binding moiety is present within the ASt Domain1 (e.g., on a nucleobase, at a terminus (e.g., the 5' terminus), or within the internucleotide linkage of ASt Domain1). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within ASt Domain1. In an embodiment, the ASGPR binding moiety is present at the 5' terminus within ASt

Domain1 or at [L1]. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of ASt Domain1. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is present within the ASt Domain2 (e.g., on a nucleobase, at a terminus (e.g., 3' terminus), or within the internucleotide linkage of ASt Domain2). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within ASt Domain2. In an embodiment, the ASGPR binding moiety is present at the 3' terminus within ASt Domain2. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of ASt Domain2. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is present within either one or both of ASt Domain1 and ASt Domain2 (e.g., on a nucleobase, at a terminus (e.g., 5' or 3' terminus), or within the internucleotide linkage of ASt Domain1 or ASt Domain2). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within ASt Domain1 or ASt Domain2. In an embodiment, the ASGPR binding moiety is present at the 5' terminus within ASt Domain1 or [L1] or the 3' terminus within ASt Domain2. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of ASt Domain1 or ASt Domain2. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is present within the DH Domain (e.g., on a nucleobase or within the internucleotide linkage of the DH Domain). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within the DH Domain. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of the DH Domain. In an embodiment, [L1] is optional.

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],

wherein the ASGPR binding moiety is within the ACH Domain (e.g., on a nucleobase or within the internucleotide linkage of the ACH Domain). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within the ACH Domain. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of the ACH Domain. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is present within the VL Domain (e.g., on a nucleobase or within the internucleotide linkage of the VL Domain). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within the VL Domain. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of the VL Domain. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is present within the TH Domain (e.g., on a nucleobase or within the internucleotide linkage of the TH Domain). In an embodiment, the ASGPR binding moiety is present on a nucleobase of a nucleotide within the TH Domain. In an embodiment, the ASGPR binding moiety is present within an internucleotide linkage of the TH Domain. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is bound to a nucleobase within one or more domains selected from [ASt Domain1], [DH Domain], [ACH Domain], [TH Domain], and/or [ASt Domain2]. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

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], wherein the ASGPR binding moiety is bound to an internucleotide linkage within one or more domains selected from [ASt Domain1], [DH Domain], [ACH Domain], [TH Domain], and/or [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, and the ASGPR binding moiety is bound to a nucleobase within a nucleotide within one or both of ASt Domain1 and ASt Domain2. In an embodiment, y=0. In an embodiment, y=1.

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, and the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the DH Domain. In an embodiment, y=0. In an embodiment, y=1.

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, and the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the ACH Domain. In an embodiment, y=0. In an embodiment, y=1.

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, and the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the TH Domain. In an embodiment, y=0. In an embodiment, y=1.

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, and the ASGPR binding moiety is bound to a nucleobase within one or more domain selected from [ASt Domain1], [DH Domain], [ACH Domain], [TH Domain], and/or [ASt Domain2]. 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 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	AUG	CUA
AAC	AUU	CUC
AAG	CAA	CUG
AAU	CAC	CUU
ACA	CAG	GAA
ACC	CAU	GAC
ACG	CCA	GAG
ACU	CCC	GAU
AGA	CCG	GCA
AGC	CCU	GCC
AGG	CGA	GCG
AGU	CGC	GCU
AUA	CGG	GGA
AUC	CGU	GGC

GGG	UAG	UGG
GGU	UAU	UGU
GUA	UCA	UUA
GUC	UCC	UUC
GUG	UCG	UUG
GUU	UCU	UUU
UAA	UGA	
UAC	UGC	

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.

In any and all embodiments, the TREM described herein comprises a consensus sequence of Formula I *zzz*,

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

wherein (i) *zzz* indicates any of the twenty amino acids; (ii) Formula I corresponds to all species; (iii) *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); and (iv) an ASGPR binding moiety is bound to a nucleobase within one or more of R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈ or (v) an ASGPR binding moiety is bound to a nucleobase within one or more of R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂.

In any and all embodiments, the TREM described herein comprises a consensus sequence of Formula II *zzz*,

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_{x1}-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

wherein (i) *zzz* indicates any of the twenty amino acids; (ii) Formula II corresponds to mammals; (iii) 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); and (iv) an ASGPR binding moiety is bound to a nucleobase within one or more of R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈ or (v) an ASGPR binding moiety is bound to a nucleobase within one or more of R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂.

In any and all embodiments, the TREM described herein comprises a consensus sequence of Formula III *zzz*,

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_{x1}-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

wherein (i) *zzz* indicates any of the twenty amino acids; (ii) Formula III corresponds to humans; (iii) $x=1-271$ (*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 $x=271$); and (iv) an ASGPR binding moiety is bound to a nucleobase within one or more of R_0 - R_1 - R_2 - R_3 - R_4 - R_5 - R_6 - R_7 - R_8 or (v) an ASGPR binding moiety is bound to a nucleobase within one or more of R_{61} - R_{62} - R_{63} - R_{64} - R_{65} - R_{66} - R_{67} - R_{68} - R_{69} - R_{70} - R_{71} - R_{72} .

Table 1.

SEQ ID NO	tRNA name	tRNA sequence
1	Ala_AGC_chr6:28763741-28763812 (-)	GGGGGTATAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGTCCCT
2	Ala_AGC_chr6:26687485-26687557 (+)	GGGGAATTAGCTCAAGTGGTAGAG CGCTTGCTTAGCACGCAAGAGGTA
3	Ala_AGC_chr6:26572092-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAG CGCTCGCTTAGCATGCGAGAGGTA
4	Ala_AGC_chr6:26682715-26682787 (+)	GGGGAATTAGCTCAAGTGGTAGAG CGCTTGCTTAGCATGCAAGAGGTA
5	Ala_AGC_chr6:26705606-26705678 (+)	GGGGAATTAGCTCAAGCGGTAGAG CGCTTGCTTAGCATGCAAGAGGTA
6	Ala_AGC_chr6:26673590-26673662 (+)	GGGGAATTAGCTCAAGTGGTAGAG CGCTTGCTTAGCATGCAAGAGGTA
7	Ala_AGC_chr14:89445442-89445514 (+)	GGGGAATTAGCTCAAGTGGTAGAG CGCTCGCTTAGCATGCGAGAGGTA
8	Ala_AGC_chr6:58196623-58196695 (-)	GGGGAATTAGCCCAAGTGGTAGAG CGCTTGCTTAGCATGCAAGAGGTA
9	Ala_AGC_chr6:28806221-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGCC
10	Ala_AGC_chr6:28574933-28575004 (+)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGTACGAGGTCCC

11	Ala_AGC_chr6:28626014-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTAGCATGCATGAGGTCCC
12	Ala_AGC_chr6:28678366-28678437 (+)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGCCCT
13	Ala_AGC_chr6:28779849-28779920 (-)	GGGGGTATAGCTCAGCGGTAGAGC GCGTGCTTAGCATGCACGAGGTCTT
14	Ala_AGC_chr6:28687481-28687552 (+)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGCC
15	Ala_AGC_chr2:27274082-27274154 (+)	GGGGGATTAGCTCAAATGGTAGAG CGCTCGCTTAGCATGCGAGAGGTA
16	Ala_AGC_chr6:26730737-26730809 (+)	GGGGAATTAGCTCAGGCGGTAGAG CGCTCGCTTAGCATGCGAGAGGTA
17	Ala_CGC_chr6:26553731-26553802 (+)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTCGCATGTATGAGGTCCC
18	Ala_CGC_chr6:28641613-28641684 (-)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTCGCATGTATGAGGCCCC
19	Ala_CGC_chr2:157257281-157257352 (+)	GGGGATGTAGCTCAGTGGTAGAGC GCGCGCTTCGCATGTGTGAGGTCCC
20	Ala_CGC_chr6:28697092-28697163 (+)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTCGCATGTACGAGGCC
21	Ala_TGC_chr6:28757547-28757618 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGTCCC
22	Ala_TGC_chr6:28611222-28611293 (+)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGTCCC
23	Ala_TGC_chr5:180633868-180633939 (+)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGCCCC
24	Ala_TGC_chr12:125424512-125424583 (+)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTTGCACGTATGAGGCCCC
25	Ala_TGC_chr6:28785012-28785083 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGCCTC
26	Ala_TGC_chr6:28726141-28726212 (-)	GGGGGTGTAGCTCAGTGGTAGAGC ACATGCTTTGCATGTGTGAGGCCCC
27	Ala_TGC_chr6:28770577-28770647 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGCCTC
28	Arg_ACG_chr6:26328368-26328440 (+)	GGGCCAGTGGCGCAATGGATAACG CGTCTGACTACGGATCAGAAGATTC
29	Arg_ACG_chr3:45730491-45730563 (-)	GGGCCAGTGGCGCAATGGATAACG CGTCTGACTACGGATCAGAAGATTC
30	Arg_CCG_chr6:28710729-28710801 (-)	GGCCGCGTGGCCTAATGGATAAAGG CGTCTGATTCCGGATCAGAAGATTG
31	Arg_CCG_chr17:66016013-66016085 (-)	GACCCAGTGGCCTAATGGATAAAGG CATCAGCCTCCGGAGCTGGGGATT
32	Arg_CCT_chr17:73030001-73030073 (+)	GCCCCAGTGGCCTAATGGATAAAGG CACTGGCCTCCTAAGCCAGGGATTG

33	Arg_CCT_chr17:73030526-73030598 (-)	GCCCCAGTGGCCTAATGGATAAAGG CACTGGCCTCCTAAGCCAGGGATTG
34	Arg_CCT_chr16:3202901-3202973 (+)	GCCCCGGTGGCCTAATGGATAAAGG CATTGGCCTCCTAAGCCAGGGATTG
35	Arg_CCT_chr7:139025446-139025518 (+)	GCCCCAGTGGCCTAATGGATAAAGG CATTGGCCTCCTAAGCCAGGGATTG
36	Arg_CCT_chr16:3243918-3243990 (+)	GCCCCAGTGGCCTGATGGATAAAGG TACTGGCCTCCTAAGCCAGGGATTG
37	Arg_TCG_chr15:89878304-89878376 (+)	GGCCGCGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAGAAGATTG
38	Arg_TCG_chr6:26323046-26323118 (+)	GACCACGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAGAAGATTG
39	Arg_TCG_chr17:73031208-73031280 (+)	GACCACGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAGAAGATTG
40	Arg_TCG_chr6:26299905-26299977 (+)	GACCACGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAGAAGATTG
41	Arg_TCG_chr6:28510891-28510963 (-)	GACCACGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAGAAGATTG
42	Arg_TCG_chr9:112960803-112960875 (+)	GGCCGTGTGGCCTAATGGATAAAGG CGTCTGACTTCGGATCAAAAAGATTG
43	Arg_TCT_chr1:94313129-94313213 (+)	GGCTCCGTGGCGCAATGGATAGCG CATTGGACTTCTAGAGGCTGAAGG
44	Arg_TCT_chr17:8024243-8024330 (+)	GGCTCTGTGGCGCAATGGATAGCG CATTGGACTTCTAGTGACGAATAGA
45	Arg_TCT_chr9:131102355-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCG CATTGGACTTCTAGCTGAGCCTAGT
46	Arg_TCT_chr11:59318767-59318852 (+)	GGCTCTGTGGCGCAATGGATAGCG CATTGGACTTCTAGATAGTTAGAGA
47	Arg_TCT_chr1:159111401-159111474 (-)	GTCTCTGTGGCGCAATGGACGAGC GCGCTGGACTTCTAATCCAGAGGTT
48	Arg_TCT_chr6:27529963-27530049 (+)	GGCTCTGTGGCGCAATGGATAGCG CATTGGACTTCTAGCCTAAATCAAG
49	Asn_GTT_chr1:161510031-161510104 (+)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTTAACCGAAAGGTTG
50	Asn_GTT_chr1:143879832-143879905 (-)	GTCTCTGTGGCGCAATCGGCTAGCG CGTTTGGCTGTTAATAAAAGGTTG
51	Asn_GTT_chr1:144301611-144301684 (+)	GTCTCTGTGGTGCAATCGGTTAGCG CGTTCCGCTGTTAACCGAAAGCTTG
52	Asn_GTT_chr1:149326272-149326345 (-)	GTCTCTGTGGCGCAATCGGCTAGCG CGTTTGGCTGTTAATAAAAAGTTG
53	Asn_GTT_chr1:148248115-148248188 (+)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTTAACCGAAAGGTTG
54	Asn_GTT_chr1:148598314-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CATTCGGCTGTTAACCGAAAGGTTG

55	Asn_GTT_chr1:17216172-17216245 (+)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTAAACCGAAAGATTG
56	Asn_GTT_chr1:16847080-16847153 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTAACTGAAAGGTTG
57	Asn_GTT_chr1:149230570-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCG CGTTCGGCTGTAAACCGAAAGGTTG
58	Asn_GTT_chr1:148000805-148000878 (+)	GTCTCTGTGGCGTAGTCGGTTAGCG CGTTCGGCTGTAAACCGAAAAGTTG
59	Asn_GTT_chr1:149711798-149711871 (-)	GTCTCTGTGGCGCAATCGGCTAGCG CGTTTGGCTGTAACTAAAAGGTTG
60	Asn_GTT_chr1:145979034-145979107 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTAACTGAAAGGTTA
61	Asp_GTC_chr12:98897281-98897352 (+)	TCCTCGTTAGTATAGTGGTTAGTAT CCCCGCCTGTCACGCGGGAGACCG
62	Asp_GTC_chr1:161410615-161410686 (-)	TCCTCGTTAGTATAGTGGTGAGTAT CCCCGCCTGTCACGCGGGAGACCG
63	Asp_GTC_chr6:27551236-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGT CCCCGTCTGTCACGCGGGAGACCG
64	Cys_GCA_chr7:149007281-149007352 (+)	GGGGGCATAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
65	Cys_GCA_chr7:149074601-149074672 (-)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
66	Cys_GCA_chr7:149112229-149112300 (-)	GGGGGTATAGCTTAGCGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
67	Cys_GCA_chr7:149344046-149344117 (-)	GGGGGTATAGCTTAGGGGTAGAGC ATTTGACTGCAGATCAAAAGGTCCC
68	Cys_GCA_chr7:149052766-149052837 (-)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
69	Cys_GCA_chr17:37017937-37018008 (-)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAAGTCCC
70	Cys_GCA_chr7:149281816-149281887 (+)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCTC
71	Cys_GCA_chr7:149243631-149243702 (+)	GGGGGTATAGCTCAGGGGTAGAGC ACTTGACTGCAGATCAAGAAGTCCT
72	Cys_GCA_chr7:149388272-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
73	Cys_GCA_chr7:149072850-149072921 (-)	GGGGGTATAGTTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
74	Cys_GCA_chr7:149310156-149310227 (-)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAAATCAAGAGGTCCC
75	Cys_GCA_chr4:124430005-124430076 (-)	GGGGGTATAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
76	Cys_GCA_chr7:149295046-149295117 (+)	GGGCGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC

77	Cys_GCA_chr7:149361915-149361986 (+)	GGGGGTATAGCTCACAGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
78	Cys_GCA_chr7:149253802-149253871 (+)	GGGCGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
79	Cys_GCA_chr7:149292305-149292376 (-)	GGGGGTATAGCTCACAGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
80	Cys_GCA_chr7:149286164-149286235 (-)	GGGGGTATAGCTCAGGGGTAGAGC ACTTGACTGCAGATCAAGAGGTCC
81	Cys_GCA_chr17:37025545-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
82	Cys_GCA_chr15:80036997-80037069 (+)	GGGGGTATAGCTCAGTGGGTAGAG CATTGACTGCAGATCAAGAGGTCC
83	Cys_GCA_chr3:131947944-131948015 (-)	GGGGGTGTAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
84	Cys_GCA_chr1:93981834-93981906 (-)	GGGGGTATAGCTCAGGTGGTAGAG CATTGACTGCAGATCAAGAGGTCC
85	Cys_GCA_chr14:73429679-73429750 (+)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
86	Cys_GCA_chr3:131950642-131950713 (-)	GGGGGTATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
87	Gln_CTG_chr6:18836402-18836473 (+)	GGTTCCATGGTGTAAATGGTTAGCAC TCTGGACTCTGAATCCAGCGATCCG
88	Gln_CTG_chr6:27515531-27515602 (-)	GGTTCCATGGTGTAAATGGTTAGCAC TCTGGACTCTGAATCCAGCGATCCG
89	Gln_CTG_chr1:145963304-145963375 (+)	GGTTCCATGGTGTAAATGGTGAGCAC TCTGGACTCTGAATCCAGCGATCCG
90	Gln_CTG_chr1:147737382-147737453 (-)	GGTTCCATGGTGTAAATGGTAAGCAC TCTGGACTCTGAATCCAGCGATCCG
91	Gln_CTG_chr6:27263212-27263283 (+)	GGTTCCATGGTGTAAATGGTTAGCAC TCTGGACTCTGAATCCGGTAATCCG
92	Gln_CTG_chr6:27759135-27759206 (-)	GGCCCCATGGTGTAAATGGTCAGCA CTCTGGACTCTGAATCCAGCGATCC
93	Gln_CTG_chr1:147800937-147801008 (+)	GGTTCCATGGTGTAAATGGTAAGCAC TCTGGACTCTGAATCCAGCCATCTG
94	Gln_TTG_chr17:47269890-47269961 (+)	GGTCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCGATCCG
95	Gln_TTG_chr6:28557156-28557227 (+)	GGTCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCAATCCG
96	Gln_TTG_chr6:26311424-26311495 (-)	GGCCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCGATCCG
97	Gln_TTG_chr6:145503859-145503930 (+)	GGTCCCATGGTGTAAATGGTTAGCAC TCTGGGCTTTGAATCCAGCAATCCG
98	Glu_CTC_chr1:145399233-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGAT TCGGCGCTCTCACC GCCGCGGCCG

99	Glu_CTC_chr1:249168447-249168518 (+)	TCCCTGGTGGTCTAGTGGTTAGGAT TCGGCGCTCTCACCGCCGCGGCCCG
100	Glu_TTC_chr2:131094701-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGAT TCCTGGTTTTTCACCCAGGTGGCCCG
101	Glu_TTC_chr13:45492062-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGAT TCCTGGTTTTTCACCCAGGCGGCCCG
102	Glu_TTC_chr1:17199078-17199149 (+)	TCCCTGGTGGTCTAGTGGCTAGGAT TCGGCGCTTTTCACCGCCGCGGCCCG
103	Glu_TTC_chr1:16861774-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGAT TCGGCGCTTTTCACCGCCGCGGCCCG
104	Gly_CCC_chr1:16872434-16872504 (-)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTCCACGCGGGAGACCCG
105	Gly_CCC_chr2:70476123-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATG CAAGATTCCCATTCTTGCGACCCGG
106	Gly_CCC_chr17:19764175-19764245 (+)	GCATTGGTGGTTC AATGGTAGAATT CTCGCCTCCACGCGAGGAGACCCA
107	Gly_GCC_chr1:161413094-161413164 (+)	GCATGGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
108	Gly_GCC_chr1:161493637-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
109	Gly_GCC_chr16:70812114-70812184 (-)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
110	Gly_GCC_chr1:161450356-161450426 (+)	GCATAGGTGGTTCAGTGGTAGAATT CTTGCCCTGCCACGCGAGGAGGCCA
111	Gly_GCC_chr16:70822597-70822667 (+)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTGCCATGCGGGCGGCCCG
112	Gly_TCC_chr19:4724082-4724153 (+)	GCGTTGGTGGTATAGTGGTAGCAT AGCTGCCTTCCAAGCAGTTGACCCG
113	Gly_TCC_chr1:145397864-145397935 (-)	GCGTTGGTGGTATAGTGGTAGCAT AGCTGCCTTCCAAGCAGTTGACCCG
114	Gly_TCC_chr17:8124866-8124937 (+)	GCGTTGGTGGTATAGTGGTAAGCAT AGCTGCCTTCCAAGCAGTTGACCCG
115	Gly_TCC_chr1:161409961-161410032 (-)	GCGTTGGTGGTATAGTGGTAGCAT AGTTGCCTTCCAAGCAGTTGACCCG
116	His_GTG_chr1:145396881-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTAC TCTGCGTTGTGGCCGCAGCAACCTC
117	His_GTG_chr1:149155828-149155899 (-)	GCCATGATCGTATAGTGGTTAGTAC TCTGCGCTGTGGCCGCAGCAACCTC
118	Ile_AAT_chr6:58149254-58149327 (+)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGCGCTAATAACGCCAAGGTC
119	Ile_AAT_chr6:27655967-27656040 (+)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC
120	Ile_AAT_chr6:27242990-27243063 (-)	GGCTGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC

121	Ile_AAT_chr17:8130309-8130382 (-)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC
122	Ile_AAT_chr6:26554350-26554423 (+)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC
123	Ile_AAT_chr6:26745255-26745328 (-)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCTAAGGTC
124	Ile_AAT_chr6:26721221-26721294 (-)	GGCCGGTTAGCTCAGTTGGTCAGA GCGTGGTGCTAATAACGCCAAGGT
125	Ile_AAT_chr6:27636362-27636435 (+)	GGCCGGTTAGCTCAGTCGGCTAGA GCGTGGTGCTAATAACGCCAAGGT
126	Ile_AAT_chr6:27241739-27241812 (+)	GGCTGGTTAGTTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC
127	Ile_GAT_chrX:3756418-3756491 (-)	GGCCGGTTAGCTCAGTTGGTAAGA GCGTGGTGCTGATAACACCAAGGT
128	Ile_TAT_chr19:39902808-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATATGACAGTGCG
129	Ile_TAT_chr2:43037676-43037768 (+)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATACAGCAGTACAT
130	Ile_TAT_chr6:26988125-26988218 (+)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATATGGCAGTATGT
131	Ile_TAT_chr6:27599200-27599293 (+)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATACAACAGTATAT
132	Ile_TAT_chr6:28505367-28505460 (+)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATAAGACAGTGCA
133	Leu_AAG_chr5:180524474-180524555 (-)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTAAGGCTCCAGTCTCT
134	Leu_AAG_chr5:180614701-180614782 (+)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTAAGGCTCCAGTCTCT
135	Leu_AAG_chr6:28956779-28956860 (+)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTAAGGCTCCAGTCTCT
136	Leu_AAG_chr6:28446400-28446481 (-)	GGTAGCGTGGCCGAGTGGTCTAAG ACGCTGGATTAAGGCTCCAGTCTCT
137	Leu_CAA_chr6:28864000-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGCTAAGCTTCCT
138	Leu_CAA_chr6:28908830-28908934 (+)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGCTTGGCTTCCT
139	Leu_CAA_chr6:27573417-27573524 (-)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGCTTACTGCTTC
140	Leu_CAA_chr6:27570348-27570454 (-)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGTTGCTACTTCC
141	Leu_CAA_chr1:249168054-249168159 (+)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGGTAAGCACCT
142	Leu_CAA_chr11:9296790-9296863 (+)	GCCTCCTTAGTGCAGTAGGTAGCGC ATCAGTCTCAAAATCTGAATGGTCC

143	Leu_CAA_chr1:161581736-161581819 (-)	GTCAGGATGGCCGAGCAGTCTTAA GGCGCTGCGTTCAAATCGCACCCCTC
144	Leu_CAG_chr1:161411323-161411405 (+)	GTCAGGATGGCCGAGCGGTCTAAG GCGCTGCGTTCAGGTCGCAGTCTCC
145	Leu_CAG_chr16:57333863-57333945 (+)	GTCAGGATGGCCGAGCGGTCTAAG GCGCTGCGTTCAGGTCGCAGTCTCC
146	Leu_TAA_chr6:144537684-144537766 (+)	ACCAGGATGGCCGAGTGGTTAAGG CGTTGGACTTAAGATCCAATGGAC
147	Leu_TAA_chr6:27688898-27688980 (-)	ACCGGGATGGCCGAGTGGTTAAGG CGTTGGACTTAAGATCCAATGGGCT
148	Leu_TAA_chr11:59319228-59319310 (+)	ACCAGAATGGCCGAGTGGTTAAGG CGTTGGACTTAAGATCCAATGGATT
149	Leu_TAA_chr6:27198334-27198416 (-)	ACCGGGATGGCTGAGTGGTTAAGG CGTTGGACTTAAGATCCAATGGAC
150	Leu_TAG_chr17:8023632-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTTAGGCTCCAGTCTCT
151	Leu_TAG_chr14:21093529-21093610 (+)	GGTAGTGTGGCCGAGCGGTCTAAG GCGCTGGATTTAGGCTCCAGTCTCT
152	Leu_TAG_chr16:22207032-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAG GCGCTGGATTTAGGCTCCAGTCATT
153	Lys_CTT_chr14:58706613-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGGGACTCTTAATCCCAGGGTCCG
154	Lys_CTT_chr19:36066750-36066822 (+)	GCCCAGCTAGCTCAGTCGGTAGAG CATAAGACTCTTAATCTCAGGGTTG
155	Lys_CTT_chr19:52425393-52425466 (-)	GCAGCTAGCTCAGTCGGTAGAGCA TGAGACTCTTAATCTCAGGGTCATG
156	Lys_CTT_chr1:145395522-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGAGACTCTTAATCTCAGGGTCCG
157	Lys_CTT_chr16:3207406-3207478 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGAGACCCTTAATCTCAGGGTCCG
158	Lys_CTT_chr16:3241501-3241573 (+)	GCCCGGCTAGCTCAGTCGGTAGAG CATGGGACTCTTAATCTCAGGGTCCG
159	Lys_CTT_chr16:3230555-3230627 (-)	GCCCGGCTAGCTCAGTCGATAGAG CATGAGACTCTTAATCTCAGGGTCCG
160	Lys_CTT_chr1:55423542-55423614 (-)	GCCCAGCTAGCTCAGTCGGTAGAG CATGAGACTCTTAATCTCAGGGTCA
161	Lys_CTT_chr16:3214939-3215011 (+)	GCCTGGCTAGCTCAGTCGGCAAAG CATGAGACTCTTAATCTCAGGGTCCG
162	Lys_CTT_chr5:26198539-26198611 (-)	GCCCGACTACCTCAGTCGGTGGAG CATGGGACTCTTCATCCCAGGGTTG
163	Lys_TTT_chr16:73512216-73512288 (-)	GCCTGGATAGCTCAGTTGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
164	Lys_TTT_chr12:27843306-27843378 (+)	ACCCAGATAGCTCAGTCAGTAGAG CATCAGACTTTTAATCTGAGGGTCC

165	Lys_TTT_chr11:122430655-122430727 (+)	GCCTGGATAGCTCAGTTGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
166	Lys_TTT_chr1:204475655-204475727 (+)	GCCCGGATAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
167	Lys_TTT_chr6:27559593-27559665 (-)	GCCTGGATAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
168	Lys_TTT_chr11:59323902-59323974 (+)	GCCCGGATAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
169	Lys_TTT_chr6:27302769-27302841 (-)	GCCTGGGTAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
170	Lys_TTT_chr6:28715521-28715593 (+)	GCCTGGATAGCTCAGTTGGTAGAA CATCAGACTTTTAATCTGACGGTGC
171	Met_CAT_chr8:124169470-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCG CGTCAGTCTCATAATCTGAAGGTCCG
172	Met_CAT_chr16:71460396-71460468 (+)	GCCCTCTTAGCGCAGTGGGCAGCG CGTCAGTCTCATAATCTGAAGGTCC
173	Met_CAT_chr6:28912352-28912424 (+)	GCCTCCTTAGCGCAGTAGGCAGCG CGTCAGTCTCATAATCTGAAGGTCC
174	Met_CAT_chr6:26735574-26735646 (-)	GCCCTCTTAGCGCAGCGGGCAGCG CGTCAGTCTCATAATCTGAAGGTCC
175	Met_CAT_chr6:26701712-26701784 (+)	GCCCTCTTAGCGCAGCTGGCAGCGC GTCAGTCTCATAATCTGAAGGTCTCT
176	Met_CAT_chr16:87417628-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCG CGTCAGTCTCATAATCTGAAGGTCCG
177	Met_CAT_chr6:58168492-58168564 (-)	GCCCTCTTAGTGCAGCTGGCAGCGC GTCAGTTTCATAATCTGAAAGTCTCT
178	Phe_GAA_chr6:28758499-28758571 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC
179	Phe_GAA_chr11:59333853-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC
180	Phe_GAA_chr6:28775610-28775682 (-)	GCCGAGATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC
181	Phe_GAA_chr6:28791093-28791166 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACCGAAGATCTTAAAGGT
182	Phe_GAA_chr6:28731374-28731447 (-)	GCTGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTTAAAGTTC
183	Pro_AGG_chr16:3241989-3242060 (+)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTAGGATGCGAGAGGTCCC
184	Pro_AGG_chr1:167684725-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTAGGGTGGAGAGAGGTCCC
185	Pro_CGG_chr1:167683962-167684033 (+)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTCGGGTGCGAGAGGTCCCG
186	Pro_CGG_chr6:27059521-27059592 (+)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTCGGGTGTGAGAGGTCCCG

187	Pro_TGG_chr14:21101165-21101236 (+)	GGCTCGTTGGTCTAGTGGTATGATT CTCGCTTTGGGTGCGAGAGGTCCCCG
188	Pro_TGG_chr11:75946869-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGGTTTGGGTCCGAGAGGTCCCCG
189	Pro_TGG_chr5:180615854-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTTGGGTGCGAGAGGTCCCCG
190	SeC_TCA_chr19:45981859-45981945 (-)	GCCCCGATGATCCTCAGTGGTCTGG GGTGCAGGCTTCAAACCTGTAGCTG
191	SeC_TCA_chr22:44546537-44546620 (+)	GCTCGGATGATCCTCAGTGGTCTGG GGTGCAGGCTTCAAACCTGTAGCTG
192	Ser_AGA_chr6:27509554-27509635 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTAGAAATCCATTGGGG
193	Ser_AGA_chr6:26327817-26327898 (+)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTAGAAATCCATTGGGG
194	Ser_AGA_chr6:27499987-27500068 (+)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTAGAAATCCATTGGGG
195	Ser_AGA_chr6:27521192-27521273 (-)	GTAGTCGTGGCCGAGTGGTTAAGG TGATGGACTAGAAACCCATTGGGG
196	Ser_CGA_chr17:8042199-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGG CGTTGGACTCGAAATCCAATGGGG
197	Ser_CGA_chr6:27177628-27177709 (+)	GCTGTGATGGCCGAGTGGTTAAGG CGTTGGACTCGAAATCCAATGGGG
198	Ser_CGA_chr6:27640229-27640310 (-)	GCTGTGATGGCCGAGTGGTTAAGG TGTTGGACTCGAAATCCAATGGGG
199	Ser_CGA_chr12:56584148-56584229 (+)	GTCACGGTGGCCGAGTGGTTAAGG CGTTGGACTCGAAATCCAATGGGG
200	Ser_GCT_chr6:27065085-27065166 (+)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT
201	Ser_GCT_chr6:27265775-27265856 (+)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT
202	Ser_GCT_chr11:66115591-66115672 (+)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT
203	Ser_GCT_chr6:28565117-28565198 (-)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT
204	Ser_GCT_chr6:28180815-28180896 (+)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT
205	Ser_GCT_chr6:26305718-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAA GGCGATGGACTGCTAATCCATTGTG
206	Ser_TGA_chr10:69524261-69524342 (+)	GCAGCGATGGCCGAGTGGTTAAGG CGTTGGACTTGAAATCCAATGGGGT
207	Ser_TGA_chr6:27513468-27513549 (+)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTTGAAATCCATTGGGGT
208	Ser_TGA_chr6:26312824-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTTGAAATCCATTGGGGT

209	Ser_TGA_chr6:27473607-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTTGAAATCCATTGGGGT
210	Thr_AGT_chr17:8090478-8090551 (+)	GGCGCCGTGGCTTAGTTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
211	Thr_AGT_chr6:26533145-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
212	Thr_AGT_chr6:28693795-28693868 (+)	GGCTCCGTAGCTTAGTTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
213	Thr_AGT_chr6:27694473-27694546 (+)	GGCTTCGTGGCTTAGCTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
214	Thr_AGT_chr17:8042770-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAA GCGCCTGTCTAGTAAACAGGAGAT
215	Thr_AGT_chr6:27130050-27130123 (+)	GGCCCTGTGGCTTAGCTGGTCAAAG CGCCTGTCTAGTAAACAGGAGATC
216	Thr_CGT_chr6:28456770-28456843 (-)	GGCTCTATGGCTTAGTTGGTTAAAG CGCCTGTCTCGTAAACAGGAGATCC
217	Thr_CGT_chr16:14379750-14379821 (+)	GGCGCGGTGGCCAAGTGGTAAGGC GTCGGTCTCGTAAACCGAAGATCA
218	Thr_CGT_chr6:28615984-28616057 (-)	GGCTCTGTGGCTTAGTTGGCTAAAG CGCCTGTCTCGTAAACAGGAGATCC
219	Thr_CGT_chr17:29877093-29877164 (+)	GGCGCGGTGGCCAAGTGGTAAGGC GTCGGTCTCGTAAACCGAAGATCG
220	Thr_CGT_chr6:27586135-27586208 (+)	GGCCCTGTAGCTCAGCGGTTGGAG CGCTGGTCTCGTAAACCTAGGGGTC
221	Thr_TGT_chr6:28442329-28442402 (-)	GGCTCTATGGCTTAGTTGGTTAAAG CGCCTGTCTTGTAACAGGAGATCC
222	Thr_TGT_chr1:222638347-222638419 (+)	GGCTCCATAGCTCAGTGGTTAGAGC ACTGGTCTTGTAACAGGGGTCGC
223	Thr_TGT_chr14:21081949-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAG CGCTGGTCTTGTAACAGGGGTCG
224	Thr_TGT_chr14:21099319-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAG CACTGGTCTTGTAACAGGGGTCG
225	Thr_TGT_chr14:21149849-21149921 (+)	GGCCCTATAGCTCAGGGGTTAGAG CACTGGTCTTGTAACAGGGGTCG
226	Thr_TGT_chr5:180618687-180618758 (-)	GGCTCCATAGCTCAGGGGTTAGAG CACTGGTCTTGTAACAGGGTCGC
227	Trp_CCA_chr17:8124187-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGC GTCTGACTCCAGATCAGAAGGTTGC
228	Trp_CCA_chr17:19411494-19411565 (+)	GACCTCGTGGCGCAATGGTAGCGC GTCTGACTCCAGATCAGAAGGTTGC
229	Trp_CCA_chr6:26319330-26319401 (-)	GACCTCGTGGCGCAACGGTAGCGC GTCTGACTCCAGATCAGAAGGTTGC
230	Trp_CCA_chr12:98898030-98898101 (+)	GACCTCGTGGCGCAACGGTAGCGC GTCTGACTCCAGATCAGAAGGCTG

231	Trp_CCA_chr7:99067307-99067378 (+)	GACCTCGTGGCGCAACGGCAGCGC GTCTGACTCCAGATCAGAAGGTTGC
232	Tyr_ATA_chr2:219110549-219110641 (+)	CCTTCAATAGTTCAGCTGGTAGAGC AGAGGACTATAGCTACTTCCTCAGT
233	Tyr_GTA_chr6:26569086-26569176 (+)	CCTTCGATAGCTCAGTTGGTAGAGC GGAGGACTGTAGTTGGCTGTGTCT
234	Tyr_GTA_chr2:27273650-27273738 (+)	CCTTCGATAGCTCAGTTGGTAGAGC GGAGGACTGTAGTTGGATAGGGCGT
235	Tyr_GTA_chr6:26577332-26577420 (+)	CCTTCGATAGCTCAGTTGGTAGAGC GGAGGACTGTAGGCTCATTAAGCA
236	Tyr_GTA_chr14:21125623-21125716 (-)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGATTGTATAGACA
237	Tyr_GTA_chr8:67025602-67025694 (+)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGCTACTTCCTCAGC
238	Tyr_GTA_chr8:67026223-67026311 (+)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGGCGCGCGCCCGT
239	Tyr_GTA_chr14:21121258-21121351 (-)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGCCTGTAGAAACA
240	Tyr_GTA_chr14:21131351-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGATTGTACAGACA
241	Tyr_GTA_chr14:21151432-21151520 (+)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGTACTTAATGTGTG
242	Tyr_GTA_chr6:26595102-26595190 (+)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGGGGTTTGAATGT
243	Tyr_GTA_chr14:21128117-21128210 (-)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGACTGCGGAAACG
244	Tyr_GTA_chr6:26575798-26575887 (+)	CTTTCGATAGCTCAGTTGGTAGAGC GGAGGACTGTAGGTTTCATTAACT
245	Tyr_GTA_chr8:66609532-66609619 (-)	TCTTCAATAGCTCAGCTGGTAGAGC GGAGGACTGTAGGTGCACGCCCGT
246	Val_AAC_chr3:169490018-169490090 (+)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTAACACGCGAAAGGTCC
247	Val_AAC_chr5:180615416-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCAC GTTTCGCCTAACACGCGAAAGGTCC
248	Val_AAC_chr6:27618707-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTAACACGCGAAAGGTCC
249	Val_AAC_chr6:27648885-27648957 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTAACACGCGAAAGGTCC
250	Val_AAC_chr6:27203288-27203360 (+)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTGCCTAACACGCGAAAGGTCCC
251	Val_AAC_chr6:28703206-28703277 (-)	GGGGGTGTAGCTCAGTTGGTAGAGC GTATGCTTAACATTCATGAGGCTCT
252	Val_CAC_chr1:161369490-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGAAAGGTCCC

253	Val_CAC_chr6:27248049-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCAC GTTTCGCTCACACGCGAAAGGTCCC
254	Val_CAC_chr19:4724647-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCAC ATTTCGCTCACACGCGAAAGGTCCC
255	Val_CAC_chr1:149298555-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCTCACACGCGAAAGGTCCC
256	Val_CAC_chr1:149684088-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCTCACACGCGTAAAGGTCC
257	Val_CAC_chr6:27173867-27173939 (-)	GTTTCCGTAGTGGAGTGGTTATCAC GTTTCGCTCACACGCGAAAGGTCCC
258	Val_TAC_chr11:59318102-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCAC GTCTGCTTTACACGCAGAAGGTCTCT
259	Val_TAC_chr11:59318460-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCAC GTCTGCTTTACACGCAGAAGGTCTCT
260	Val_TAC_chr10:5895674-5895746 (-)	GGTTCCATAGTGTAGTGGTTATCAC ATCTGCTTTACACGCAGAAGGTCTCT
261	Val_TAC_chr6:27258405-27258477 (+)	GTTTCCGTGGTGTAGTGGTTATCAC ATTTCGCTTACACGCGAAAGGTCTCT
262	iMet_CAT_chr1:153643726-153643797 (+)	AGCAGAGTGGCGCAGCGGAAGCGT GCTGGGCCCATAACCCAGAGGTCTG
263	iMet_CAT_chr6:27745664-27745735 (+)	AGCAGAGTGGCGCAGCGGAAGCGT GCTGGGCCCATAACCCAGAGGTCTG
264	Glu_TTC_chr1:16861773-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGAT TCGGCGCTTTCACCGCCGCGGCCCCG
265	Gly_CCC_chr1:17004765-17004836 (-)	GCGTTGGTGGTTTAGTGGTAGAATT CTCGCCTCCCATGCGGGAGACCCG
266	Gly_CCC_chr1:17053779-17053850 (+)	GGCCTTGGTGGTGCAGTGGTAGAA TTCTCGCCTCCACGTGGGAGACCC
267	Glu_TTC_chr1:17199077-17199149 (+)	GTCCCTGGTGGTCTAGTGGCTAGGA TTCGGCGCTTTCACCGCCGCGGCCCC
268	Asn_GTT_chr1:17216171-17216245 (+)	TGTCTCTGTGGCGCAATCGGTTAGC GCGTTCGGCTGTAAACCGAAAGATT
269	Arg_TCT_chr1:94313128-94313213 (+)	TGGCTCCGTGGCGCAATGGATAGC GCATTGGACTTCTAGAGGCTGAAG
270	Lys_CTT_chr1:145395521-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGAGACTCTTAATCTCAGGGTCTG
271	His_GTG_chr1:145396880-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTAC TCTGCGTTGTGGCCGCAGCAACCTC
272	Gly_TCC_chr1:145397863-145397935 (-)	GCGTTGGTGGTATAGTGGTGAGCAT AGCTGCCTTCCAAGCAGTTGACCCG
273	Glu CTC_chr1:145399232-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGAT TCGGCGCTCTCACCGCCGCGGCCCCG
274	Gln_CTG_chr1:145963303-145963375 (+)	AGGTTCATGGTGTAAATGGTGAGC ACTCTGGACTCTGAATCCAGCGATC

275	Asn_GTT_chr1:148000804-148000878 (+)	TGCTCTGTGGCGTAGTCGGTTAGC GCGTTCGGCTGTTAACCGAAAAGTT
276	Asn_GTT_chr1:148248114-148248188 (+)	TGCTCTGTGGCGCAATCGGTTAGC GCGTTCGGCTGTTAACCGAAAAGTT
277	Asn_GTT_chr1:148598313-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CATTTCGGCTGTTAACCGAAAAGTTG
278	Asn_GTT_chr1:149230569-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCG CGTTCGGCTGTTAACCGAAAAGTTG
279	Val_CAC_chr1:149294665-149294736 (-)	GCACTGGTGGTTCAGTGGTAGAATT CTCGCCTCACACGCGGGACACCCG
280	Val_CAC_chr1:149298554-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGAAAGGTCCC
281	Gly_CCC_chr1:149680209-149680280 (-)	GCACTGGTGGTTCAGTGGTAGAATT CTCGCCTCCACGCGGGAGACCCG
282	Val_CAC_chr1:149684087-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGTAAAGGTCC
283	Met_CAT_chr1:153643725-153643797 (+)	TAGCAGAGTGGCGCAGCGGAAGCG TGCTGGGCCATAACCCAGAGGTC
284	Val_CAC_chr1:161369489-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGAAAGGTCCC
285	Asp_GTC_chr1:161410614-161410686 (-)	TCCTCGTTAGTATAGTGGTGAAGTAT CCCCGCCTGTCACGCGGGAGACCG
286	Gly_GCC_chr1:161413093-161413164 (+)	TGCATGGGTGGTTCAGTGGTAGAAT TCTCGCCTGCCACGCGGGAGGCC
287	Glu_CTC_chr1:161417017-161417089 (-)	TCCCTGGTGGTCTAGTGGTTAGGAT TCGGCGCTCTCACCGCCGCGGCCG
288	Asp_GTC_chr1:161492934-161493006 (+)	ATCCTTGTTACTATAGTGGTGAGTA TCTCTGCCTGTCATGCGTGAGAGAG
289	Gly_GCC_chr1:161493636-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
290	Leu_CAG_chr1:161500131-161500214 (-)	GTCAGGATGGCCGAGCGGTCTAAG GCGCTGCGTTCAGGTCGAGTCTCC
291	Gly_TCC_chr1:161500902-161500974 (+)	CGCGTTGGTGGTATAGTGGTGAGC ATAGCTGCCTTCCAAGCAGTTGACC
292	Asn_GTT_chr1:161510030-161510104 (+)	CGTCTCTGTGGCGCAATCGGTTAGC GCGTTCGGCTGTTAACCGAAAAGTT
293	Glu_TTC_chr1:161582507-161582579 (+)	CGCGTTGGTGGTGTAGTGGTGAGC ACAGCTGCCTTTCAGCAGTTAACG
294	Pro_CGG_chr1:167683961-167684033 (+)	CGGCTCGTTGGTCTAGGGGTATGAT TCTCGCTTCGGGTGCGAGAGGTCCC
295	Pro_AGG_chr1:167684724-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTAGGGTGCGAGAGGTCCC
296	Lys_TTT_chr1:204475654-204475727 (+)	CGCCCGGATAGCTCAGTCGGTAGA GCATCAGACTTTTAATCTGAGGGTC

297	Lys_TTT_chrl:204476157-204476230 (-)	GCCCGGATAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
298	Leu_CAA_chrl:249168053-249168159 (+)	TGTCAGGATGGCCGAGTGGTCTAA GGCGCCAGACTCAAGGTAAGCACC
299	Glu_CTC_chrl:249168446-249168518 (+)	TTCCCTGGTGGTCTAGTGGTTAGGA TTCGGCGCTCTCACCGCCGCGGCCC
300	Tyr_GTA_chr2:27273649-27273738 (+)	GCCTTCGATAGCTCAGTTGGTAGAG CGGAGGACTGTAGTGGATAGGGCG
301	Ala_AGC_chr2:27274081-27274154 (+)	CGGGGGATTAGCTCAAATGGTAGA GCGCTCGCTTAGCATGCGAGAGGT
302	Ile_TAT_chr2:43037675-43037768 (+)	AGCTCCAGTGGCGCAATCGGTTAG CGCGCGGTAATTATACAGCAGTAC
303	Gly_CCC_chr2:70476122-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATG CAAGATTCCCATTCTTGCGACCCGG
304	Glu_TTC_chr2:131094700-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGAT TCCTGGTTTTACCCAGGTGGCCCG
305	Ala_CGC_chr2:157257280-157257352 (+)	GGGGGATGTAGCTCAGTGGTAGAG CGCGCGCTTCGCATGTGTGAGGTCC
306	Gly_GCC_chr2:157257658-157257729 (-)	GCATTGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
307	Arg_ACG_chr3:45730490-45730563 (-)	GGGCCAGTGGCGCAATGGATAACG CGTCTGACTACGGATCAGAAGATTC
308	Val_AAC_chr3:169490017-169490090 (+)	GGTTTCCGTAGTGTAGTGGTTATCA CGTTCGCCTAACACGCGAAAGGTC
309	Val_AAC_chr5:180596609-180596682 (+)	AGTTTCCGTAGTGTAGTGGTTATCA CGTTCGCCTAACACGCGAAAGGTC
310	Leu_AAG_chr5:180614700-180614782 (+)	AGGTAGCGTGGCCGAGCGGTCTAA GGCGCTGGATTAAGGCTCCAGTCTC
311	Val_AAC_chr5:180615415-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCAC GTTTCGCCTAACACGCGAAAGGTCC
312	Pro_TGG_chr5:180615853-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTTGGGTGCGAGAGGTCCCCG
313	Thr_TGT_chr5:180618686-180618758 (-)	GGCTCCATAGCTCAGGGGTAGAG CACTGGTCTTGTAACACAGGGTCGC
314	Ala_TGC_chr5:180633867-180633939 (+)	TGGGGATGTAGCTCAGTGGTAGAG CGCATGCTTTGCATGTATGAGGCC
315	Lys_CTT_chr5:180634754-180634827 (+)	CGCCCGGCTAGCTCAGTCGGTAGA GCATGAGACTCTTAATCTCAGGGTC
316	Val_AAC_chr5:180645269-180645342 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTAACACGCGAAAGGTCC
317	Lys_CTT_chr5:180648978-180649051 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGAGACTCTTAATCTCAGGGTCG
318	Val_CAC_chr5:180649394-180649467 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGAAAGGTCCC

319	Met_CAT_chr6:26286753-26286825 (+)	CAGCAGAGTGGCGCAGCGGAAGCG TGCTGGGCCCATTAACCCAGAGGTC
320	Ser_GCT_chr6:26305717-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAA GGCGATGGACTGCTAATCCATTGTG
321	Gln_TTG_chr6:26311423-26311495 (-)	GGCCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCGATCCG
322	Gln_TTG_chr6:26311974-26312046 (-)	GGCCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCGATCCG
323	Ser_TGA_chr6:26312823-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTTGAAATCCATTGGGGT
324	Met_CAT_chr6:26313351-26313423 (-)	AGCAGAGTGGCGCAGCGGAAGCGT GCTGGGCCCATTAACCCAGAGGTCG
325	Arg_TCG_chr6:26323045-26323118 (+)	GGACCACGTGGCCTAATGGATAAG GCGTCTGACTTCGGATCAGAAGATT
326	Ser_AGA_chr6:26327816-26327898 (+)	TGTAGTCGTGGCCGAGTGGTTAAG GCGATGGACTAGAAATCCATTGGG
327	Met_CAT_chr6:26330528-26330600 (-)	AGCAGAGTGGCGCAGCGGAAGCGT GCTGGGCCCATTAACCCAGAGGTCG
328	Leu_CAG_chr6:26521435-26521518 (+)	CGTCAGGATGGCCGAGCGGTCTAA GGCGCTGCGTTCAGGTTCGAGTCTC
329	Thr_AGT_chr6:26533144-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
330	Arg_ACG_chr6:26537725-26537798 (+)	AGGGCCAGTGGCGCAATGGATAAC GCGTCTGACTACGGATCAGAAGAT
331	Val_CAC_chr6:26538281-26538354 (+)	GGTTTCCGTAGTGTAGTGGTTATCA CGTTCGCCTCACACGCGAAAGGTCC
332	Ala_CGC_chr6:26553730-26553802 (+)	AGGGGATGTAGCTCAGTGGTAGAG CGCATGCTTCGCATGTATGAGGTCC
333	Ile_AAT_chr6:26554349-26554423 (+)	TGGCCGGTTAGCTCAGTTGGTTAGA GCGTGGTGCTAATAACGCCAAGGT
334	Pro_AGG_chr6:26555497-26555569 (+)	CGGCTCGTTGGTCTAGGGGTATGAT TCTCGCTTAGGGTGCGAGAGGTCCC
335	Lys_CTT_chr6:26556773-26556846 (+)	AGCCCGGCTAGCTCAGTCGGTAGA GCATGAGACTCTTAATCTCAGGGTC
336	Tyr_GTA_chr6:26569085-26569176 (+)	TCCTTCGATAGCTCAGTTGGTAGAG CGGAGGACTGTAGTTGGCTGTGTCC
337	Ala_AGC_chr6:26572091-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAG CGCTCGCTTAGCATGCGAGAGGTA
338	Met_CAT_chr6:26766443-26766516 (+)	CGCCCTCTTAGCGCAGCGGGCAGC GCGTCAGTCTCATAATCTGAAGGTC
339	Ile_TAT_chr6:26988124-26988218 (+)	TGCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATATGGCAGTATGT
340	His_GTG_chr6:27125905-27125977 (+)	TGCCGTGATCGTATAGTGGTTAGTA CTCTGCGTTGTGGCCGAGCAACCT

341	Ile_AAT_chr6:27144993-27145067 (-)	GGCCGGTTAGCTCAGTTGGTTAGAG CGTGGTGCTAATAACGCCAAGGTC
342	Val_AAC_chr6:27203287-27203360 (+)	AGTTTCCGTAGTGTAGTGGTTATCA CGTTTGCCTAACACGCGAAAGGTCC
343	Val_CAC_chr6:27248048-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCAC GTTTCGCCTCACACGCGAAAGGTCCC
344	Asp_GTC_chr6:27447452-27447524 (+)	TTCCTCGTTAGTATAGTGGTGAGTA TCCCCGCCTGTCACGCGGGAGACC
345	Ser_TGA_chr6:27473606-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTTGAAATCCATTGGGGT
346	Gln_CTG_chr6:27487307-27487379 (+)	AGGTTCCATGGTGTAAATGGTTAGCA CTCTGGACTCTGAATCCAGCGATCC
347	Asp_GTC_chr6:27551235-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGT CCCCGTCTGTCACGCGGGAGACCG
348	Val_AAC_chr6:27618706-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCAC GTTTCGCCTAACACGCGAAAGGTCC
349	Ile_AAT_chr6:27655966-27656040 (+)	CGGCCGGTTAGCTCAGTTGGTTAGA GCGTGGTGCTAATAACGCCAAGGT
350	Gln_CTG_chr6:27759134-27759206 (-)	GGCCCCATGGTGTAAATGGTCAGCA CTCTGGACTCTGAATCCAGCGATCC
351	Gln_TTG_chr6:27763639-27763711 (-)	GGCCCCATGGTGTAAATGGTTAGCAC TCTGGACTTTGAATCCAGCGATCCG
352	Ala_AGC_chr6:28574932-28575004 (+)	TGGGGGTGTAGCTCAGTGGTAGAG CGCGTGCTTAGCATGTACGAGGTCC
353	Ala_AGC_chr6:28626013-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTAGCATGCATGAGGTCCC
354	Ala_CGC_chr6:28697091-28697163 (+)	AGGGGGTGTAGCTCAGTGGTAGAG CGCGTGCTTCGCATGTACGAGGCCC
355	Ala_AGC_chr6:28806220-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGCCC
356	Ala_AGC_chr6:28831461-28831533 (-)	GGGGGTGTAGCTCAGTGGTAGAGC GCGTGCTTAGCATGCACGAGGCCC
357	Leu_CAA_chr6:28863999-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAG GCGCCAGACTCAAGCTAAGCTTCCT
358	Leu_CAA_chr6:28908829-28908934 (+)	TGTCAGGATGGCCGAGTGGTCTAA GGCGCCAGACTCAAGCTTGGCTTCC
359	Gln_CTG_chr6:28909377-28909449 (-)	GGTTCCATGGTGTAAATGGTTAGCAC TCTGGACTCTGAATCCAGCGATCCG
360	Leu_AAG_chr6:28911398-28911480 (-)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTAAAGGCTCCAGTCTCT
361	Met_CAT_chr6:28912351-28912424 (+)	TGCCTCCTTAGCGCAGTAGGCAGCG CGTCAGTCTCATAATCTGAAGGTCC
362	Lys_TTT_chr6:28918805-28918878 (+)	AGCCCGGATAGCTCAGTCGGTAGA GCATCAGACTTTTAATCTGAGGGTC

363	Met_CAT_chr6:28921041-28921114 (-)	GCCTCCTTAGCGCAGTAGGCAGCG CGTCAGTCTCATAATCTGAAGGTCC
364	Glu_CTC_chr6:28949975-28950047 (+)	TTCCCTGGTGGTCTAGTGGTTAGGA TTCGGCGCTCTCACCGCCGCGGCC
365	Leu_TAA_chr6:144537683-144537766 (+)	CACCAGGATGGCCGAGTGGTTAAG GCGTTGGACTTAAGATCCAATGGA
366	Pro_AGG_chr7:128423503-128423575 (+)	TGGCTCGTTGGTCTAGGGGTATGAT TCTCGCTTAGGGTGCGAGAGGTCCC
367	Arg_CCT_chr7:139025445-139025518 (+)	AGCCCCAGTGGCCTAATGGATAAG GCATTGGCCTCCTAAGCCAGGGATT
368	Cys_GCA_chr7:149388271-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
369	Tyr_GTA_chr8:67025601-67025694 (+)	CCCTTCGATAGCTCAGCTGGTAGAG CGGAGGACTGTAGCTACTTCCTCAG
370	Tyr_GTA_chr8:67026222-67026311 (+)	CCCTTCGATAGCTCAGCTGGTAGAG CGGAGGACTGTAGGCGCGCGCCCCG
371	Ala_AGC_chr8:67026423-67026496 (+)	TGGGGGATTAGCTCAAATGGTAGA GCGCTCGCTTAGCATGCGAGAGGT
372	Ser_AGA_chr8:96281884-96281966 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTAGAAATCCATTGGGG
373	Met_CAT_chr8:124169469-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCG CGTCAGTCTCATAATCTGAAGGTCCG
374	Arg_TCT_chr9:131102354-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCG CATTGGACTTCTAGCTGAGCCTAGT
375	Asn_GTT_chr10:22518437-22518511 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTAAACCGAAAGGTTG
376	Ser_TGA_chr10:69524260-69524342 (+)	GGCAGCGATGGCCGAGTGGTTAAG GCGTTGGACTTGAAATCCAATGGG
377	Val_TAC_chr11:59318101-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCAC GTCTGCTTTACACGCAGAAGGTCCT
378	Val_TAC_chr11:59318459-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCAC GTCTGCTTTACACGCAGAAGGTCCT
379	Arg_TCT_chr11:59318766-59318852 (+)	TGGCTCTGTGGCGCAATGGATAGC GCATTGGACTTCTAGATAGTTAGAG
380	Leu_TAA_chr11:59319227-59319310 (+)	TACCAGAATGGCCGAGTGGTTAAG GCGTTGGACTTAAGATCCAATGGAT
381	Lys_TTT_chr11:59323901-59323974 (+)	GGCCCGGATAGCTCAGTCGGTAGA GCATCAGACTTTTAATCTGAGGGTC
382	Phe_GAA_chr11:59324969-59325042 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC
383	Lys_TTT_chr11:59327807-59327880 (-)	GCCCGGATAGCTCAGTCGGTAGAG CATCAGACTTTTAATCTGAGGGTCC
384	Phe_GAA_chr11:59333852-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC

385	Ser_GCT_chr11:66115590-66115672 (+)	GGACGAGGTGGCCGAGTGGTTAAG GCGATGGACTGCTAATCCATTGTGC
386	Pro_TGG_chr11:75946868-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGGTTTGGGTCCGAGAGGTCCCCG
387	Ser_CGA_chr12:56584147-56584229 (+)	AGTCACGGTGGCCGAGTGGTTAAG GCGTTGGACTCGAAATCCAATGGG
388	Asp_GTC_chr12:98897280-98897352 (+)	CTCCTCGTTAGTATAGTGGTTAGTA TCCCCGCCTGTCACGCGGGAGACC
389	Trp_CCA_chr12:98898029-98898101 (+)	GGACCTCGTGGCGCAACGGTAGCG CGTCTGACTCCAGATCAGAAGGCT
390	Ala_TGC_chr12:125406300-125406372 (-)	GGGGATGTAGCTCAGTGGTAGAGC GCATGCTTTGCATGTATGAGGCCCC
391	Phe_GAA_chr12:125412388-125412461 (-)	GCCGAAATAGCTCAGTTGGGAGAG CGTTAGACTGAAGATCTAAAGGTC
392	Ala_TGC_chr12:125424511-125424583 (+)	AGGGGATGTAGCTCAGTGGTAGAG CGCATGCTTTGCACGTATGAGGCCC
393	Asn_GTT_chr13:31248100-31248174 (-)	GTCTCTGTGGCGCAATCGGTTAGCG CGTTCGGCTGTAAACCGAAAGGTTG
394	Glu_TTC_chr13:45492061-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGAT TCCTGGTTTTACCCAGGCGGCCCG
395	Thr_TGT_chr14:21081948-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAG CGCTGGTCTTGTAACACAGGGGTCG
396	Leu_TAG_chr14:21093528-21093610 (+)	TGGTAGTGTGGCCGAGCGGTCTAA GGCGCTGGATTTAGGCTCCAGTCTC
397	Thr_TGT_chr14:21099318-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAG CACTGGTCTTGTAACACAGGGGTCG
398	Pro_TGG_chr14:21101164-21101236 (+)	TGGCTCGTTGGTCTAGTGGTATGAT TCTCGCTTTGGGTGCGAGAGGTCCC
399	Tyr_GTA_chr14:21131350-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGC GGAGGACTGTAGATTGTACAGACA
400	Thr_TGT_chr14:21149848-21149921 (+)	AGGCCCTATAGCTCAGGGGTTAGA GCACTGGTCTTGTAACACAGGGGTC
401	Tyr_GTA_chr14:21151431-21151520 (+)	TCCTTCGATAGCTCAGCTGGTAGAG CGGAGGACTGTAGTACTTAATGTGT
402	Pro_TGG_chr14:21152174-21152246 (+)	TGGCTCGTTGGTCTAGGGGTATGAT TCTCGCTTTGGGTGCGAGAGGTCCC
403	Lys_CTT_chr14:58706612-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAG CATGGGACTCTTAATCCCAGGGTCCG
404	Ile_AAT_chr14:102783428-102783502 (+)	CGGCCGGTTAGCTCAGTTGGTTAGA GCGTGGTGCTAATAACGCCAAGGT
405	Glu_TTC_chr15:26327380-26327452 (-)	TCCCACATGGTCTAGCGGTTAGGAT TCCTGGTTTTACCCAGGCGGCCCG
406	Ser_GCT_chr15:40886022-40886104 (-)	GACGAGGTGGCCGAGTGGTTAAGG CGATGGACTGCTAATCCATTGTGCT

407	His_GTG_chr15:45490803-45490875 (-)	GCCGTGATCGTATAGTGGTTAGTAC TCTGCGTTGTGGCCGCAGCAACCTC
408	His_GTG_chr15:45493348-45493420 (+)	CGCCGTGATCGTATAGTGGTTAGTA CTCTGCGTTGTGGCCGCAGCAACCT
409	Gln_CTG_chr15:66161399-66161471 (-)	GGTTCCATGGTGTAAATGGTTAGCAC TCTGGACTCTGAATCCAGCGATCCG
410	Lys_CTT_chr15:79152903-79152976 (+)	TGCCCCGGCTAGCTCAGTCGGTAGA GCATGGGACTCTTAATCCCAGGGTC
411	Arg_TCG_chr15:89878303-89878376 (+)	GGGCCGCGTGGCCTAATGGATAAG GCGTCTGACTTCGGATCAGAAGATT
412	Gly_CCC_chr16:686735-686806 (-)	GCGCCGCTGGTGTAGTGGTATCATG CAAGATTCCCATTCTTGCGACCCGG
413	Arg_CCG_chr16:3200674-3200747 (+)	GGGCCGCGTGGCCTAATGGATAAG GCGTCTGATTCCGGATCAGAAGATT
414	Arg_CCT_chr16:3202900-3202973 (+)	CGCCCCGGTGGCCTAATGGATAAG GCATTGGCCTCCTAAGCCAGGGATT
415	Lys_CTT_chr16:3207405-3207478 (-)	GCCCCGGCTAGCTCAGTCGGTAGAG CATGAGACCCTTAATCTCAGGGTCTG
416	Thr_CGT_chr16:14379749-14379821 (+)	AGGCGCGGTGGCCAAGTGGTAAGG CGTCGGTCTCGTAAACCGAAGATC
417	Leu_TAG_chr16:22207031-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAG GCGCTGGATTAGGCTCCAGTCATT
418	Leu_AAG_chr16:22308460-22308542 (+)	GGGTAGCGTGGCCGAGCGGTCTAA GGCGCTGGATTAAGGCTCCAGTCTC
419	Leu_CAG_chr16:57333862-57333945 (+)	AGTCAGGATGGCCGAGCGGTCTAA GGCGCTGCGTTCAGGTCGCAGTCTC
420	Leu_CAG_chr16:57334391-57334474 (-)	GTCAGGATGGCCGAGCGGTCTAAG GCGCTGCGTTCAGGTCGCAGTCTCC
421	Met_CAT_chr16:87417627-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCG CGTCAGTCTCATAATCTGAAGGTCTG
422	Leu_TAG_chr17:8023631-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAG GCGCTGGATTAGGCTCCAGTCTCT
423	Arg_TCT_chr17:8024242-8024330 (+)	TGGCTCTGTGGCGCAATGGATAGC GCATTGGACTTCTAGTGACGAATAG
424	Gly_GCC_chr17:8029063-8029134 (+)	CGCATTGGTGGTTCAGTGGTAGAAT TCTCGCCTGCCACGCGGGAGGCC
425	Ser_CGA_chr17:8042198-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGG CGTTGGACTCGAAATCCAATGGGG
426	Thr_AGT_chr17:8042769-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAA GCGCCTGTCTAGTAAACAGGAGAT
427	Trp_CCA_chr17:8089675-8089747 (+)	CGACCTCGTGGCGCAACGGTAGCG CGTCTGACTCCAGATCAGAAGGTTG
428	Ser_GCT_chr17:8090183-8090265 (+)	AGACGAGGTGGCCGAGTGGTTAAG GCGATGGACTGCTAATCCATTGTGC

429	Thr_AGT_chr17:8090477-8090551 (+)	CGGCGCCGTGGCTTAGTTGGTTAAA GCGCCTGTCTAGTAAACAGGAGAT
430	Trp_CCA_chr17:8124186-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGC GTCTGACTCCAGATCAGAAGGTTGC
431	Gly_TCC_chr17:8124865-8124937 (+)	AGCGTTGGTGGTATAGTGGTAAGC ATAGCTGCCTTCCAAGCAGTTGACC
432	Asp_GTC_chr17:8125555-8125627 (-)	TCCTCGTTAGTATAGTGGTGAGTAT CCCCGCCTGTCACGCGGGAGACCG
433	Pro_CGG_chr17:8126150-8126222 (-)	GGCTCGTTGGTCTAGGGGTATGATT CTCGCTTCGGGTGCGAGAGGTCCCC
434	Thr_AGT_chr17:8129552-8129626 (-)	GGCGCCGTGGCTTAGTTGGTTAAAG CGCCTGTCTAGTAAACAGGAGATC
435	Ser_AGA_chr17:8129927-8130009 (-)	GTAGTCGTGGCCGAGTGGTTAAGG CGATGGACTAGAAATCCATTGGGG
436	Trp_CCA_chr17:19411493-19411565 (+)	TGACCTCGTGGCGCAATGGTAGCG CGTCTGACTCCAGATCAGAAGGTTG
437	Thr_CGT_chr17:29877092-29877164 (+)	AGGCGCGGTGGCCAAGTGGTAAGG CGTCGGTCTCGTAAACCGAAGATC
438	Cys_GCA_chr17:37023897-37023969 (+)	AGGGGGTATAGCTCAGTGGTAGAG CATTTGACTGCAGATCAAGAGGTCC
439	Cys_GCA_chr17:37025544-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
440	Cys_GCA_chr17:37309986-37310058 (-)	GGGGGTATAGCTCAGTGGTAGAGC ATTTGACTGCAGATCAAGAGGTCCC
441	Gln_TTG_chr17:47269889-47269961 (+)	AGGTCCCATGGTGTAATGGTTAGCA CTCTGGACTTTGAATCCAGCGATCC
442	Arg_CCG_chr17:66016012-66016085 (-)	GACCCAGTGGCCTAATGGATAAGG CATCAGCCTCCGAGCTGGGGATT
443	Arg_CCT_chr17:73030000-73030073 (+)	AGCCCCAGTGGCCTAATGGATAAG GCACTGGCCTCCTAAGCCAGGGATT
444	Arg_CCT_chr17:73030525-73030598 (-)	GCCCCAGTGGCCTAATGGATAAGG CACTGGCCTCCTAAGCCAGGGATTG
445	Arg_TCG_chr17:73031207-73031280 (+)	AGACCGCGTGGCCTAATGGATAAG GCGTCTGACTTCGGATCAGAAGATT
446	Asn_GTT_chr19:1383561-1383635 (+)	CGTCTCTGTGGCGCAATCGGTTAGC GCGTTCGGCTGTTAACCGAAAGGTT
447	Gly_TCC_chr19:4724081-4724153 (+)	GGCGTTGGTGGTATAGTGGTTAGCA TAGCTGCCTTCCAAGCAGTTGACCC
448	Val_CAC_chr19:4724646-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCAC ATTTCGCTCACACGCGAAAGGTCCC
449	Thr_AGT_chr19:33667962-33668036 (+)	TGGCGCCGTGGCTTAGTTGGTTAAA GCGCCTGTCTAGTAAACAGGAGAT
450	Ile_TAT_chr19:39902807-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGC GCGCGGTACTTATATGACAGTGCG

451	Gly_GCC_chr21:18827106-18827177 (-)	GCATGGGTGGTTCAGTGGTAGAATT CTCGCCTGCCACGCGGGAGGCCCG
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Asialoglycoprotein Receptor Binding Moieties

The present disclosure features a TREM comprising an asialoglycoprotein receptor (ASGPR) binding moiety. The ASGPR is a C-type lectin primarily expressed on the sinusoidal surface of hepatocytes, and comprises a major (48 kDa, ASGPR-1) and a minor (40 kDa, ASGPR-2) subunit. The ASGPR is involved in the binding, internalization, and subsequent clearance of glycoproteins containing an N-terminal galactose (Gal) or N-terminal N-acetylgalactosamine (GalNAc) residues from circulation, such as antibodies. ASGPRs have also been shown to be involved in the clearance of low density lipoprotein, fibronectin, and certain immune cells, and may be utilized by certain viruses for hepatocyte entry (see, e.g., Yang J., et al (2006) *J Viral Hepat* 13:158-165 and Guy, CS et al (2011) *Nat Rev Immunol* 8:874-887).

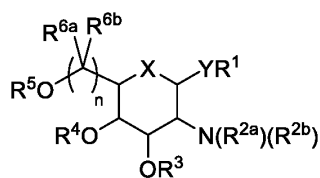
The ASGPR binding moiety as described herein may refer to structure comprising: (i) a ASGPR carbohydrate and (ii) an ASGPR linker (e.g., a linker connecting the carbohydrate to the TREM). The term “carbohydrate” as used herein refers to compound comprising one or more monosaccharide moieties comprising at least 3 carbon atoms (e.g., arranged in a linear, branched, or cyclic structure) and an oxygen, nitrogen, or sulfur atom, or a fragment or variant of a monosaccharide moiety comprising at least 3 carbon atoms (e.g., arranged in a linear, branched, or cyclic structure) and an oxygen, nitrogen, or sulfur atom. Each monosaccharide moiety or fragment or variant thereof may be a tetrose, pentose, hexose, or heptose. Each monosaccharide moiety or fragment or variant thereof may exist as an aldose, ketose, sugar alcohol, and, where appropriate, in the L or D form. Exemplary monosaccharide moieties may be amino sugars, N-acetylamino sugars, imino sugars, deoxysugars, or sugar acids. Carbohydrates may comprise individual monosaccharide moieties, or may further comprise a disaccharide, oligosaccharide (e.g., a trisaccharide, tetrasaccharide, pentasaccharide, hexasaccharide, heptasaccharide, octasaccharide), a polysaccharide, or combinations thereof. Exemplary carbohydrates include ribose, arabinose, lyxose, xylose, deoxyribose, ribulose, xylulose, glucose, galactose, mannose, gulose, idose, talose, allose, altrose, psicose, fructose, sorbose, tagatose, rhamnose, pneumose, quinovose, fucose, mannuheptulose, sedoheptulose, galactosamine, mannosamine, glucosamine, N-acetylglucosamine, N-acetylgalactosamine, N-acetylmannosamine, glucuronic acid, galacturonic acid, mannuronic acid, guluronic acid, iduronic acid, tagaturonic acid, frucuronic

acid, galactosaminuronic acid, mannosaminuronic acid, glucosaminuronic acid, N-acetylglucosaminuronic acid, N-acetylgalactosaminuronic acid, N-acetylmannosaminuronic acid, maltose, lactose, sucrose, trehalose, gentiobiose, cellobiose, chitobiose, kojibiose, nigerose, sophorose, trehalulose, isomaltose, xylobiose, starch, cellulose, chitin, and dextran.

The carbohydrate may comprise one or more monosaccharide moieties linked by a glycosidic bond. In some embodiments, the glycosidic bond comprises a 1->2 glycosidic bond, a 1->3 glycosidic bond, a 1->4 glycosidic bond, or a 1->6 glycosidic bond. In some embodiments, each glycosidic bonds may be present in the alpha or beta configuration. In an embodiment, the one or more monosaccharide moieties are linked directly by a glycosidic bond or are separated by a linker.

In some embodiments, the ASGPR binding moiety comprises a galactose (Gal), galactosamine (GalNH₂), or an N-acetylgalactosamine (GalNAc) moiety, for example, a Gal, GalNH₂, or GalNAc, or an analog thereof. In an embodiment, the ASGPR binding moiety comprises a GalNAc moiety (e.g., GalNAc). In an embodiment, the ASGPR binding moiety comprises a plurality of GalNAc moieties (e.g., GalNAcs), e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more GalNAc moieties (e.g., GalNAcs). In an embodiment, the ASGPR binding moiety comprises between 2 and 20 GalNAcs moieties (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 GalNAc moieties). In an embodiment, the ASGPR binding moiety comprises between 2 and 10 GalNAc moieties (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 GalNAc moieties). In an embodiment, the ASGPR binding moiety comprises between 2 and 5 GalNAc moieties (e.g., 2, 3, 4, or 5 GalNAc moieties). In an embodiment, the ASGPR binding moiety comprises 2 GalNAc moieties. In an embodiment, the ASGPR binding moiety comprises 3 GalNAc moieties. In an embodiment, the ASGPR binding moiety comprises 4 GalNAc moieties. In an embodiment, the ASGPR moieties comprises 5 GalNAc moieties.

In some embodiments, the GalNAc moiety comprises a structure of Formula (I):

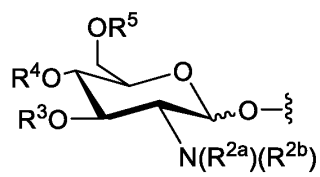


(I) or a salt thereof, wherein each of X and Y is independently O, N(R⁷), or S; each of R¹, R³, R⁴, and R⁵ are independently hydrogen, alkyl, alkenyl, alkynyl,

heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ; R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃); each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ; R^7 is hydrogen, alkyl, or C(O)-alkyl; each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; R^A is hydrogen, or alkyl, alkenyl, alkynyl, and n is an integer between 0 and 6, wherein the structure of Formula (I) may be connected to a linker or a nucleobase within the ASt of a TREM.

In some embodiments, X is O. In some embodiments, Y is O. In some embodiments, each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH₃). In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2b} is C(O)CH₃. In some embodiments, each of R^{6a} and R^{6b} is hydrogen. In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 1, 2, or 3. In some embodiments, n is 1. In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^{2a} . In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^{2b} . In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^3 . In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^4 . In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^5 . In some embodiments, the GalNAc moiety is connected to a linker or TREM at R^{6a} or R^{6b} . In some embodiments, the GalNAc moiety is connected to a linker or TREM at a plurality of positions, e.g., at least two of R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} .

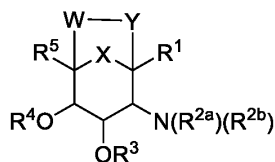
In some embodiments, the GalNAc moiety comprises a structure of Formula (I-a)



(I-a), or a salt thereof, wherein R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃); each of R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ; and R^8 is hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl, wherein the “~” represents a bond in any configuration, and “ξ” represents an attachment point to a TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

In some embodiments, each of R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH₃). In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2b} is C(O)CH₃.

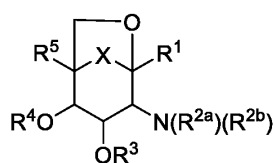
In some embodiments, the GalNAc moiety comprises a structure of Formula (II):



(II) or a salt thereof, wherein X is O, N(R^7), or S; each of W or Y is independently O or C(R^{10a})(R^{10b}), wherein one of W and Y is O; each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ; R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃); each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl,

haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ; R^7 is hydrogen, alkyl, or C(O)-alkyl; each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; each of R^{10a} and R^{10b} is independently hydrogen, heteroalkyl, haloalkyl, or halo; and R^A is hydrogen, or alkyl, alkenyl, alkynyl, wherein the structure of Formula (I) may be connected to a TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

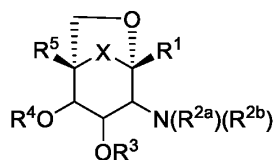
In some embodiments, the GalNAc moiety comprises a structure of Formula (II-a):



(II-a) or a salt thereof, wherein X is O, N(R^7), or S; each of R^1 , R^3 , R^4 ,

and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ; R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃); each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ; R^7 is hydrogen, alkyl, or C(O)-alkyl; each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; and R^A is hydrogen, or alkyl, alkenyl, alkynyl, wherein the structure of Formula (I) may be connected to a TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

In some embodiments, the GalNAc moiety comprises a structure of Formula (II-b):

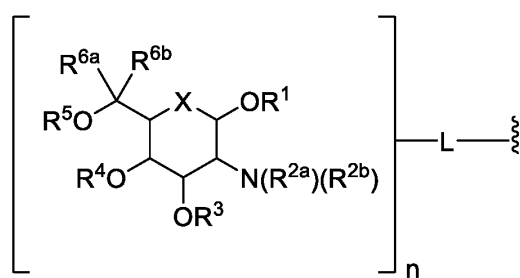


(II-b) or a salt thereof, wherein X is O, N(R^7), or S; each of R^1 , R^3 , R^4 ,

and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl,

heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ; R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃); each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ; R^7 is hydrogen, alkyl, or C(O)-alkyl; each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; and R^A is hydrogen, or alkyl, alkenyl, alkynyl, wherein the structure of Formula (I) may be connected to a TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

In some embodiments, the ASGPR binding moiety comprises a structure of Formula (III):



(III), or a salt thereof, wherein each of R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} and subvariables thereof are as defined for Formula (I), L is a linker, and n is an integer between 1 and 100, wherein “ $\sim$ ” represents an attachment point to a branching point, additional linker, or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

In some embodiments, X is O. In some embodiments, each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH₃). In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2b} is C(O)CH₃. In some embodiments, each of R^{6a} and R^{6b} is hydrogen. In some embodiments, n is an integer between 1 and 50. In some embodiments, n is an integer between 1 and 25. In some embodiments, n is an integer between 1 and 10. In some embodiments, n is an

integer between 1 and 5. In some embodiments, n is 1, 2, 3, 4, or 5. In some embodiments, n is 1.

In an embodiment, L comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, L comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclyl group. In an embodiment, L is cleavable or non-cleavable.

The term “linker” as used herein refers to an organic moiety that connects two or more parts of a compound, e.g., through a covalent bond. A linker may linear or branched. In some embodiments, a linker comprises a heteroatom, such as a nitrogen, sulfur, oxygen, phosphorus, silicon, or boron atom. In some embodiments, the linker comprises a cyclic group (e.g., an aryl, heteroaryl, cycloalkyl, or heterocyclyl group). In some embodiments, a linker comprises a functional group such as an amide, ketone, ester, ether, thioester, thioether, thiol, hydroxyl, amine, cyano, nitro, azide, triazole, pyrroline, p-nitrophenyl, alkene, or alkyne group. Any atom within a linker may be substituted or unsubstituted. In some embodiments, a linker comprises an arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, or alkynylheteroaryl group. In some embodiments, a linker comprises a polyethylene glycol group (e.g., PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG10, PEG12, PEG14, PEG16, PEG18, PEG20, PEG24, PEG28, PEG32, PEG100, PEG200, PEG250, PEG500, PEG600, PEG700, PEG750, PEG800, PEG900, PEG1000, PEG2000, or PEG3000). In some embodiments, L comprises a PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 group. In some embodiments, L comprises a plurality of PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups (e.g., 2, 3, 4, or 5 PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6

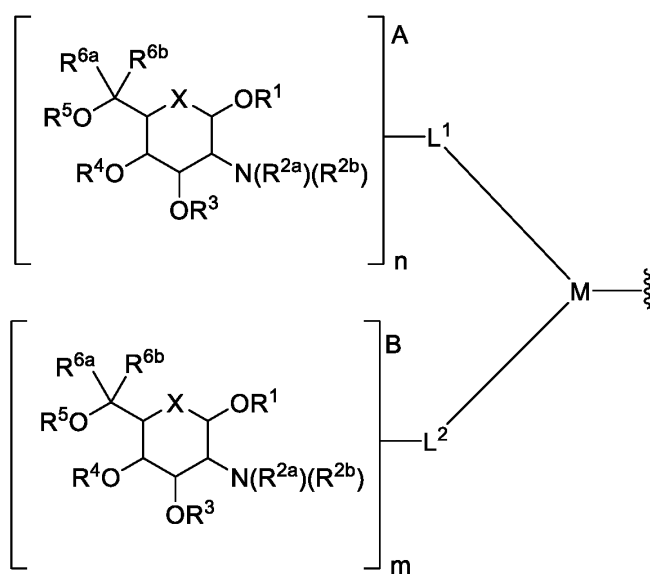
groups). In some embodiments, L comprises a PEG2 group. In some embodiments, L comprises a plurality of PEG2 groups. In some embodiments, L comprises a PEG3 group. In some embodiments, L comprises a plurality of PEG3 groups. In some embodiments, L comprises a PEG4 group. In some embodiments, L comprises a plurality of PEG4 groups.

In some embodiments, the linker comprises between 1 and 1000 atoms (e.g., between 1 and 750 atoms, 1 and 500 atoms, 1 and 250 atoms, 1 and 100 atoms, 1 and 75 atoms, 1 and 50 atoms, 1 and 25 atoms, and 1 and 10 atoms). In some embodiments, the linker comprises between 1 and 100 atoms. In some embodiments, the linker comprises between 1 and 50 atoms. In some embodiments, the linker comprises between 1 and 25 atoms.

In some embodiments, the linker is linear and comprises between 1 and 1000 atoms (e.g., between 1 and 750 atoms, 1 and 500 atoms, 1 and 250 atoms, 1 and 100 atoms, 1 and 75 atoms, 1 and 50 atoms, 1 and 25 atoms, and 1 and 10 atoms). In some embodiments, the linker is linear and comprises between 1 and 100 atoms. In some embodiments, the linker is linear and comprises between 1 and 50 atoms. In some embodiments, the linker is linear and comprises between 1 and 25 atoms.

In some embodiments, the linker is branched, and each branch comprises between 1 and 1000 atoms (e.g., between 1 and 750 atoms, 1 and 500 atoms, 1 and 250 atoms, 1 and 100 atoms, 1 and 75 atoms, 1 and 50 atoms, 1 and 25 atoms, and 1 and 10 atoms). In some embodiments, the linker is branched, and each branch comprises between 1 and 100 atoms. In some embodiments, the linker is branched, and each branch comprises between 1 and 50 atoms. In some embodiments, the linker is branched, and each branch comprises between 1 and 25 atoms.

In some embodiments, the ASGPR binding moiety comprises a structure of Formula (III-a):



(III-a), or a salt thereof, wherein each

of R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} and subvariables thereof are as defined for Formula (I), each of L^1 and L^2 is independently a linker, each of m and n is independently an integer between 1 and 100, and M is a linker, wherein “ $\sim$ ” represents an attachment point to a branching point, additional linker, or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence..

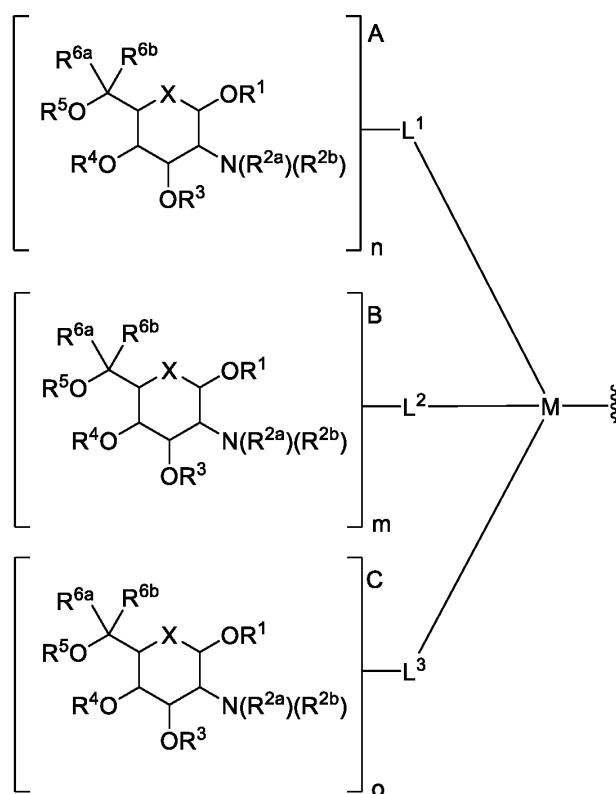
In some embodiments, X is O (e.g., X in each of A and B is O). In some embodiments, each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH_3) (e.g., R^1 , R^3 , R^4 , and R^5 in each of A and B is independently hydrogen or alkyl). In some embodiments, R^{2a} is hydrogen (e.g., R^{2a} in each of A and B is hydrogen). In some embodiments, R^{2b} is $C(O)CH_3$ (e.g., R^{2b} in each of A and B is $C(O)CH_3$). In some embodiments, each of R^{6a} and R^{6b} is hydrogen (e.g., R^{6a} and R^{6b} in each of A and B is hydrogen). In some embodiments, each of m and n is independently an integer between 1 and 50. In some embodiments, each of m and n is independently an integer between 1 and 25. In some embodiments, each of m and n is independently an integer between 1 and 10. In some embodiments, each of m and n is independently an integer between 1 and 5. In some embodiments, each of m and n is independently 1, 2, 3, 4, or 5. In some embodiments, each of m and n is independently 1.

In an embodiment, each of L^1 and L^2 independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, each of L^1 and L^2 independently comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl,

or heterocyclyl group. In an embodiment, each of L^1 and L^2 independently is cleavable or non-cleavable. In some embodiments, each of L^1 and L^2 independently comprises a polyethylene glycol group (e.g., PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG10, PEG12, PEG14, PEG16, PEG18, PEG20, PEG24, PEG28, PEG32, PEG100, PEG200, PEG250, PEG500, PEG600, PEG700, PEG750, PEG800, PEG900, PEG1000, PEG2000, or PEG3000). In some embodiments, each of L^1 and L^2 independently comprises a PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 group. In some embodiments, each of L^1 and L^2 independently comprises a plurality of PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups (e.g., 2, 3, 4, or 5 PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups). In some embodiments, each of L^1 and L^2 independently comprises a PEG2 group. In some embodiments, each of L^1 and L^2 independently comprises a plurality of PEG2 groups. In some embodiments, each of L^1 and L^2 independently comprises a PEG3 group. In some embodiments, each of L^1 and L^2 independently comprises a plurality of PEG3 groups. In some embodiments, each of L^1 and L^2 independently comprises a PEG4 group. In some embodiments, each of L^1 and L^2 independently comprises a plurality of PEG4 groups.

In some embodiments, M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, M comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclyl group. In an embodiment, M is cleavable or non-cleavable.

In some embodiments, the ASGPR binding moiety comprises a structure of Formula (III-b):



(III-b), or a salt thereof, wherein each of

R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} and subvariables thereof are as defined for Formula (I), each of L^1 , L^2 , and L^3 is independently a linker, each of m , n , and o is independently an integer

between 1 and 100, and M is a linker, wherein “ $\frac{1}{2}$ ” represents an attachment point to a branching point, additional linker, or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

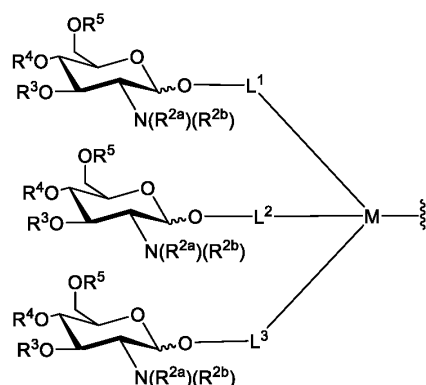
In some embodiments, X is O (e.g., X in each of A, B, and C is O). In some embodiments, each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH_3) (e.g., R^1 , R^3 , R^4 , and R^5 in each of A, B, and C is independently hydrogen or alkyl). In some embodiments, R^{2a} is hydrogen (e.g., R^{2a} in each of A, B, and C is hydrogen). In some embodiments, R^{2b} is $C(O)CH_3$ (e.g., R^{2b} in each of A, B, and C is $C(O)CH_3$). In some embodiments, each of R^{6a} and R^{6b} is hydrogen (e.g., R^{6a} and R^{6b} in each of A, B, and C is hydrogen). In some embodiments, each of m , n , and o is independently an integer between 1 and 50. In some embodiments, each of m , n , and o is independently an integer between 1 and 25. In some embodiments, each of m , n , and o is independently an integer between 1 and 10. In some

embodiments, each of m, n, and o is independently an integer between 1 and 5. In some embodiments, each of m, n, and o is independently 1, 2, 3, 4, or 5. In some embodiments, each of m, n, and o is independently 1.

In an embodiment, each of L¹, L², and L³ independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, each of L¹, L², and L³ independently comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclcyl group. In an embodiment, each of L¹, L², and L³ independently is cleavable or non-cleavable. In an embodiment, each of L¹ and L² independently is cleavable or non-cleavable. In some embodiments, each of L¹, L², and L³ independently comprises a polyethylene glycol group (e.g., PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG10, PEG12, PEG14, PEG16, PEG18, PEG20, PEG24, PEG28, PEG32, PEG100, PEG200, PEG250, PEG500, PEG600, PEG700, PEG750, PEG800, PEG900, PEG1000, PEG2000, or PEG3000). In some embodiments, each of L¹, L², and L³ independently comprises a PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 group. In some embodiments, each of L¹, L², and L³ independently comprises a plurality of PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups (e.g., 2, 3, 4, or 5 PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups). In some embodiments, each of L¹, L², and L³ independently comprises a PEG2 group. In some embodiments, each of L¹, L², and L³ independently comprises a plurality of PEG2 groups. In some embodiments, each of L¹, L², and L³ independently comprises a PEG3 group. In some embodiments, each of L¹, L², and L³ independently comprises a plurality of PEG3 groups. In some embodiments, each of L¹, L², and L³ independently comprises a PEG4 group. In some embodiments, each of L¹, L², and L³ independently comprises a plurality of PEG4 groups.

In some embodiments, M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, M comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclcyl group. In an embodiment, M is cleavable or non-cleavable.

In some embodiments, the ASGPR binding moiety comprises a structure of Formula (III-c):



(III-c), or a salt thereof, wherein each of R^{2a} , R^{2b} , R^3 , R^4 , R^5 , and subvariables thereof are as defined for Formula (I), each of L^1 , L^2 , and L^3 is independently a linker, and M is a linker, wherein “ ξ ” represents an attachment point to a branching point, additional linker, or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

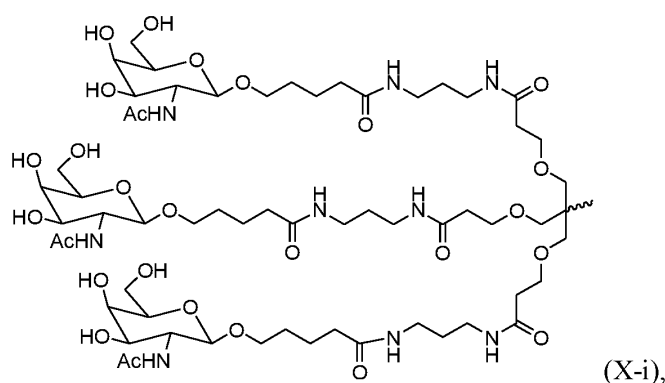
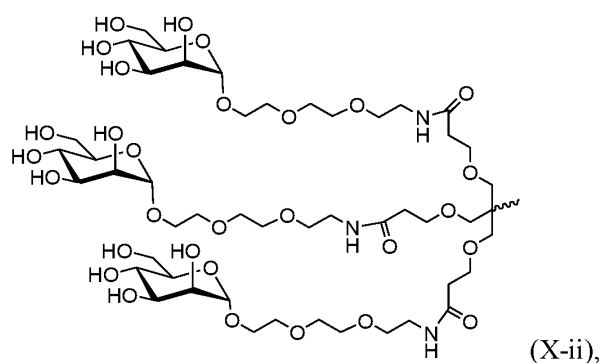
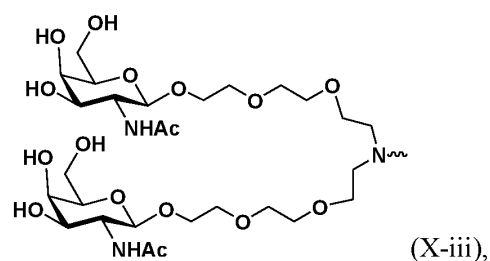
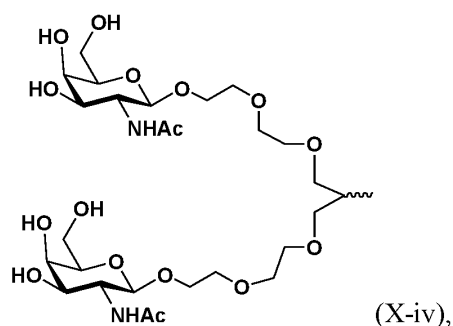
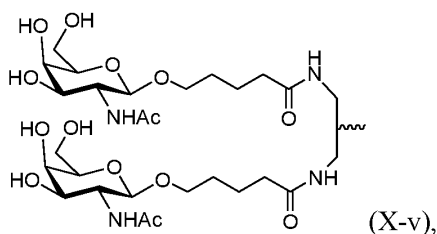
In some embodiments, each of R^3 , R^4 , and R^5 are independently hydrogen or alkyl (e.g., CH_3). In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2b} is $\text{C}(\text{O})\text{CH}_3$.

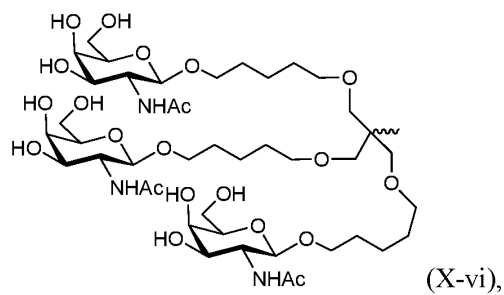
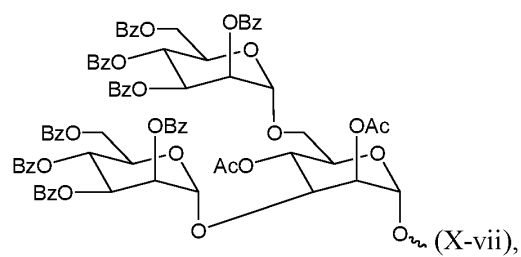
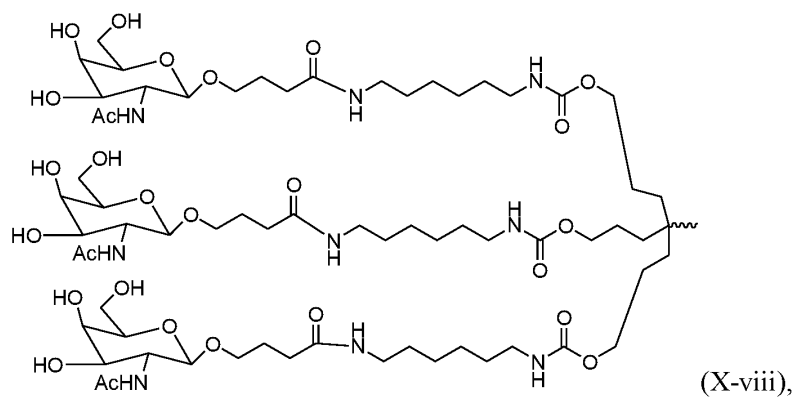
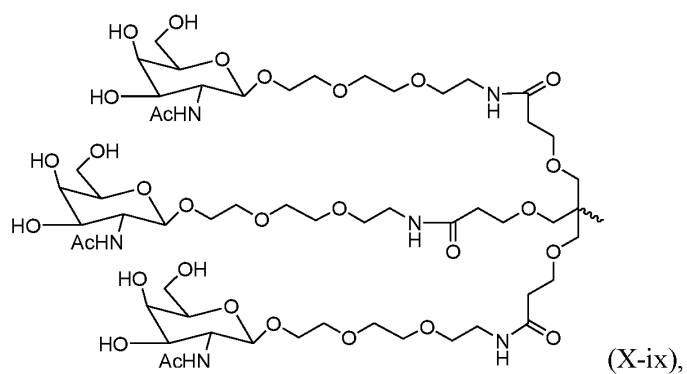
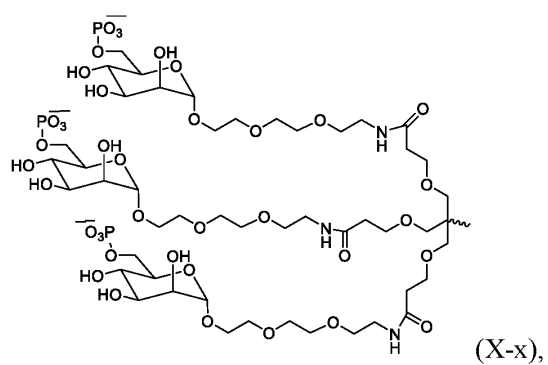
In an embodiment, each of L^1 , L^2 , and L^3 independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, each of L^1 , L^2 , and L^3 independently comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclyl group. In an embodiment, each of L^1 , L^2 , and L^3 independently is cleavable or non-cleavable. In an embodiment, each of L^1 and L^2 independently is cleavable or non-cleavable. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a polyethylene glycol group (e.g., PEG1, PEG2, PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG10, PEG12, PEG14, PEG16, PEG18, PEG20, PEG24, PEG28, PEG32, PEG100, PEG200, PEG250, PEG500, PEG600, PEG700, PEG750, PEG800, PEG900, PEG1000, PEG2000, or PEG3000). In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 group. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a plurality of PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups (e.g., 2, 3, 4, or 5 PEG1, PEG2, PEG3, PEG4, PEG5, or PEG6 groups). In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a PEG2 group. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a plurality of PEG2 groups. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a PEG3 group. In some embodiments, each of L^1 , L^2 , and L^3

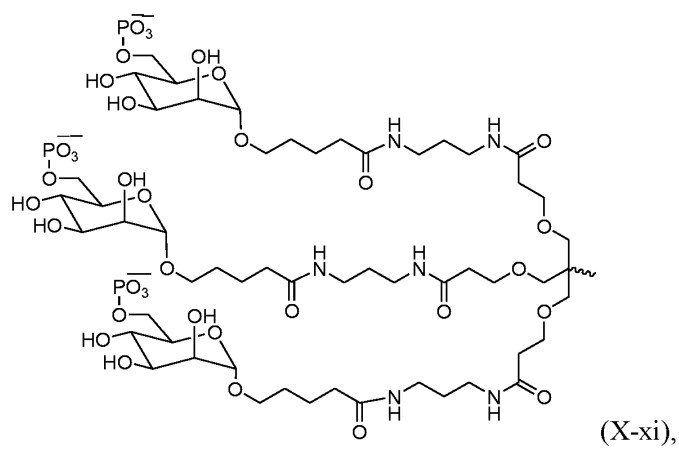
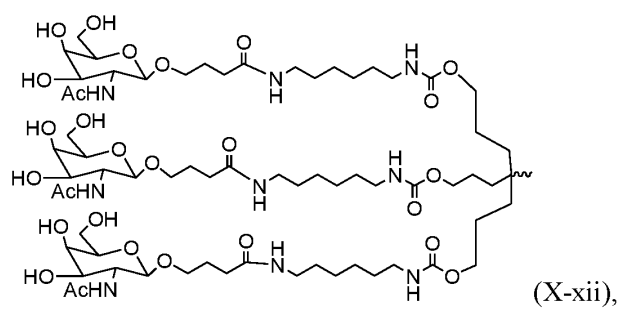
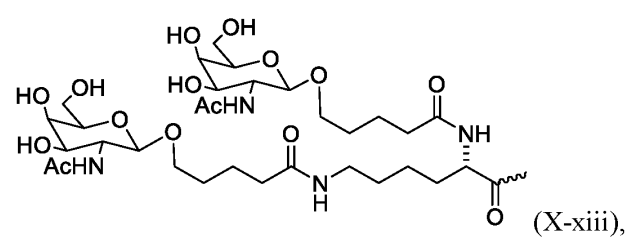
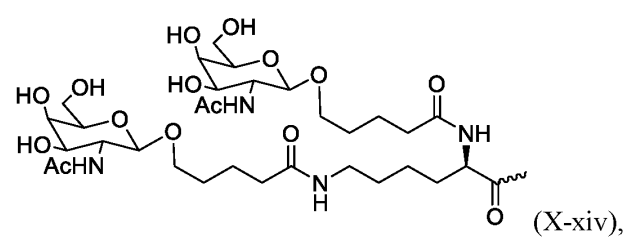
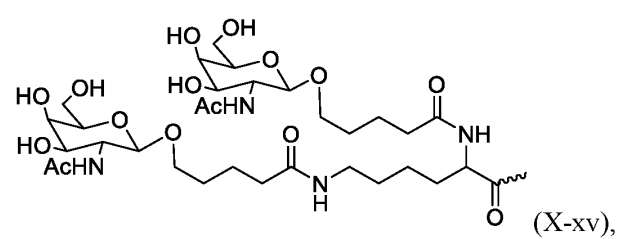
independently comprises a plurality of PEG3 groups. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a PEG4 group. In some embodiments, each of L^1 , L^2 , and L^3 independently comprises a plurality of PEG4 groups.

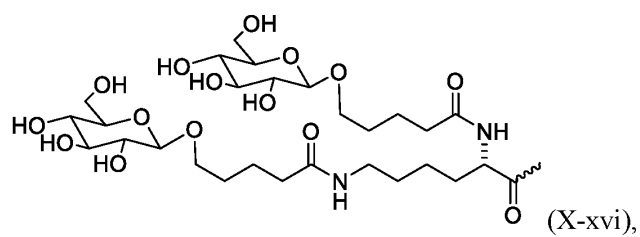
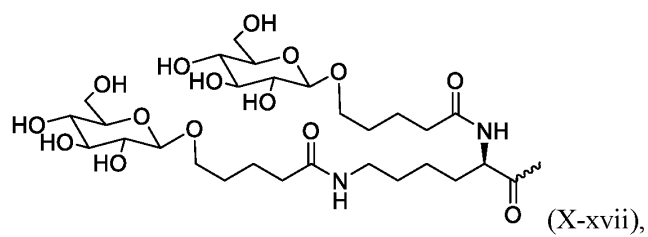
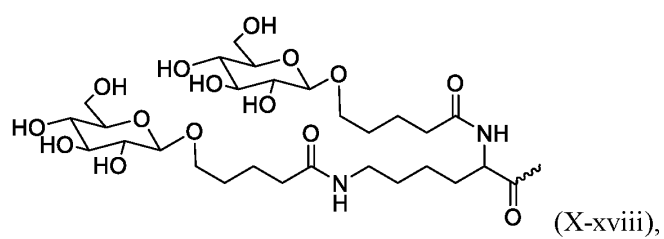
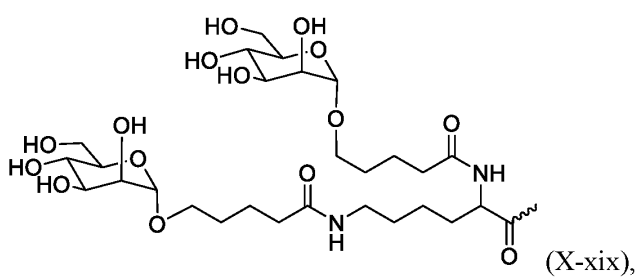
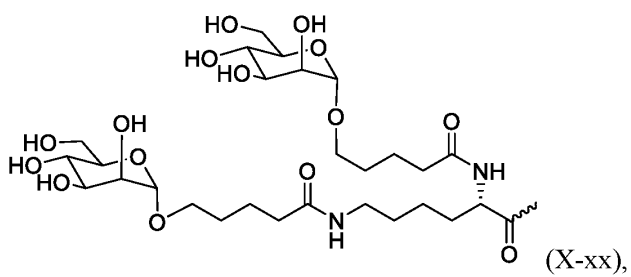
In some embodiments, M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group. In an embodiment, M comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclyl group. In an embodiment, M is cleavable or non-cleavable.

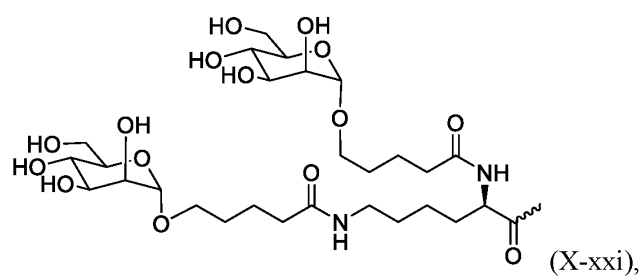
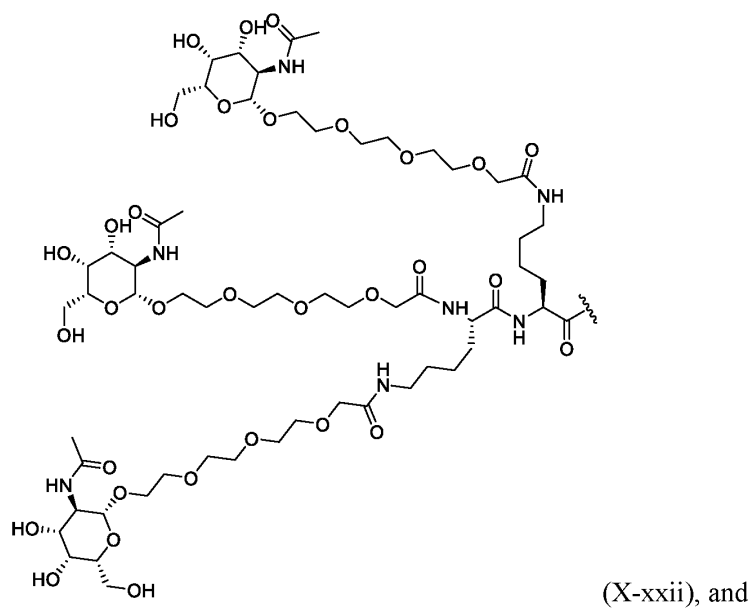
In some embodiments, the ASGPR binding moiety comprises a compound selected from:

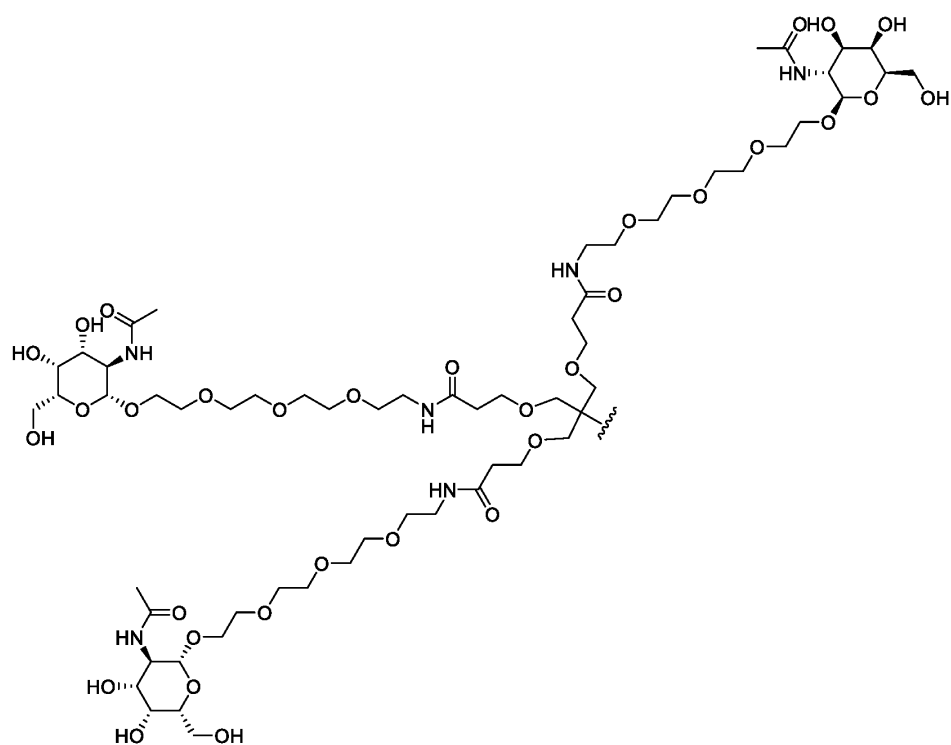












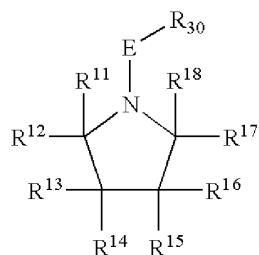
(X-xxiii).

In some embodiments, the ASGPR binding moiety is a compound (X-i). In some embodiments, the ASGPR binding moiety is compound (X-ii). In some embodiments, the ASGPR binding moiety is compound (X-iii). In some embodiments, the ASGPR binding moiety is compound (X-iv). In some embodiments, the ASGPR binding moiety is compound (X-v). In some embodiments, the ASGPR binding moiety is compound (X-vi). In some embodiments, the ASGPR binding moiety is compound (X-vii). In some embodiments, the ASGPR binding moiety is compound (X-viii). In some embodiments, the ASGPR binding moiety is compound (X-ix). In some embodiments, the ASGPR binding moiety is compound (X-x). In some embodiments, the ASGPR binding moiety is compound (X-xi). In some embodiments, the ASGPR binding moiety is compound (X-xii). In some embodiments, the ASGPR binding moiety is compound (X-xiii). In some embodiments, the ASGPR binding moiety is compound (X-xiv). In some embodiments, the ASGPR binding moiety is compound (X-xv). In some embodiments, the ASGPR binding moiety is compound (X-xvi). In some embodiments, the ASGPR binding moiety is compound (X-xvii). In some embodiments, the ASGPR binding moiety is compound (X-xviii). In some embodiments, the ASGPR binding moiety is compound (X-xix). In some embodiments, the ASGPR binding moiety is compound (X-xx). In some embodiments, the ASGPR binding moiety

is compound (X-xxi). In some embodiments, the ASGPR binding moiety is compound (X-xxii). In some embodiments, the ASGPR binding moiety is compound (X-xxiii). In some embodiments, the ASGPR binding moiety is a compound selected from compound (X-i), (X-xxii), and (X-xxiii).

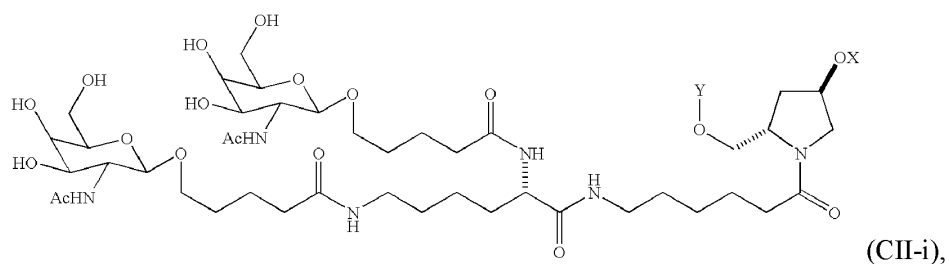
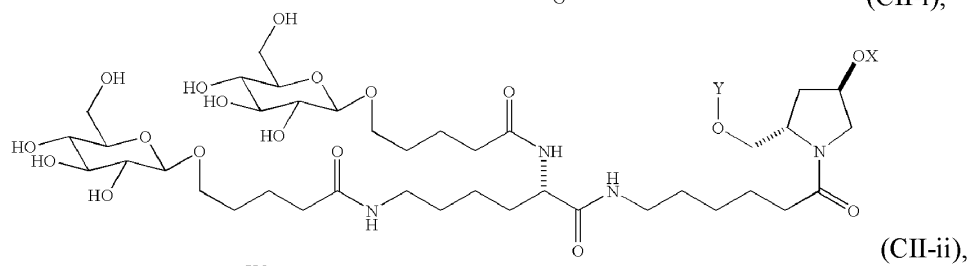
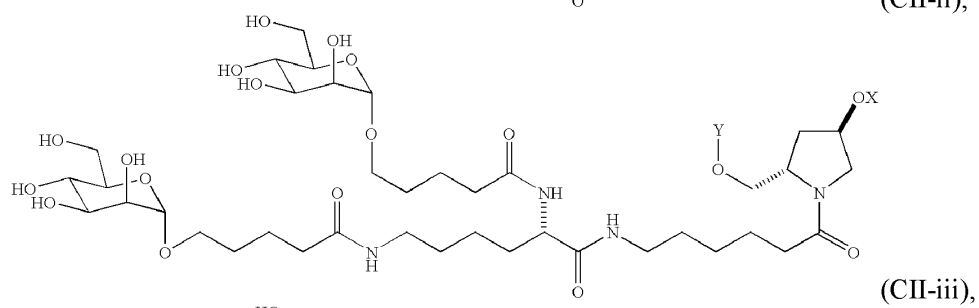
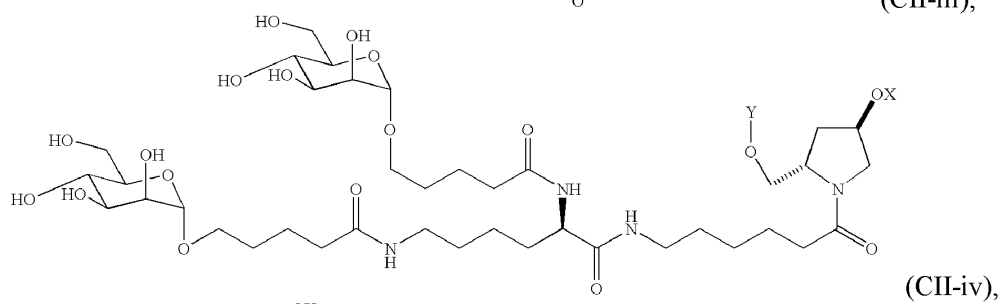
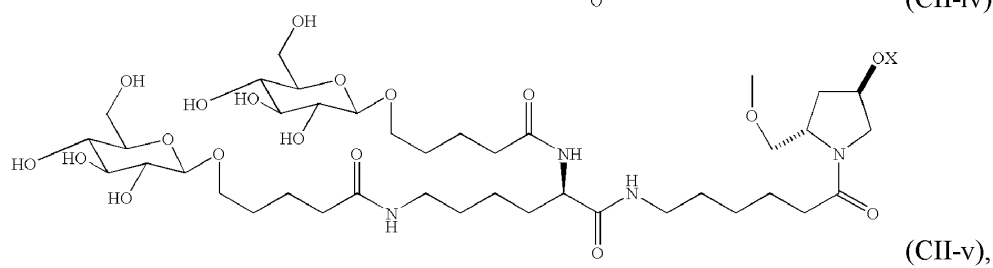
In some embodiments, the ASGPR binding moiety comprises a linker comprising a cyclic moiety, such as a pyrrolidine ring. In an embodiment, the ASGPR binding moiety comprises a structure of Formula (CII):

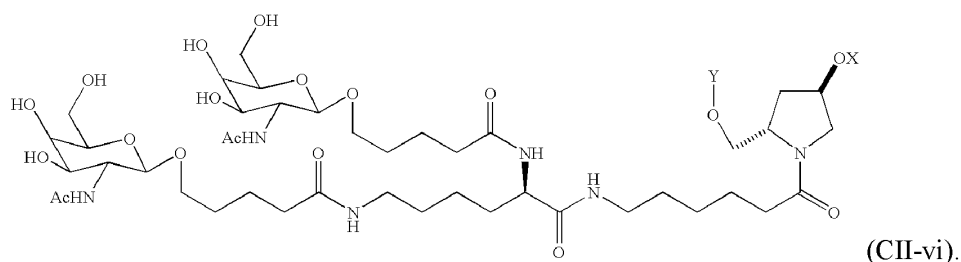
Formula (CII)



, or a salt thereof, wherein E is absent or C(O), C(O)O, C(O)NH, C(S), C(S)NH, SO, SO₂, or SO₂NH; R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently for each occurrence H, —CH₂OR^a, or OR^b; R^a and R^b are each independently for each occurrence hydrogen, a hydroxyl protecting group, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted heteroaryl, polyethyleneglycol (PEG), a phosphate, a diphosphate, a triphosphate, a phosphonate, a phosphonothioate, a phosphonodithioate, a phosphorothioate, a phosphorothiolate, a phosphorodithioate, a phosphorothiolothionate, a phosphodiester, a phosphotriester, an activated phosphate group, an activated phosphite group, a phosphoramidite, a solid support, —P(Z¹)(Z²)—O-nucleoside, —P(Z¹)(Z²)—O-oligonucleotide, —P(Z¹)(O-linker-R^L)—O-nucleoside, or —P(Z¹)(O-linker-R^L)—O-oligonucleotide; R³⁰ is independently for each occurrence -linker-R^L or R³¹; R^L is hydrogen or a ligand; R³¹ is —C(O)CH(N(R³²)₂)(CH₂)_hN(R³²)₂; R³² is independently for each occurrence H, —R^L, -linker-R^L or R³¹; Z¹ is independently for each occurrence O or S; Z² is independently for each occurrence O, S, N(alkyl) or optionally substituted alkyl; and h is independently for each occurrence 1-20.

In some embodiments, the compound of Formula (CII) is selected from:

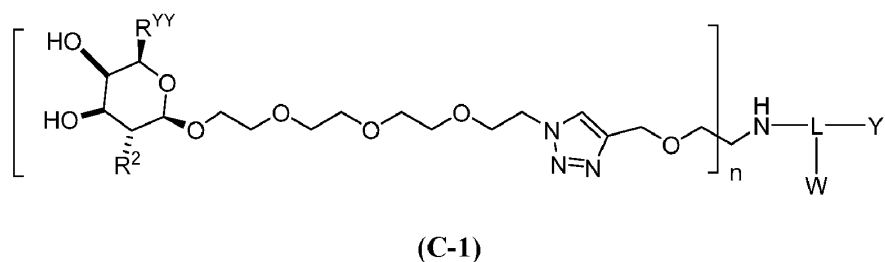
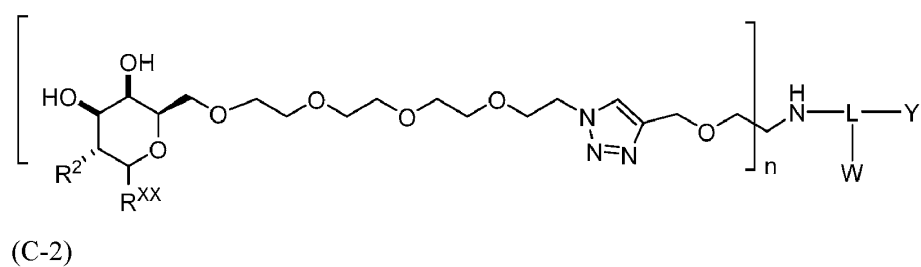


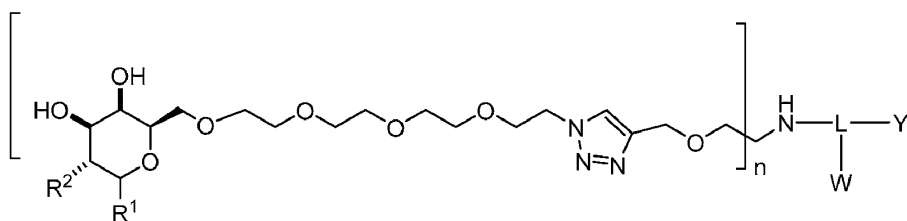


In some embodiments, the ASGPR binding moiety is a compound or substructure disclosed in U.S. Patent No. 8,106,022, which is incorporated herein by reference in its entirety.

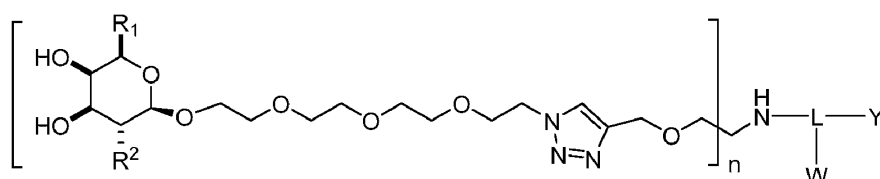
In some embodiments, the ASGPR binding moiety is a compound (CII-i). In some embodiments, the ASGPR binding moiety is a compound (CII-ii). In some embodiments, the ASGPR binding moiety is a compound (CII-iii). In some embodiments, the ASGPR binding moiety is a compound (CII-iv). In some embodiments, the ASGPR binding moiety is a compound (CII-v). In some embodiments, the ASGPR binding moiety is a compound (CII-vi).

In some embodiments, the ASGPR binding moiety is a compound of Formula (C-1), (C-2), (C-3) or (C4):





(C-3)



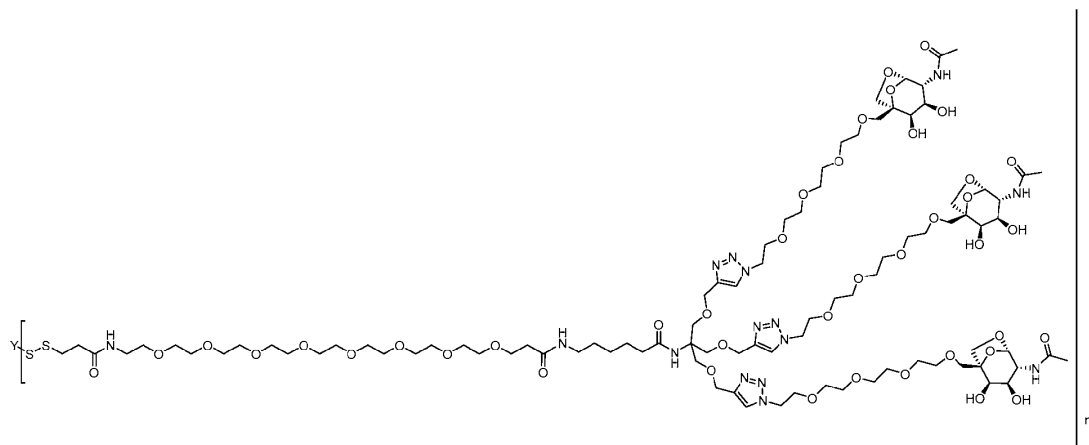
(C-4),

or a pharmaceutically acceptable salt thereof, wherein: n is 1, 2, or 3; W is absent or a peptide; L is $-(T-Q-T-Q)_m-$, wherein each T is independently absent or is (C_1-C_{10}) alkylene, (C_2-C_{10}) alkenylene, or (C_2-C_{10}) alkynylene, wherein one or more carbon groups of said T may each independently be replaced with a heteroatom group independently selected from $-O-$, $-S-$, and $-N(R^4)-$ wherein the heteroatom groups are separated by at least 2 carbon atoms, and wherein alkylene, alkenylene, and alkynylene may each be independently substituted with one or more halo atoms; each Q is independently absent or is $C(O)$, $C(O)-NR^4$, $NR^4-C(O)$, $O-C(O)-NR^4$, $NR^4-C(O)-O$, $-CH_2-$, a heteroaryl, or a heteroatom group selected from O, S, S-S, S(O), S(O)₂, and NR^4 , wherein at least two carbon atoms separate the heteroatom groups O, S, S-S, S(O), S(O)₂ and NR^4 from any other heteroatom group; each R^4 is independently $-H$, $-(C_1-C_{20})$ alkyl, or (C_3-C_8) cycloalkyl wherein one to six $-CH_2-$ groups of the alkyl or cycloalkyl separated by at least two carbon atoms may be replaced with $-O-$, $-S-$, or $-N(R^4)-$, and $-CH_3-$ of the alkyl may each be independently replaced with a heteroatom group selected from $-N(R^4)_2$, $-OR^4$, and $-S(R^4)$ wherein the heteroatom groups are separated by at least 2 carbon atoms; and wherein the alkyl and cycloalkyl may be substituted with halo atoms; and m is independently 0, 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.

In some embodiments, the ASGPR binding moiety is a compound (C-1). In some embodiments, the ASGPR binding moiety is a compound (C-2). In some embodiments, the

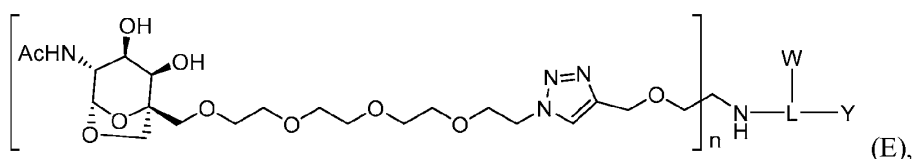
ASGPR binding moiety is a compound (C-3). In some embodiments, the ASGPR binding moiety is a compound (C-4).

In some embodiments, the compound of Formula (C-1), (C-2), (C-3) or (C4) comprises:



wherein n' is 1 or 2 or a pharmaceutically acceptable salt thereof.

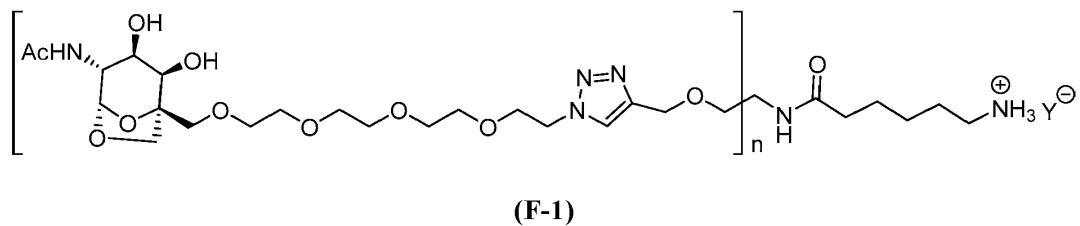
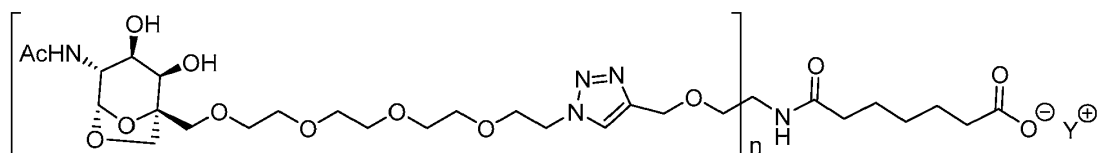
In some embodiments, the ASGPR binding moiety is a compound of Formula (E):



or a pharmaceutically acceptable salt thereof, wherein: n is 1, 2 or 3; W is absent or is a peptide; L is $-(T-Q-T-Q)_m-$, wherein each T is independently absent or is (C_1-C_{10}) alkylene, (C_2-C_{10}) alkenylene, or (C_2-C_{10}) alkynylene, wherein one or more carbon groups of said T may each independently be replaced with a heteroatom group independently selected from $-O-$, $-S-$, and $-N(R^4)-$ wherein the heteroatom groups are separated by at least 2 carbon atoms, wherein said alkylene, alkenylene, alkynylene, may each independently be substituted by one or more halo atoms; each Q is independently absent or is $C(O)$, $C(O)-R^4$, $R^4-C(O)$, $O-C(O)-R^4$, $R^4-C(O)-O$, $-CH_2-$, a heteroaryl, or a heteroatom group selected from O , S , $S-S$, $S(O)$, $S(O)_2$, and NR^4 , wherein at least two carbon atoms separate the heteroatom groups O , S , $S-S$, $S(O)$, $S(O)_2$ and NR^4 from any other heteroatom group; each R^4 is independently $-H$, $-(C_1-C_{20})$ alkyl, $-(C_1-C_{20})$ alkenyl, $-(C_2-C_{20})$ alkynyl, or (C_3-C_6) cycloalkyl wherein one to six $-CH_2-$ groups of the alkyl or cycloalkyl separated by at least two carbon atoms may be replaced with $-O-$, $-S-$, or $-N(R^4)-$, and $-CH_3$ of the alkyl may be replaced with a heteroatom group selected from $-N(R^4)_2$, $-OR^4$, and

-S(R⁴) wherein the heteroatom groups are separated by at least 2 carbon atoms; and wherein the alkyl, alkenyl, alkynyl, and cycloalkyl may be substituted with halo atoms; each m is independently 0, 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.

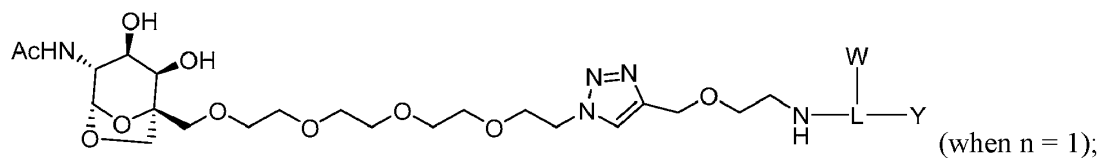
In some embodiments, the compound of Formula (E) is selected from:



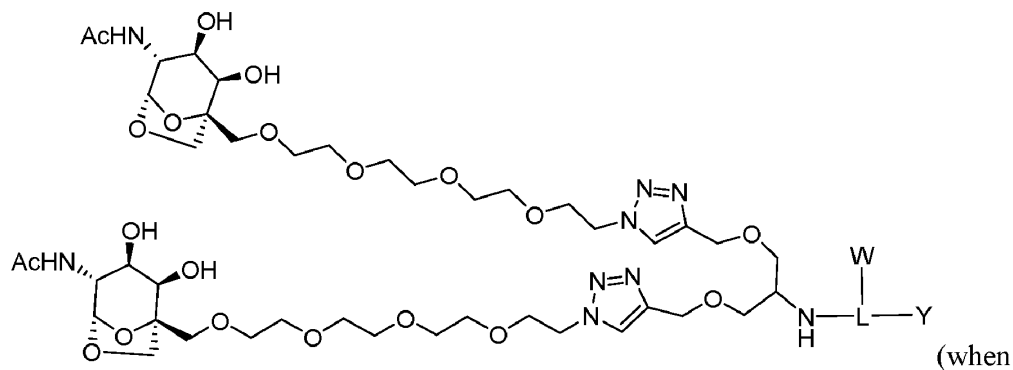
(F-2), or a pharmaceutically acceptable salt thereof, and Y is as defined in Formula (E).

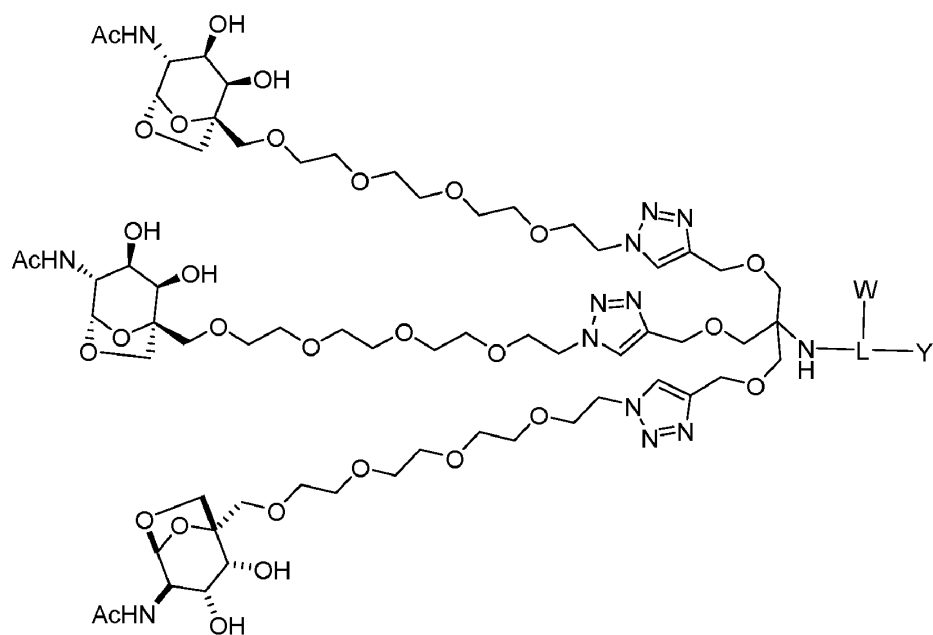
In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

In some embodiments of a compound of Formula (E), the compound is:



(E-1)

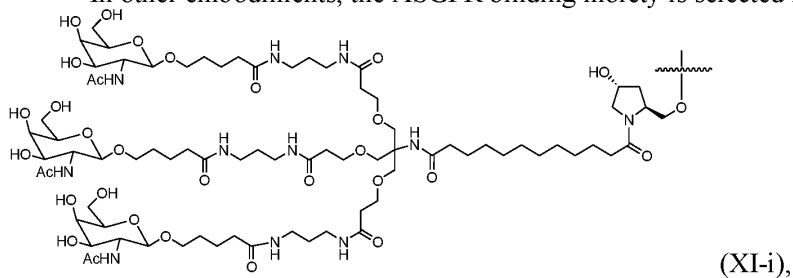
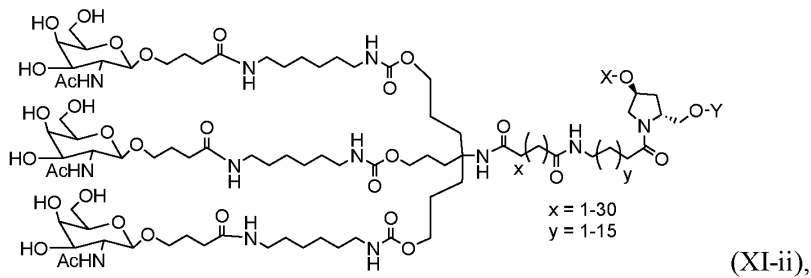


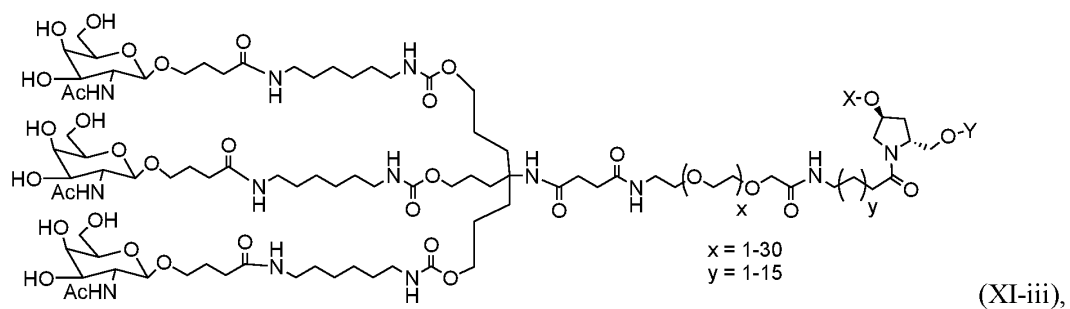
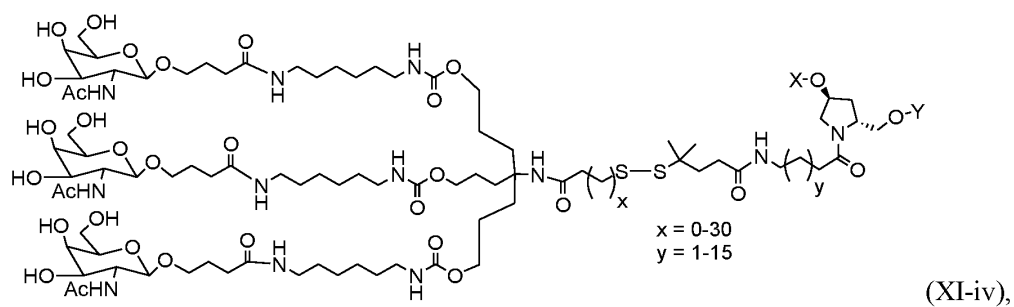
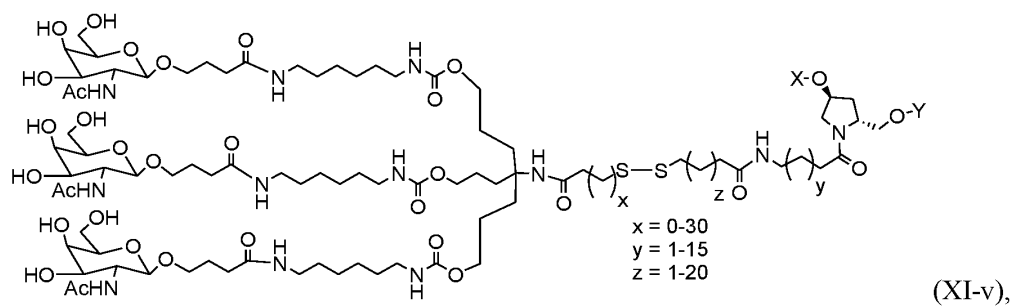
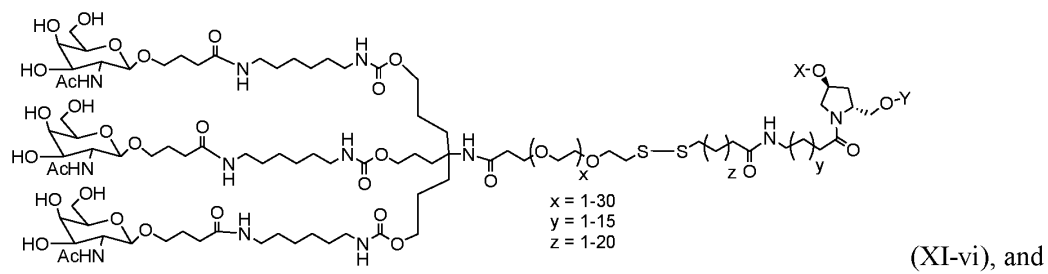
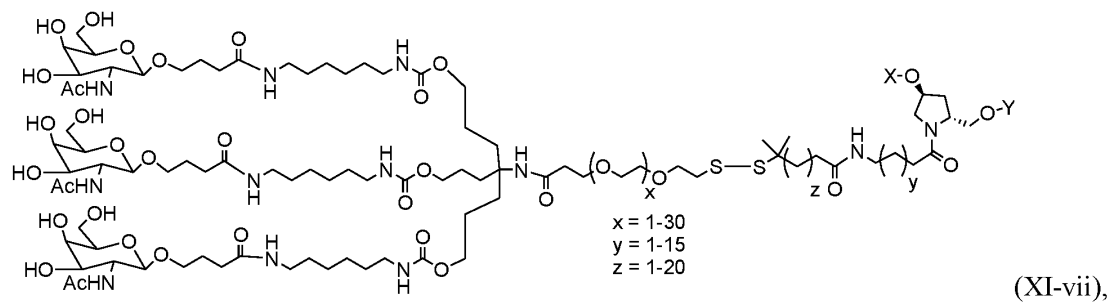


(E-3), or a pharmaceutically acceptable salt thereof.

In some embodiments, the ASGPR binding moiety is a compound or substructure disclosed in WO2017/083368, which is incorporated herein by reference in its entirety.

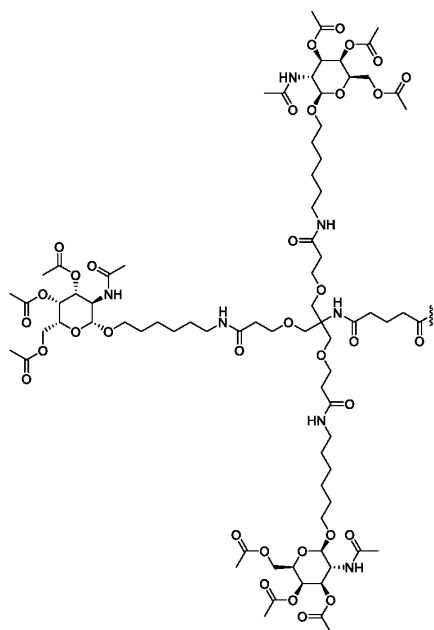
In other embodiments, the ASGPR binding moiety is selected from:





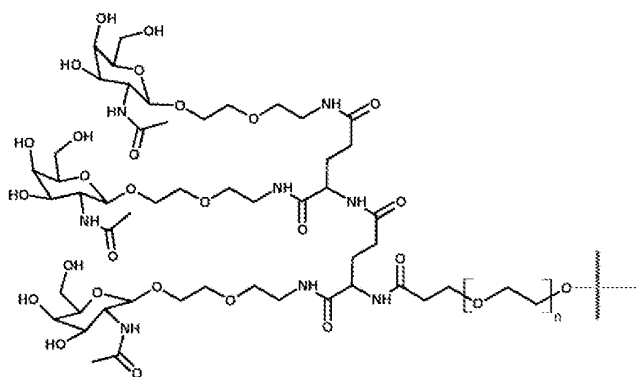
wherein one of X or Y is a branching point, a linker, or a TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence, and the other of X and Y is hydrogen.

In an embodiment, the ASGPR binding moiety comprises a structure of Formula (XII-a):

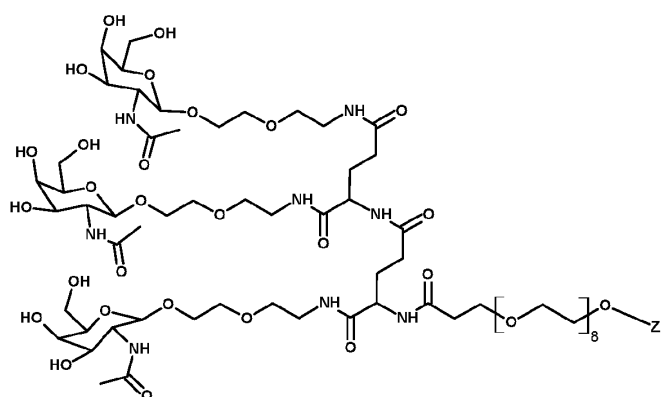


. In an embodiment, the ASGPR binding moiety is a compound or substructure disclosed in *Nucleic Acids* (2016) 5:e317 or WO2015/042447, each of which is incorporated herein by reference in its entirety.

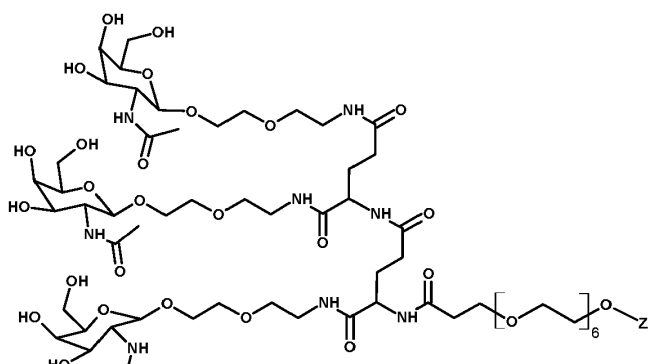
In some embodiments, the ASGPR binding moiety comprises a structure of Formula (V-a):



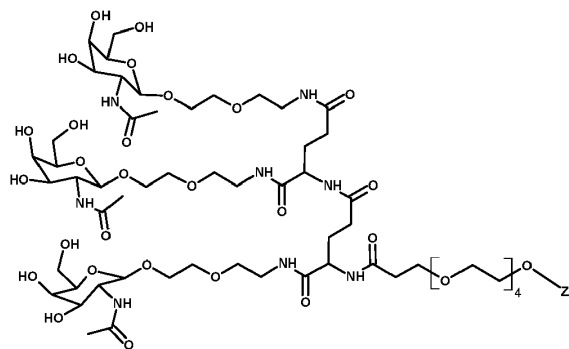
20. In some embodiments, the compound of Formula (V-a) is selected from:



(V-a-i),



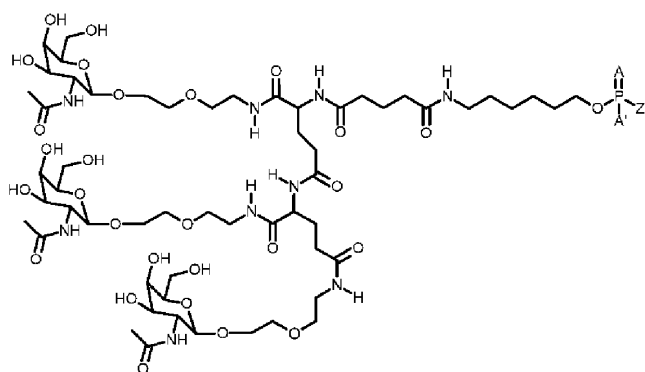
(V-a-ii), and



(V-a-iii), wherein Z is an oligomeric

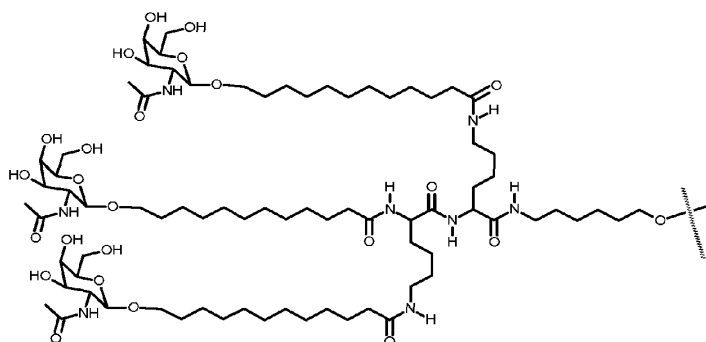
compound, e.g., a linker or a nucleobase within the AS_t of a TREM.

In another embodiment, the ASGPR binding moiety comprises a structure of Formula (V-b):



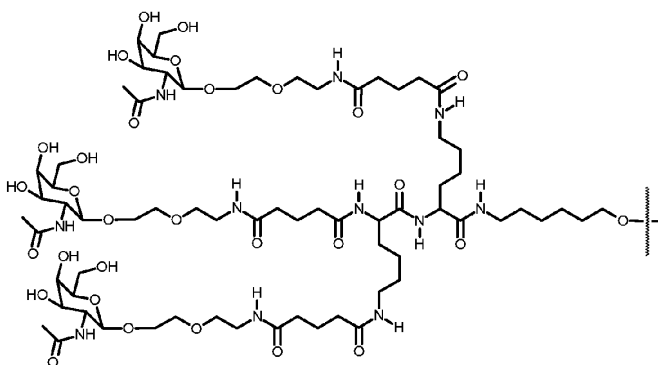
(V-b), wherein A is O or S, A' is O, S, or NH, and Z is an oligomeric compound, e.g., a linker or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

In some embodiments, the ASGPR binding moiety comprises

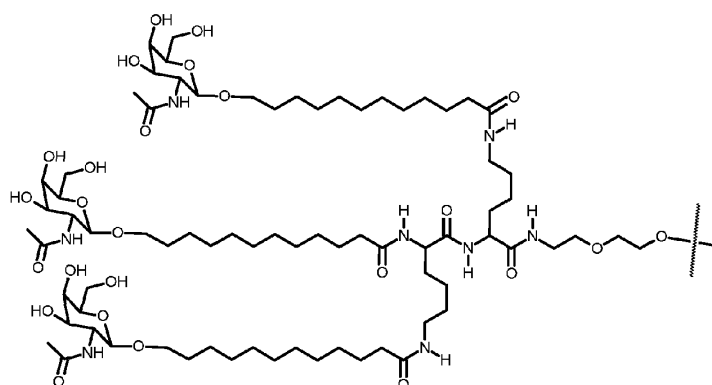


(V-b-i).

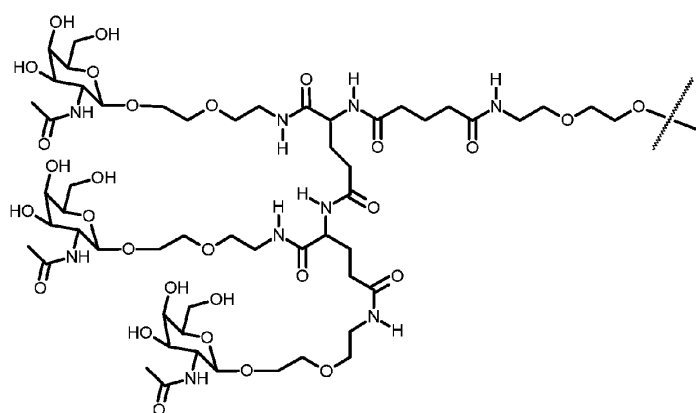
In some embodiments, the ASGPR binding moiety is selected from:



(V-c-i),



(V-d-i), and



(V-e-i).

In an embodiment, the ASGPR binding moiety is a compound or substructure disclosed in WO 2017/156012, which is incorporated herein by reference in its entirety.

In some embodiments, a hydroxyl group within an ASGPR binding moiety is protected, for example, with an acetyl or acetonide moiety. In some embodiments, a hydroxyl group within an ASGPR binding moiety is protected with an acetyl group. In some embodiments, a hydroxyl group within an ASGPR binding moiety is protected with acetonide group. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more hydroxyl groups within an ASGPR binding moiety may be protected, e.g., with an acetyl group or an acetonide group. In some embodiments, all of the hydroxyl groups within an ASGPR binding moiety are protected.

Exemplary TREMs comprising an ASGPR binding moiety may have a binding affinity for an ASGPR of between 0.01 nM to 100 mM. In some embodiments, a TREM comprising an ASGPR binding moiety has a binding affinity of less than 10 mM, e.g., 7.5 mM, 5 mM, 2.5 mM, 1 mM, 0.75 mM, 0.5 mM, 0.25 mM, 0.1 mM, 75 nM, 50 nM, 25 nM, 10 nM, 5 nM, or less.

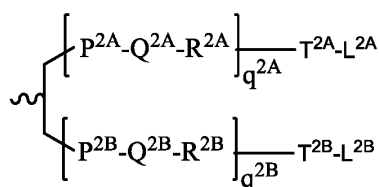
Exemplary TREMs comprising an ASGPR binding moiety may be internalized into a cell, e.g., a hepatocyte. In some embodiments, a TREM comprising an ASGPR binding moiety has an increased uptake into a cell compared with a TREM that does not comprise an ASGPR binding moiety. For example, a TREM comprising an ASGPR binding moiety may be internalized into a cell more than 1.1, 1.2, 1.3, 1.4, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100 times or more than a TREM that does not comprise an ASGPR binding moiety.

Additional exemplary ASGPR moieties are described in further detail in U.S. Patent Nos. 8,828,956; 9,867,882; 10,450,568; 10,808,246; U.S. Patent Publication Nos. 2015/0246133; 2015/0203843; and 2012/0095200; and PCT Publication Nos. WO 2013/166155, 2012/030683, and 2013/166121, each of which are incorporated herein by reference in its entirety.

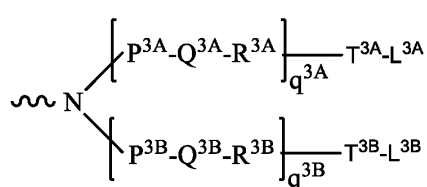
ASGPR Linkers

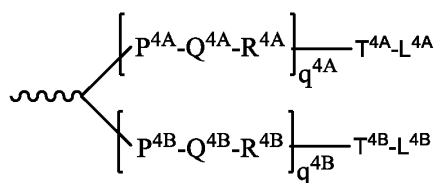
The ASGPR binding moiety comprises at least one linker that connects the carbohydrate to the TREM. In some embodiments, the TREM is connected to one or more carbohydrates (e.g., GalNAc moieties, e.g., of Formula (I)), through a linker as described herein. The linker may be monovalent or multivalent, e.g., bivalent, trivalent, tetravalent, or pentavalent. In some embodiments, the linker comprises a structure selected from:

Formula XXXI

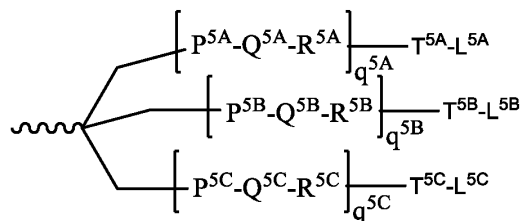


Formula XXXII





Formula (VI)



Formula (VII)

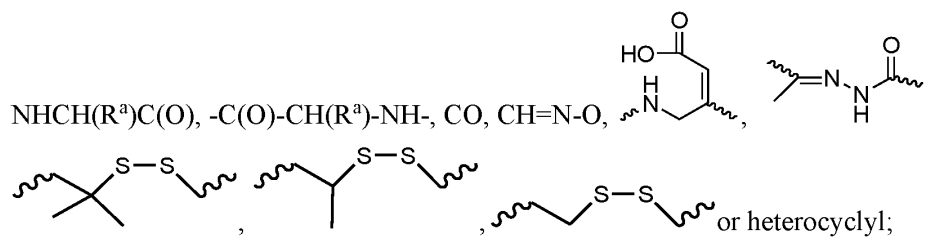
, or

;

Formula XXXIII

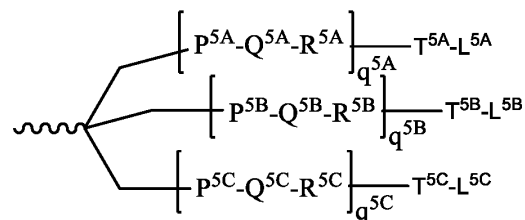
Formula XXXIV

wherein q^{2A} , q^{2B} , q^{3A} , q^{3B} , q^{4A} , q^{4B} , q^{5A} , q^{5B} and q^{5C} represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different; P^{2A} , P^{2B} , P^{3A} , P^{3B} , P^{4A} , P^{4B} , P^{5A} , P^{5B} , P^{5C} , T^{2A} , T^{2B} , T^{3A} , T^{3B} , T^{4A} , T^{4B} , T^{4A} , T^{5B} , T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH₂, CH₂NH or CH₂O; Q^{2A} , Q^{2B} , Q^{3A} , Q^{3B} , Q^{4A} , Q^{4B} , Q^{5A} , Q^{5B} , Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO₂, N(R^N), C(R')=C(R''), C≡C or C(O); R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{5C} are each independently for each occurrence absent, NH, O, S, CH₂, C(O)O, C(O)NH,



L^{2A} , L^{2B} , L^{3A} , L^{3B} , L^{4A} , L^{4B} , L^{5A} , L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain.

In some embodiments, the linker comprises:



Formula (VI)

,

wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative, e.g., as described herein.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, e.g., be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, e.g., be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, e.g., pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, e.g., oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, e.g., those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a preferred pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-

types rich in esterases include cells of the lung, renal cortex, and testis. Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

In one embodiment, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular TREM moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions

chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

In another embodiment, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Preferred embodiments are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O-, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

In another embodiment, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

In another embodiment, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – NHCHRAC(O)NHCHRBC(O)– (SEQ ID NO: 13), where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

The ASGPR binding moiety may be bound to any nucleotide position within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of a TREM. In an embodiment, the ASGPR moiety is bound to a nucleobase, terminus, or internucleotide linkage within a TREM. In an embodiment, the ASGPR moiety is bound to a nucleobase within a TREM. In an embodiment, the ASGPR binding moiety is bound to any adenine nucleobase within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of the TREM. In an embodiment, ASGPR binding moiety is bound to any cytosine nucleobase within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of the TREM. In an embodiment, it is bound to any guanosine nucleobase within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of the TREM. In an embodiment, it is bound to any uracil nucleobase within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of the TREM. In an embodiment, it is bound to any thymine nucleobase within a domain (ASt Domain1, DH Domain, ACH Domain, VL Domain, TH Domain, and/or ASt Domain2) of the TREM.

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 1 (*e.g.*, present within a nucleobase at TREM position 1). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 2 (*e.g.*, present within a

nucleobase at TREM position 2). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 3 (e.g., present within a nucleobase at TREM position 3). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 4 (e.g., present within a nucleobase at TREM position 4). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 5 (e.g., present within a nucleobase at TREM position 5). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 6 (e.g., present within a nucleobase at TREM position 6). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 7 (e.g., present within a nucleobase at TREM position 7). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 8 (e.g., present within a nucleobase at TREM position 8). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 9 (e.g., present within a nucleobase at TREM position 9).

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 10 (e.g., present within a nucleobase at TREM position 10). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 11 (e.g., present within a nucleobase at TREM position 11). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 12 (e.g., present within a nucleobase at TREM position 12). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 13 (e.g., present within a nucleobase at TREM position 13). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 14 (e.g., present within a nucleobase at TREM position 14). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 15 (e.g., present within a nucleobase at TREM position 15). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 16 (e.g., present within a nucleobase at TREM position 16). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 17 (e.g., present within a nucleobase at TREM position 17). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 18 (e.g., present within a nucleobase at TREM position 18). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 19 (e.g., present within a nucleobase at TREM position 19). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 20 (e.g., present within a nucleobase at TREM position 20). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 21 (e.g., present within

a nucleobase at TREM position 21). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 22 (e.g., present within a nucleobase at TREM position 22). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 23 (e.g., present within a nucleobase at TREM position 23). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 24 (e.g., present within a nucleobase at TREM position 24). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 25 (e.g., present within a nucleobase at TREM position 25). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 26 (e.g., present within a nucleobase at TREM position 26).

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 27 (e.g., present within a nucleobase at TREM position 27). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 28 (e.g., present within a nucleobase at TREM position 28). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 29 (e.g., present within a nucleobase at TREM position 29). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 30 (e.g., present within a nucleobase at TREM position 30). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 31 (e.g., present within a nucleobase at TREM position 31). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 32 (e.g., present within a nucleobase at TREM position 32). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 33 (e.g., present within a nucleobase at TREM position 33). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 34 (e.g., present within a nucleobase at TREM position 34). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 35 (e.g., present within a nucleobase at TREM position 35). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 36 (e.g., present within a nucleobase at TREM position 36). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 37 (e.g., present within a nucleobase at TREM position 37). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 38 (e.g., present within a nucleobase at TREM position 38). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 39 (e.g., present within a nucleobase at TREM position 39). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 40

(e.g., present within a nucleobase at TREM position 40). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 41 (e.g., present within a nucleobase at TREM position 41). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 42 (e.g., present within a nucleobase at TREM position 42). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 43 (e.g., present within a nucleobase at TREM position 43).

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 44 (e.g., present within a nucleobase at TREM position 44). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 45 (e.g., present within a nucleobase at TREM position 45). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 46 (e.g., present within a nucleobase at TREM position 46). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 47 (e.g., present within a nucleobase at TREM position 47). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 48 (e.g., present within a nucleobase at TREM position 48). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 49 (e.g., present within a nucleobase at TREM position 49).

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 50 (e.g., present within a nucleobase at TREM position 50). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 51 (e.g., present within a nucleobase at TREM position 51). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 52 (e.g., present within a nucleobase at TREM position 52). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 53 (e.g., present within a nucleobase at TREM position 53). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 54 (e.g., present within a nucleobase at TREM position 54). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 55 (e.g., present within a nucleobase at TREM position 55). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 56 (e.g., present within a nucleobase at TREM position 56). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 57 (e.g., present within a nucleobase at TREM position 57). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 58 (e.g., present within a nucleobase at TREM position 58). In an embodiment, the ASGPR binding

moiety is present within a TREM at TREM position 59 (e.g., present within a nucleobase at TREM position 59). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 60 (e.g., present within a nucleobase at TREM position 60). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 61 (e.g., present within a nucleobase at TREM position 61). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 62 (e.g., present within a nucleobase at TREM position 62). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 63 (e.g., present within a nucleobase at TREM position 63). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 64 (e.g., present within a nucleobase at TREM position 64).

In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 65 (e.g., present within a nucleobase at TREM position 65). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 66 (e.g., present within a nucleobase at TREM position 66). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 67 (e.g., present within a nucleobase at TREM position 67). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 68 (e.g., present within a nucleobase at TREM position 68). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 69 (e.g., present within a nucleobase at TREM position 69). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 70 (e.g., present within a nucleobase at TREM position 70). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 71 (e.g., present within a nucleobase at TREM position 71). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 72 (e.g., present within a nucleobase at TREM position 72). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 73 (e.g., present within a nucleobase at TREM position 73). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 74 (e.g., present within a nucleobase at TREM position 74). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 75 (e.g., present within a nucleobase at TREM position 75). In an embodiment, the ASGPR binding moiety is present within a TREM at TREM position 76 (e.g., present within a nucleobase at TREM position 76).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 1 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 2 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 3 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 4 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 5 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 6 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 7 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 8 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 9 (G).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 10 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 11 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 12 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 13 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 14 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 15 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 16 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 17 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 18 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 19 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 20 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 21 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 22 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 23 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 24 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 25 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 26 (A).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 27 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at

TREM position 28 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 29 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 30 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 31 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 32 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 33 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 34 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 35 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 36 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 37 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 38 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 39 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 40 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 41 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 42 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 43 (A).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 44 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 45 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 46 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 47 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 48 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 49 (C).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 50 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 51 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 52 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 53 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 54 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 55 (U). In an embodiment, the ASGPR binding moiety

is bound to a nucleobase at TREM position 56 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 57 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 58 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 59 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 60 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 61 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 62 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 63 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 64 (G).

In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 76 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 75 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 74 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 73 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 72 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 71 (U). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 70 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 69 (A). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 68 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 67 (G). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 66 (C). In an embodiment, the ASGPR binding moiety is bound to a nucleobase at TREM position 65 (G).

In an embodiment, the TREM comprising an ASGPR binding moiety 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 the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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, the TREM comprising an ASGPR binding moiety 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. In an embodiment the TREM comprising an ASGPR binding moiety 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 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4. In an embodiment, the TREM comprising an ASGPR binding moiety 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 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4.

In an embodiment, the TREM comprising an ASGPR binding moiety 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 provided in Table 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4. In an embodiment, the TREM comprising an ASGPR binding moiety 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 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4. In an embodiment, the TREM comprising an ASGPR binding moiety 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 4, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 4.

In an embodiment, the TREM comprising an ASGPR binding moiety is a compound provided in Table 12, *e.g.*, any one of Compound Nos. 99-131. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 99. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 100. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 101. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 102. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 103. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 104. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 105. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 106. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 107. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 108. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 109. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 110. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 111. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 112. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 113. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 114. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 115. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 116. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 117. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 118. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 119. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 120. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 121. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 122. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 123. In an embodiment, the TREM

comprising an ASGPR binding moiety is Compound 124. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 125. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 126. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 127. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 128. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 129. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 130. In an embodiment, the TREM comprising an ASGPR binding moiety is Compound 131.

In an embodiment, the TREM comprising an ASGPR binding moiety comprises a compound having 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 of a TREM provided in Table 12, *e.g.*, any one of Compounds 100-131 provided in Table 12. In an embodiment, the TREM comprising an ASGPR binding moiety 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 a TREM provided in Table 12, *e.g.*, any one of Compounds 100-131 disclosed in Table 12. In an embodiment, the TREM comprising an ASGPR binding moiety 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 a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of Compounds 100-131 disclosed in Table 12.

In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence provided in Table 12, *e.g.*, any one of SEQ ID NOs: 622-654. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 622. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 623. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 624. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 625. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 626. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 627. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 628. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 629. In an embodiment, the TREM comprising an ASGPR binding moiety

comprises SEQ ID NO. 630. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 631. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 632. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 633. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 634. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 635. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 636. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 637. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 638. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 639. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 640. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 641. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 642. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 643. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 644. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 645. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 646. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 647. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 648. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 649. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 650. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 651. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 652. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 653. In an embodiment, the TREM comprising an ASGPR binding moiety comprises SEQ ID NO. 654.

In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 provided in Table 12. In an embodiment, the TREM comprising an

ASGPR binding moiety 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 a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12. In an embodiment, the TREM comprising an ASGPR binding moiety 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 a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-652 provided in Table 12.

In an embodiment, the TREM comprising an ASGPR binding moiety is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 622. In an embodiment, the TREM comprising an ASGPR binding moiety is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 650. In an embodiment, the TREM comprising an ASGPR binding moiety is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 653.

In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs comprises by least 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18 nt, 20 nt, 25 nt, 30 nt, 40 nt, 45 nt, 50 nt, 55 nt, or more from SEQ ID NO. 622. In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from SEQ ID NO. 622. In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs comprises by least 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18 nt, 20 nt, 25 nt, 30 nt, 40 nt, 45 nt, 50 nt, 55 nt, or more from SEQ ID NO. 650. In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from SEQ ID NO. 650. In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs comprises by least 1 ribonucleotide

(nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18 nt, 20 nt, 25 nt, 30 nt, 40 nt, 45 nt, 50 nt, 55 nt, or more from SEQ ID NO. 653. In an embodiment, the TREM comprising an ASGPR binding moiety comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from SEQ ID NO. 653.

Chemically Modified TREMs

In some embodiments, a TREM entity (e.g., a TREM, a TREM core fragment or a TREM fragment described herein) further comprises a chemical modification, e.g., a modification described in any one of Tables 5-9, in addition to an ASGPR binding moiety. A chemical modification can be made according to methods known in the art. In an embodiment, a chemical modification is a modification that a cell, e.g., a human cell, does not make on an endogenous tRNA.

In an embodiment, a chemical 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 chemical modification is in a domain, linker or arm which does not have such modification in nature. In an embodiment, the chemical modification is at a position within a domain, linker or arm, which does not have such modification in nature. In an embodiment, the chemical modification is on a nucleotide which does not have such modification in nature. In an embodiment, the chemical modification is on a nucleotide at a position within a domain, linker or arm, which does not have such modification in nature.

Any of the nucleic acids featured in the disclosure can be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. et al. (Eds.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, e.g., 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, etc.); base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (e.g., at the 2'-position or 4'-position) or replacement of the sugar; and/or

backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of TREM compounds useful in the embodiments described herein include, but are not limited to TREMs containing modified backbones or no natural internucleoside linkages. TREMs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified TREMs will have a phosphorus atom in its internucleoside backbone.

Modified TREM backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that disclose the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301 ; 5,023,243; 5,177, 195; 5, 188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321, 131 ; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821 ; 5,541,316; 5,550, 111 ; 5,563,253; 5,571,799; 5,587,361 ; 5,625,050; 6,028,188; 6,124,445; 6, 160,109; 6,169, 170; 6, 172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683, 167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified TREM backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide,

sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

In other embodiments, suitable RNA mimetics are contemplated for use in TREMs, in which both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the TREMs of the disclosure are described in, for example, in Nielsen et al., *Science*, 1991, 254, 1497-1500.

Some embodiments featured in the disclosure include TREMs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular—CH₂—NH—CH₂—, —CH₂—N(CH₃)—O—CH₂— [known as a methylene (methylimino) or MMI backbone], —CH₂—O—N(CH₃)—CH₂—, —CH₂—N(CH₃)—N(CH₃)—CH₂— and —N(CH₃)—CH₂—CH₂— [wherein the native phosphodiester backbone is represented as—O—P—O—CH₂—] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the TREMs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506.

The TREMs featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Exemplary suitable modifications include O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. In other embodiments, TREMs may include one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of a TREM, or a group for improving the pharmacodynamic properties of a TREM, and other substituents having similar properties.

In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O—CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78:486- 504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₃)₂.

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions within the TREM, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked TREMs and the 5' position of 5' terminal nucleotide. TREMs can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application. The entire contents of each of the foregoing are hereby incorporated herein by reference.

TREMs can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the

purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as deoxy-thymine (dT), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie, International Edition*, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., *dsRNA Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

The TREM can also be modified to include one or more bicyclic sugar moieties. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring. Thus, in some embodiments an agent of the invention may include the RNA of a TREM can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH₂-O-2' bridge. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to oligonucleotide sequences has been shown to increase their stability in serum, and to reduce off-target effects (Elmen, J. et al, (2005) Nucleic Acids Research 33(1):439-447; Mook, OR. et al, (2007) Mol Cane Ther 6(3):833-843; Grunweller, A. et al, (2003) Nucleic Acids Research 31(12):3185-3193)

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a chemical modification provided in Table 5, or a combination thereof.

Table 5: Exemplary modifications

Name	
7-deaza-adenosine	2-(propyl)adenine
N1-methyl-adenosine	2'-azido-2'-deoxy-adenosine
N6, N6 (dimethyl)adenine	2'-Deoxy-2'-alpha-aminoadenosine
N6-cis-hydroxy-isopentenyl-adenosine	2'-Deoxy-2'-alpha-azidoadenosine
thio-adenosine	6-(alkyl)adenine
2-(amino)adenine	6-(methyl)adenine
2-(aminopropyl)adenine	6-(alkyl)adenine
2-(methylthio) N6 (isopentenyl)adenine	6-(methyl)adenine
2-(alkyl)adenine	7-(deaza)adenine
2-(aminoalkyl)adenine	8-(alkenyl)adenine
2-(aminopropyl)adenine	8-(alkynyl)adenine
2-(halo)adenine	8-(amino)adenine
	8-(thioalkyl)adenine

8-(alkenyl)adenine
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
2'-beta-Trifluoromethyladenosine
2-Chloroadenosine
2'-Deoxy-2',2'-difluoroadenosine
2'-Deoxy-2'-alpha-mercaptopadenosine
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-mercaptopadenosine
2'-Deoxy-2'-beta-thiomethoxyadenosine
2-Fluoroadenosine
2-Iodoadenosine
2-Mercaptopadenosine
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
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
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
1-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- 1-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
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
5-Trifluoromethyl-Cytidine
N4-Amino-cytidine
N4-Benzoyl-cytidine
pseudoisocytidine
6-thio-guanosine
7-deaza-guanosine
8-oxo-guanosine
N1-methyl-guanosine
alpha-thio-guanosine
2-(propyl)guanine
2-(alkyl)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-(alkyl)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
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
1-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
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
allylamino- thymidine

aza thymidine
deaza thymidine
deoxy-thymidine
5-propynyl uracil
alpha-thio-uridine
1-(aminoalkylamino-carbonylethynyl)-2(thio)-pseudouracil
1-(aminoalkylaminocarbonylethynyl)-2,4-(dithio)pseudouracil
1-(aminoalkylaminocarbonylethynyl)-4(thio)pseudouracil
1-(aminoalkylaminocarbonylethynyl)-pseudouracil
1-(aminocarbonylethynyl)-2(thio)-pseudouracil
1-(aminocarbonylethynyl)-2,4-(dithio)pseudouracil
1-(aminocarbonylethynyl)-4(thio)pseudouracil
1-(aminocarbonylethynyl)-pseudouracil
1-substituted 2-(thio)-pseudouracil
1-substituted 2,4-(dithio)pseudouracil
1-substituted 4 (thio)pseudouracil
1-substituted pseudouracil
1-(aminoalkylamino-carbonylethynyl)-2- (thio)-pseudouracil
1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine
1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-Uridine
1-Methyl-pseudo-UTP
2 (thio)pseudouracil
2' deoxy uridine
2' fluorouridine
2-(thio)uracil
2,4-(dithio)pseudouracil
2'-methyl, 2'-amino, 2'azido, 2'fluoro-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
5-(1,3-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-(alkyl)-2-(thio)pseudouracil
5-(alkyl)-2,4 (dithio)pseudouracil
5-(alkyl)-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-1-alkyl)uracil
5-(methoxy)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-(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-(propynyl)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
1-methyl-1-deaza-pseudouridine
1-propynyl-uridine
1-taurinomethyl-1-methyl-uridine
1-taurinomethyl-4-thio-uridine
1-taurinomethyl-pseudouridine
2-methoxy-4-thio-pseudouridine
2-thio- 1-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)- 1 -(2-Hydroxypropyl)pseudouridine
(2S)- 1 -(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-Diethoxyethyl)pseudouridine
1-(2,4,6-Trimethylbenzyl)pseudouridine
1-(2,4,6-Trimethyl-benzyl)pseudo-uridine
1-(2,4,6-Trimethyl-phenyl)pseudo-uridine
1-(2-Amino-2-carboxyethyl)pseudo-uridine
1-(2-Amino-ethyl)pseudouridine
1-(2-Hydroxyethyl)pseudouridine
1-(2-Methoxyethyl)pseudouridine
1-(3,4-Bis-trifluoromethoxybenzyl)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-Methanesulfonylbenzyl)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-benzyl)pseudouridine
1-(4-Nitro-phenyl)pseudouridine
1-(4-Thiomethoxybenzyl)pseudouridine
1-(4-Trifluoromethoxybenzyl)pseudouridine
1-(4-Trifluoromethylbenzyl)pseudouridine
1-(5-Amino-pentyl)pseudouridine
1-(6-Amino-hexyl)pseudouridine
1,6-Dimethyl-pseudouridine
1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine
1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionyl} pseudouridine
1-Acetyl-pseudouridine
1-Alkyl-6-(1-propynyl)-pseudo-uridine
1-Alkyl-6-(2-propynyl)-pseudo-uridine
1-Alkyl-6-allyl-pseudo-uridine
1-Alkyl-6-ethynyl-pseudo-uridine
1-Alkyl-6-homoallyl-pseudo-uridine
1-Alkyl-6-vinyl-pseudo-uridine
1-Allyl-pseudouridine
1-Aminomethyl-pseudo-uridine
1-Benzoyl-pseudouridine
1-Benzylloxymethylpseudouridine
1-Benzyl-pseudo-uridine
1-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
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
1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-uridine
1-Methyl-6-(4-morpholino)-pseudo-uridine
1-Methyl-6-(4-thiomorpholino)-pseudo-uridine
1-Methyl-6-(substituted phenyl)pseudo-uridine
1-Methyl-6-amino-pseudo-uridine
1-Methyl-6-azido-pseudo-uridine
1-Methyl-6-bromo-pseudo-uridine
1-Methyl-6-butyl-pseudo-uridine
1-Methyl-6-chloro-pseudo-uridine
1-Methyl-6-cyano-pseudo-uridine
1-Methyl-6-dimethylamino-pseudo-

uridine
1-Methyl-6-ethoxy-pseudo-uridine
1-Methyl-6-ethylcarboxylate-pseudo-uridine
1-Methyl-6-ethyl-pseudo-uridine
1-Methyl-6-fluoro-pseudo-uridine
1-Methyl-6-formyl-pseudo-uridine
1-Methyl-6-hydroxyamino-pseudo-uridine
1-Methyl-6-hydroxy-pseudo-uridine
1-Methyl-6-iodo-pseudo-uridine
1-Methyl-6-iso-propyl-pseudo-uridine
1-Methyl-6-methoxy-pseudo-uridine
1-Methyl-6-methylamino-pseudo-uridine
1-Methyl-6-phenyl-pseudo-uridine
1-Methyl-6-propyl-pseudo-uridine
1-Methyl-6-tert-butyl-pseudo-uridine
1-Methyl-6-trifluoromethoxy-pseudo-uridine
1-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-Trifluoroacetylpsudouridine
1-Trifluoromethyl-pseudouridine
1-Vinylpseudouridine

2,2'-anhydro-uridine
2'-bromo-deoxyuridine
2'-F-5-Methyl-2'-deoxy-uridine
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-mercaptopuridin
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-mercaptopuridine
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
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
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) TP
Pseudouridine 1-(4-methylbenzoic acid) TP
Pseudouridine 1-[3-(2-ethoxy)]propionic acid
Pseudouridine 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine 1-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine 1-[3-{2-(2-ethoxy)-ethoxy}]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-N1-7-heptanoic acid
Pseudo-uridine-N1-methyl-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

Name	
2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine	5-formylcytidine
2-methylthio-N6-methyladenosine	5-hydroxymethylcytidine
2-methylthio-N6-threonyl carbamoyladenosine	5-methylcytidine
N6-glycylcarbamoyladenosine	N4-acetylcytidine
N6-isopentenyladenosine	2'-O-methylcytidine
N6-methyladenosine	2'-O-methylcytidine
N6-threonylcarbamoyladenosine	5,2'-O-dimethylcytidine
1,2'-O-dimethyladenosine	5-formyl-2'-O-methylcytidine
1-methyladenosine	lysidine
2'-O-methyladenosine	N4,2'-O-dimethylcytidine
2'-O-ribosyladenosine (phosphate)	N4-acetyl-2'-O-methylcytidine
2-methyladenosine	N4-methylcytidine
2-methylthio-N6 isopentenyladenosine	N4,N4-Dimethyl-2'-OMe-Cytidine
2-methylthio-N6-hydroxynorvalyl carbamoyladenosine	7-methylguanosine
2'-O-methyladenosine	N2,2'-O-dimethylguanosine
2'-O-ribosyladenosine (phosphate)	N2-methylguanosine
isopentenyladenosine	wyosine
N6-(cis-hydroxyisopentenyl)adenosine	1,2'-O-dimethylguanosine
N6,2'-O-dimethyladenosine	1-methylguanosine
N6,2'-O-dimethyladenosine	2'-O-methylguanosine
N6,N6,2'-O-trimethyladenosine	2'-O-ribosylguanosine (phosphate)
N6,N6-dimethyladenosine	2'-O-methylguanosine
N6-acetyladenosine	2'-O-ribosylguanosine (phosphate)
N6-hydroxynorvalylcarbamoyladenosine	7-aminomethyl-7-deazaguanosine
N6-methyl-N6-threonylcarbamoyladenosine	7-cyano-7-deazaguanosine
2-methyladenosine	archaeosine
2-methylthio-N ⁶ -isopentenyladenosine	methylwyosine
2-thiocytidine	N2,7-dimethylguanosine
3-methylcytidine	

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
1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine
1-methylpseduouridine
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-aminomethyl-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-methoxycarbonylmethyl-2-thiouridine
5-methoxycarbonylmethyluridine
5-methoxyuridine
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
N1-methyl-pseudo-uridine

uridine 5-oxyacetic acid
uridine 5-oxyacetic acid methyl ester
3-(3-Amino-3-carboxypropyl)-Uridine
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 chemical modification provided in Table 7, or a combination thereof.

Table 7: Additional exemplary chemical modifications

Name
2,6-(diamino)purine
1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
1,3-(diaza)-2-(oxo)-phenthiazin-1-yl
1,3-(diazia)-2-(oxo)-phenoxazin-1-yl
1,3,5-(triazia)-2,6-(dioxo)-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'fluro-2 '-deoxyribose
2' -fluro-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)isocarbostyryl
3-(methyl)isocarbostyryl
4-(fluoro)-6-(methyl)benzimidazole
4-(methyl)benzimidazole
4-(methyl)indolyl
4,6-(dimethyl)indolyl
5 nitroindole
5 substituted pyrimidines
5-(methyl)isocarbostyryl
5-nitroindole
6-(aza)pyrimidine
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-(diazia)-2-(oxo)-phenoxazin-1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin- 1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-

(oxo)-phenoxazin-1-yl
7-(aza)indolyl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-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-(diaz)-2-(oxo)-phenoxazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl
7-(propynyl)isocarbostyryl
7-(propynyl)isocarbostyryl, propynyl-7-(aza)indolyl
7-deaza-inosinyl
7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
7-substituted 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl
9-(methyl)-imidizopyridinyl
aminoindolyl
anthracenyl
bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
difluorotolyl
hypoxanthine
imidizopyridinyl
inosinyl
isocarbostyryl
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
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
Formycin A
Formycin B
Pyrrolosine
2'-OH-ara-adenosine
2'-OH-ara-cytidine

2' -OH-ara-uridine	5-(2-carbomethoxyvinyl)uridine
2' -OH-ara-guanosine	N6-(19-Amino-pentaoxonadecyl)adenosine

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a chemical modification provided in Table 8, or a combination thereof.

Table 8: Exemplary backbone modifications

Name	
3'-alkylene phosphonates	phosphorothioates
3'-amino phosphoramidate	phosphotriesters
alkene containing backbones	PNA
aminoalkylphosphoramidates	siloxane backbones
aminoalkylphosphotriesters	sulfamate backbones
boranophosphates	sulfide sulfoxide and sulfone backbones
-CH ₂ -O-N(CH ₃)-CH ₂ -	sulfonate and sulfonamide backbones
-CH ₂ -N(CH ₃)-N(CH ₃)-CH ₂ -	thionoalkylphosphonates
-CH ₂ -NH-CH ₂ -	thionoalkylphosphotriesters
chiral phosphonates	thionophosphoramidates
chiral phosphorothioates	methylphosphonates
formacetyl and thioformacetyl backbones	phosphonoacetates
methylene (methylimino)	Phosphorothioate
methylene formacetyl and thioformacetyl backbones	Constrained nucleic acid (CNA)
methyleneimino and methylenehydrazino backbones	2'-O-methyl
morpholino linkages	2'-O-methoxyethyl (MOE)
-N(CH ₃)-CH ₂ -CH ₂ -	2' Fluoro
oligonucleosides with heteroatom internucleoside linkage	Locked nucleic acid (LNA)
phosphinates	(S)-constrained ethyl (<i>cEt</i>)
phosphoramidates	Fluoro hexitol nucleic acid (FHNA)
phosphorodithioates	5'-phosphorothioate
phosphorothioate internucleoside linkages	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
Constrained nucleic acid (CNA)
2'-O-methyl
2'-O-methoxyethyl (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(S)-constrained ethyl (<i>cEt</i>)

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 modifications

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 (<i>cEt</i>)
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

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 R₀ forms a linker region, *e.g.*, a Linker 1 region;
- b) under physiological conditions residues R₁-R₂-R₃-R₄-R₅-R₆-R₇ and residues R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁ form a stem region, *e.g.*, an AStD stem region;

- c) under physiological conditions residues R₈-R₉ forms a linker region, *e.g.*, a Linker 2 region;
- d) under physiological conditions residues -R₁₀-R₁₁-R₁₂-R₁₃-R₁₄ R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈ form a stem-loop region, *e.g.*, a D arm Region;
- e) under physiological conditions residue -R₂₉ forms a linker region, *e.g.*, a Linker 3 Region;
- f) under physiological conditions residues -R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆ form a stem-loop region, *e.g.*, an AC arm region;
- g) under physiological conditions residue -[R₄₇]_x comprises a variable region, *e.g.*, as described herein;
- h) under physiological conditions residues -R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄ form a stem-loop region, *e.g.*, a T arm Region; or
- i) under physiological conditions residue R₇₂ 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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀= absent;

R₁₄, R₅₇=are independently A or absent;

R₂₆= A, C, G or absent;

R₅, R₆, R₁₅, R₁₆, R₂₁, R₃₀, R₃₁, R₃₂, R₃₄, R₃₇, R₄₁, R₄₂, R₄₃, R₄₄, R₄₅, R₄₈, R₄₉, R₅₀, R₅₈, R₅₉, R₆₃, R₆₄, R₆₆, R₆₇= are independently N or absent;

R₁₁, R₃₅, R₆₅= are independently A, C, U or absent;

R₁, R₉, R₂₀, R₃₈, R₄₀, R₅₁, R₅₂, R₅₆= are independently A, G or absent;

R₇, R₂₂, R₂₅, R₂₇, R₂₉, R₄₆, R₅₃, R₇₂= are independently A, G, U or absent;

R₂₄, R₆₉= are independently A, U or absent;

R₇₀, R₇₁= are independently C or absent;

R₃, R₄= are independently C, G or absent;

R₁₂, R₃₃, R₃₆, R₆₂, R₆₈= are independently C, G, U or absent;

R₁₃, R₁₇, R₂₈, R₃₉, R₅₅, R₆₀, R₆₁= are independently C, U or absent;

R₁₀, R₁₉, R₂₃= are independently G or absent;

R₂= G, U or absent;

R₈, R₁₈, R₅₄= are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀, R₁₈= are absent;

R₁₄, R₂₄, R₅₇= are independently A or absent;

R₁₅, R₂₆, R₆₄= are independently A, C, G or absent;

R₁₆, R₃₁, R₅₀, R₅₉= are independently N or absent;

R₁₁, R₃₂, R₃₇, R₄₁, R₄₃, R₄₅, R₄₉, R₆₅, R₆₆= are independently A, C, U or absent;

R₁, R₅, R₉, R₂₅, R₂₇, R₃₈, R₄₀, R₄₆, R₅₁, R₅₆= are independently A, G or absent;

R₇, R₂₂, R₂₉, R₄₂, R₄₄, R₅₃, R₆₃, R₇₂= are independently A, G, U or absent;

R₆, R₃₅, R₆₉= are independently A, U or absent;

R₅₅, R₆₀, R₇₀, R₇₁= are independently C or absent;

R₃= C, G or absent;

R₁₂, R₃₆, R₄₈= are independently C, G, U or absent;

R₁₃, R₁₇, R₂₈, R₃₀, R₃₄, R₃₉, R₅₈, R₆₁, R₆₂, R₆₇, R₆₈= are independently C, U or absent;

R₄, R₁₀, R₁₉, R₂₀, R₂₃, R₅₂= are independently G or absent;

R₂, R₈, R₃₃= are independently G, U or absent;

R₂₁, R₅₄= are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-

R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀, R₁₈= are absent;

R₁₄, R₂₄, R₅₇, R₇₂=are independently A or absent;

R₁₅, R₂₆, R₆₄= are independently A, C, G or absent;

R₁₆, R₃₁, R₅₀= are independently N or absent;

R₁₁, R₃₂, R₃₇, R₄₁, R₄₃, R₄₅, R₄₉, R₆₅, R₆₆= are independently A, C, U or absent;

R₅, R₉, R₂₅, R₂₇, R₃₈, R₄₀, R₄₆, R₅₁, R₅₆= are independently A, G or absent;

R₇, R₂₂, R₂₉, R₄₂, R₄₄, R₅₃, R₆₃= are independently A, G, U or absent;

R₆, R₃₅= are independently A, U or absent;

R₅₅, R₆₀, R₆₁, R₇₀, R₇₁= are independently C or absent;

R₁₂, R₄₈, R₅₉= are independently C, G, U or absent;

R₁₃, R₁₇, R₂₈, R₃₀, R₃₄, R₃₉, R₅₈, R₆₂, R₆₇, R₆₈= are independently C, U or absent;

R₁, R₂, R₃, R₄, R₁₀, R₁₉, R₂₀, R₂₃, R₅₂= are independently G or absent;

R₃₃, R₃₆= are independently G, U or absent;

R₈, R₂₁, R₅₄, R₆₉= are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₅₇=A or absent;

R₉,R₂₇=are independently A,C,G or absent;

R₁,R₂,R₃,R₄,R₅,R₆,R₇,R₁₁,R₁₂,R₁₆,R₂₁,R₂₂,R₂₃,R₂₅,R₂₆,R₂₉,R₃₀,R₃₁,R₃₂,R₃₃,R₃₄,R₃₇,R₄₂,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₁,R₅₈,R₆₂,R₆₃,R₆₄,R₆₅,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀,R₇₁=are independently N or absent;

R₁₃,R₁₇,R₄₁=are independently A,C,U or absent;

R₁₉,R₂₀,R₂₄,R₄₀,R₅₆=are independently A,G or absent;

R₁₄,R₁₅,R₇₂=are independently A,G,U or absent;

R₁₈= A,U or absent;

R₃₈= C or absent;

R₃₅,R₄₃,R₆₁=are independently C,G,U or absent;

R₂₈,R₅₅,R₅₉,R₆₀=are independently C,U or absent;

R₀,R₁₀,R₅₂=are independently G or absent;

R₈,R₃₉=are independently G,U or absent;

R₃₆,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₁₈= absent;

R₂₄,R₅₇=are independently A or absent;

R₄₁= A,C or absent;

R₃,R₇,R₃₄,R₅₀=are independently A,C,G or absent;

R₂,R₅,R₆,R₁₂,R₂₆,R₃₂,R₃₇,R₄₄,R₅₈,R₆₆,R₆₇,R₆₈,R₇₀=are independently N or absent;

R₄₉,R₇₁=are independently A,C,U or absent;

R₁,R₁₅,R₁₉,R₂₅,R₂₇,R₄₀,R₄₅,R₄₆,R₅₆,R₇₂=are independently A,G or absent;

R₁₄,R₂₉,R₆₃=are independently A,G,U or absent;

R₁₆,R₂₁=are independently A,U or absent;

R₃₈,R₆₁=are independently C or absent;

R₃₃,R₄₈=are independently C,G or absent;

R₄,R₉,R₁₁,R₄₃,R₆₂,R₆₄,R₆₉=are independently C,G,U or absent;

R₁₃,R₂₂,R₂₈,R₃₀,R₃₁,R₃₅,R₅₅,R₆₀,R₆₅=are independently C,U or absent;

R₀,R₁₀,R₂₀,R₂₃,R₅₁,R₅₂=are independently G or absent;

R₈,R₃₉,R₄₂=are independently G,U or absent;

R₁₇,R₃₆,R₅₃,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₁₈=is absent;

R₁₅,R₂₁,R₂₄,R₄₁,R₅₇=are independently A or absent;

R₃₄,R₄₄=are independently A,C or absent;

R₃,R₅,R₅₈=are independently A,C,G or absent;

R₂,R₆,R₆₆,R₇₀=are independently N or absent;

R₃₇,R₄₉=are independently A,C,U or absent;

R₁,R₂₅,R₂₉,R₄₀,R₄₅,R₄₆,R₅₀=are independently A,G or absent;

R₁₄,R₆₃,R₆₈=are independently A,G,U or absent;

R₁₆= A,U or absent;

R₃₈,R₆₁=are independently C or absent;

R₇,R₁₁,R₁₂,R₂₆,R₄₈=are independently C,G or absent;

R₆₄,R₆₇,R₆₉=are independently C,G,U or absent;

R₄,R₁₃,R₂₂,R₂₈,R₃₀,R₃₁,R₃₅,R₄₃,R₅₅,R₆₀,R₆₂,R₆₃,R₇₁=are independently C,U or absent;

R₀,R₁₀,R₁₉,R₂₀,R₂₃,R₂₇,R₃₃,R₅₁,R₅₂,R₅₆,R₇₂=are independently G or absent;

R₈,R₉,R₃₂,R₃₉,R₄₂=are independently G,U or absent;

R₁₇,R₃₆,R₅₃,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈=are absent;

R₄₁= A or absent;

R₁₄,R₄₈,R₅₆=are independently A,C,G or absent;

R₂,R₄,R₅,R₆,R₁₂,R₁₇,R₂₆,R₂₉,R₃₀,R₃₁,R₄₄,R₄₅,R₄₆,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₅,R₆₆,R₆₇,R₆₈,R₇₀,R₇₁=
are independently N or absent;

R₁₁,R₁₃,R₂₂,R₄₂,R₅₅,R₅₉=are independently A,C,U or absent;

R₉,R₁₅,R₂₄,R₂₇,R₃₄,R₃₇,R₅₁,R₇₂=are independently A,G or absent;

R₁,R₇,R₂₅,R₆₉=are independently A,G,U or absent;

R₄₀,R₅₇=are independently A,U or absent;

R₆₀= C or absent;

R₃₃= C,G or absent;

R₂₁,R₃₂,R₄₃,R₆₄=are independently C,G,U or absent;

R₃,R₁₆,R₂₈,R₃₅,R₃₆,R₆₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₅₂=are independently G or absent;

R₅₄= G,U or absent;

R₈,R₂₃,R₃₈,R₃₉,R₅₃=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈=are absent

R₂₄,R₄₁,R₄₆,R₆₂=are independently A or absent;

R₅₉= A,C or absent;

R₁₄,R₅₆,R₆₆=are independently A,C,G or absent;

R₁₇,R₂₉=are independently N or absent;

R₁₁,R₂₆,R₄₂,R₅₅=are independently A,C,U or absent;

R₁,R₉,R₁₂,R₁₅,R₂₅,R₃₄,R₃₇,R₄₈,R₅₁,R₆₇,R₆₈,R₆₉,R₇₀,R₇₂=are independently A,G or absent;

R₄₄,R₄₅,R₅₈=are independently A,G,U or absent;

R₄₀,R₅₇=are independently A,U or absent;

R₅,R₂₈,R₆₀=are independently C or absent;

R₃₃,R₆₅=are independently C,G or absent;

R₂₁,R₄₃,R₇₁=are independently C,G,U or absent;

R₃,R₆,R₁₃,R₂₂,R₃₂,R₃₅,R₃₆,R₆₁,R₆₃,R₆₄=are independently C,U or absent;

R₇,R₁₀,R₁₉,R₂₀,R₂₇,R₄₉,R₅₂=are independently G or absent;

R₅₄= G,U or absent;

R₂,R₄,R₈,R₁₆,R₂₃,R₃₀,R₃₁,R₃₈,R₃₉,R₅₀,R₅₃=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-
R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈=are absent

R₂₄,R₄₀,R₄₁,R₄₆,R₆₂=are independently A or absent;

R₅₉= A,C or absent;

R₁₄,R₅₆,R₆₆=are independently A,C,G or absent;

R₁₁,R₂₆,R₄₂,R₅₅=are independently A,C,U or absent;

R₁,R₉,R₁₂,R₁₅,R₃₄,R₃₇,R₄₈,R₅₁,R₆₇,R₆₈,R₆₉,R₇₀=are independently A,G or absent;

R₄₄,R₄₅,R₅₈=are independently A,G,U or absent;

R₅₇= A,U or absent;

R₅,R₂₈,R₆₀=are independently C or absent;

R₃₃,R₆₅=are independently C,G or absent;

R₁₇,R₂₁,R₂₉=are independently C,G,U or absent;

R₃,R₆,R₁₃,R₂₂,R₃₂,R₃₅,R₃₆,R₄₃,R₆₁,R₆₃,R₆₄,R₇₁=are independently C,U or absent;

R₇,R₁₀,R₁₉,R₂₀,R₂₅,R₂₇,R₄₉,R₅₂,R₇₂=are independently G or absent;

R₅₄= G,U or absent;

R₂,R₄,R₈,R₁₆,R₂₃,R₃₀,R₃₁,R₃₈,R₃₉,R₅₀,R₅₃=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent

R₂₄,R₇₁=are independently A,C or absent;

R₃₃,R₄₆=are independently A,C,G or absent;

R₂,R₃,R₄,R₅,R₆,R₁₂,R₁₆,R₂₂,R₂₆,R₂₉,R₃₁,R₃₂,R₄₄,R₄₈,R₄₉,R₅₈,R₆₃,R₆₄,R₆₆,R₆₇,R₆₈,R₆₉=are independently N or absent;

R₁₃,R₂₁,R₃₄,R₄₁,R₅₇,R₆₅=are independently A,C,U or absent;

R₉,R₁₀,R₁₄,R₁₅,R₂₀,R₂₇,R₃₇,R₄₀,R₅₁,R₅₆,R₇₂=are independently A,G or absent;

R₇,R₂₅,R₄₂=are independently A,G,U or absent;

R₃₉= C or absent;

R₅₀,R₆₂=are independently C,G or absent;

R₃₀,R₄₃,R₄₅,R₅₅,R₇₀=are independently C,G,U or absent;

R₈,R₁₁,R₁₇,R₁₈,R₂₈,R₃₅,R₅₃,R₅₉,R₆₀,R₆₁=are independently C,U or absent;

R₁₉,R₅₂=are independently G or absent;

R₁= G,U or absent;

R₂₃,R₃₆,R₃₈,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₃=are independently absent;

R₉,R₄₀=are independently A or absent;

R₂₄,R₇₁=are independently A,C or absent;

R₆₇,R₆₈=are independently A,C,G or absent;

R₂,R₆,R₆₆=are independently N or absent;

R₅₇,R₆₃=are independently A,C,U or absent;

R₁₀,R₁₄,R₂₇,R₃₃,R₃₇,R₄₄,R₄₆,R₅₁,R₅₆,R₆₄,R₇₂=are independently A,G or absent;

R₇,R₁₂,R₂₆,R₆₅=are independently A,U or absent;

R₃₉,R₆₁,R₆₂=are independently C or absent;

R₃,R₃₁,R₄₅,R₇₀=are independently C,G or absent;

R₄,R₅,R₂₉,R₄₃,R₅₅=are independently C,G,U or absent;

R₈,R₁₁,R₁₃,R₃₀,R₃₂,R₃₄,R₃₅,R₄₁,R₄₈,R₅₃,R₅₉,R₆₀=are independently C,U or absent;

R₁₅,R₁₉,R₂₀,R₂₅,R₄₂,R₅₀,R₅₂=are independently G or absent;

R₁,R₂₂,R₄₉,R₅₈,R₆₉=are independently G,U or absent;

R₁₆,R₂₁,R₂₈,R₃₆,R₃₈,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₃=are absent

R₉,R₁₂,R₄₀,R₆₅,R₇₁=are independently A or absent;

R₂,R₂₄,R₅₇=are independently A,C or absent;

R₆,R₁₄,R₂₇,R₄₆,R₅₁,R₅₆,R₆₄,R₆₇,R₆₈=are independently A,G or absent;

R₃,R₃₁,R₃₅,R₃₉,R₆₁,R₆₂=are independently C or absent;

R₆₆= C,G or absent;

R₅,R₈,R₂₉,R₃₀,R₃₂,R₃₄,R₄₁,R₄₃,R₄₈,R₅₅,R₅₉,R₆₀,R₆₃=are independently C,U or absent;

R₁₀,R₁₅,R₁₉,R₂₀,R₂₅,R₃₃,R₃₇,R₄₂,R₄₄,R₄₅,R₄₉,R₅₀,R₅₂,R₆₉,R₇₀,R₇₂=are independently G or absent;

R₂₂,R₅₈=are independently G,U or absent;

R₁, R₄, R₇, R₁₁, R₁₃, R₁₆, R₂₁, R₂₆, R₂₈, R₃₆, R₃₈, R₅₃, R₅₄ are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀ =absent

R₁₄, R₃₉, R₅₇ are independently A or absent;

R₄₁ = A, C or absent;

R₁₀, R₁₅, R₂₇, R₃₃, R₆₂ are independently A, C, G or absent;

R₃, R₄, R₅, R₆, R₁₂, R₁₃, R₁₆, R₂₄, R₂₆, R₂₉, R₃₀, R₃₁, R₃₂, R₃₄, R₄₂, R₄₄, R₄₅, R₄₆, R₄₈, R₄₉, R₅₈, R₆₃, R₆₄, R₆₆, R₆₇, R₆₈, R₆₉, R₇₀ are independently N or absent;

R₆₅ = A, C, U or absent;

R₉, R₂₅, R₃₇, R₄₀, R₅₂, R₅₆ are independently A, G or absent;

R₇, R₂₀, R₅₁ are independently A, G, U or absent;

R₁₈,R₃₈,R₅₅=are independently C or absent;

R₂= C, G or absent;

R₂₁,R₂₈,R₄₃,R₅₀=are independently C,G,U or absent;

R₁₁,R₂₂,R₂₃,R₃₅,R₃₆,R₅₉,R₆₀,R₆₁,R₇₁,R₇₂=are independently C,U or absent;

R₁,R₁₉=are independently G or absent;

R₁₇= G,U or absent;

R₈,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent;

R₁₄,R₂₄,R₂₆,R₂₉,R₃₉,R₄₁,R₄₅,R₅₇=are independently A or absent;

R₄₄= A,C or absent;

R₂₇,R₆₂=are independently A,C,G or absent;

R₁₆= A,C,G,U or absent;

R₃₀,R₇₀=are independently A,C,U or absent;

R₅,R₇,R₉,R₂₅,R₃₄,R₃₇,R₄₀,R₄₆,R₅₂,R₅₆,R₅₈,R₆₆=are independently A,G or absent;

R₂₀,R₅₁=are independently A,G,U or absent;

R₃₅,R₃₈,R₄₃,R₅₅,R₆₉=are independently C or absent;

R₂,R₄,R₁₅=are independently C,G or absent;

R₁₃= C,G,U or absent;

R₆,R₁₁,R₂₈,R₃₆,R₄₈,R₄₉,R₅₀,R₆₀,R₆₁,R₆₇,R₆₈,R₇₁,R₇₂=are independently C,U or absent;

R₁,R₃,R₁₀,R₁₉,R₃₃,R₆₃=are independently G or absent;

R₈,R₁₇,R₂₁,R₆₄=are independently G,U or absent;

R₁₂,R₂₂,R₃₁,R₃₂,R₄₂,R₅₃,R₅₄,R₆₅=are independently U or absent;

R₅₉= U, or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₄,R₂₄,R₂₆,R₂₉,R₃₄,R₃₉,R₄₁,R₄₅,R₅₇,R₅₈=are independently A or absent;

R₄₄,R₇₀=are independently A,C or absent;

R₆₂= A,C,G or absent;

R₁₆= N or absent;

R₅,R₇,R₉,R₂₀,R₄₀,R₄₆,R₅₁,R₅₂,R₅₆,R₆₆=are independently A,G or absent;

R₂₈,R₃₅,R₃₈,R₄₃,R₅₅,R₆₇,R₆₉=are independently C or absent;

R₄,R₁₅=are independently C,G or absent;

R₆,R₁₁,R₁₃,R₃₀,R₄₈,R₄₉,R₅₀,R₆₀,R₆₁,R₆₈,R₇₁,R₇₂=are independently C,U or absent;

R₁,R₂,R₃,R₁₀,R₁₉,R₂₅,R₂₇,R₃₃,R₃₇,R₆₃=are independently G or absent;

R₈,R₂₁,R₆₄=are independently G,U or absent;

R₁₂,R₁₇,R₂₂,R₃₁,R₃₂,R₃₆,R₄₂,R₅₃,R₅₄, R₅₉,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-
R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈=are absent;

R₁₄,R₂₄,R₅₇=are independently A or absent;

R₉,R₂₆,R₂₇,R₃₃,R₅₆=are independently A,C,G or absent;

R₂,R₄,R₅,R₆,R₁₂,R₁₃,R₁₆,R₂₁,R₂₂,R₂₅,R₂₉,R₃₀,R₃₁,R₃₂,R₃₄,R₄₁,R₄₂,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₁₇,R₂₃,R₄₃,R₆₅,R₇₁=are independently A,C,U or absent;

R₁₅,R₄₀,R₅₁,R₅₂=are independently A,G or absent;

R₁,R₇,R₇₂=are independently A,G,U or absent;

R₃,R₁₁,R₃₇,R₆₀,R₆₄=are independently C,G,U or absent;

R₂₈,R₃₅,R₅₅,R₅₉,R₆₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀=are independently G or absent;

R₃₉= G,U or absent;

R₈,R₃₆,R₃₈,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₄,R₂₄,R₅₇=are independently A or absent;

R₁₇,R₇₁=are independently A,C or absent;

R₂₅,R₂₆,R₃₃,R₄₄,R₄₆,R₅₆,R₆₉=are independently A,C,G or absent;

R₄,R₅,R₁₂,R₂₂,R₂₉,R₃₀,R₄₈,R₄₉,R₆₃,R₆₇,R₆₈=are independently N or absent;

R₃₁,R₄₃,R₆₂,R₆₅,R₇₀=are independently A,C,U or absent;

R₁₅,R₂₇,R₃₄,R₄₀,R₄₁,R₅₁,R₅₂=are independently A,G or absent;

R₂,R₇,R₂₁,R₄₅,R₅₀,R₅₈,R₆₆,R₇₂=are independently A,G,U or absent;

R₃,R₁₃,R₃₂,R₃₇,R₄₂,R₆₀,R₆₄=are independently C,G,U or absent;

R₆,R₁₁,R₂₈,R₃₅,R₅₅,R₅₉,R₆₁=are independently C,U or absent;

R₉,R₁₀,R₁₉,R₂₀=are independently G or absent;

R₁,R₁₆,R₃₉=are independently G,U or absent;

R₈,R₃₆,R₃₈,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₄,R₂₄,R₄₁,R₅₇=are independently A or absent;

R₁₇,R₇₁=are independently A,C or absent;

R₅,R₂₅,R₂₆,R₄₆,R₅₆,R₆₉=are independently A,C,G or absent;

R₄,R₂₂,R₂₉,R₃₀,R₄₈,R₄₉,R₆₃,R₆₈=are independently N or absent;

R₄₃,R₆₂,R₆₅,R₇₀=are independently A,C,U or absent;

R₁₅,R₂₇,R₃₃,R₃₄,R₄₀,R₅₁,R₅₂=are independently A,G or absent;

R₂,R₇,R₁₂,R₄₅,R₅₀,R₅₈,R₆₆=are independently A,G,U or absent;

R₃₁= A,U or absent;

R₃₂,R₄₄,R₆₀=are independently C,G or absent;

R₃,R₁₃,R₃₇,R₄₂,R₆₄,R₆₇=are independently C,G,U or absent;

R₆,R₁₁,R₂₈,R₃₅,R₅₅,R₅₉,R₆₁=are independently C,U or absent;

R₉,R₁₀,R₁₉,R₂₀=are independently G or absent;

R₁,R₂₁,R₃₉,R₇₂=are independently G,U or absent;

R₈,R₁₆,R₃₆,R₃₈,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent;

R₃₄,R₄₃,R₆₈,R₆₉=are independently A,C,G or absent;

R₁,R₂,R₅,R₆,R₉,R₁₂,R₁₆,R₂₀,R₂₁,R₂₆,R₂₇,R₂₉,R₃₀,R₃₁,R₃₂,R₃₃,R₄₁,R₄₄,R₄₅,R₄₆,R₄₈,R₅₀,R₅₁,R₅₈,R₆₃,R₆₄,R₆₅,R₆₆,R₇₀,R₇₁=are independently N or absent;

R₁₃,R₁₇,R₂₃,R₆₁=are independently A,C,U or absent;

R₁₀,R₁₄,R₂₄,R₄₀,R₅₂,R₅₆=are independently A,G or absent;

R₇,R₁₅,R₂₅,R₆₇,R₇₂=are independently A,G,U or absent;

R₁₁,R₅₇=are independently A,U or absent;

R₃₉= C,G or absent;

R₃,R₄,R₂₂,R₄₂,R₄₉,R₅₅,R₆₂=are independently C,G,U or absent;

R₁₈,R₂₈,R₃₅,R₃₇,R₅₃,R₅₉,R₆₀=are independently C,U or absent;

R₁₉= G or absent;

R₈,R₃₆,R₃₈,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₇,R₄₀=are independently A or absent;

R₂₆,R₂₇,R₃₄,R₄₃,R₆₈,R₆₉,R₇₁=are independently A,C,G or absent;

R₁,R₂,R₅,R₁₂,R₂₁,R₃₁,R₃₃,R₄₁,R₄₅,R₄₈,R₅₁,R₅₈,R₆₆,R₇₀=are independently N or absent;

R₄₄,R₆₁=are independently A,C,U or absent;

R₉,R₁₄,R₂₄,R₂₅,R₅₂,R₅₆,R₆₃=are independently A,G or absent;

R₇,R₁₅,R₄₆,R₅₀,R₆₇,R₇₂=are independently A,G,U or absent;

R₂₉,R₅₇=are independently A,U or absent;

R₆₀= C or absent;

R₃₉= C,G or absent;

R₃,R₆,R₂₀,R₃₀,R₃₂,R₄₂,R₅₅,R₆₂,R₆₅=are independently C,G,U or absent;

R₄,R₈,R₁₆,R₂₈,R₃₅,R₃₇,R₄₉,R₅₃,R₅₉=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;

R₂₉,R₅₇,R₆₇,R₇₂=are independently A,U or absent;

R₂,R₃₉,R₆₀=are independently C or absent;

R₃,R₁₂,R₂₀,R₂₆,R₃₄,R₆₉=are independently C,G or absent;

R₆,R₃₀,R₄₂,R₄₈,R₆₅=are independently C,G,U or absent;

R₄,R₁₆,R₂₈,R₃₅,R₃₇,R₄₉,R₅₃,R₅₅,R₅₈,R₆₁,R₆₂=are independently C,U or absent;

R₉,R₁₀,R₁₉,R₆₄=are independently G or absent;

R₁₅,R₂₂,R₃₂=are independently G,U or absent;

R₈,R₁₁,R₁₃,R₃₆,R₃₈,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent;

R₂₄= A or absent;

R₃,R₉,R₄₀,R₅₀,R₅₁=are independently A,C,G or absent;

R₄,R₅,R₆,R₇,R₁₂,R₁₆,R₂₁,R₂₂,R₂₆,R₂₉,R₃₀,R₃₁,R₃₂,R₃₃,R₃₄,R₄₁,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₈,R₆₃,R₆₄,R₆₅,R₆₆,R₆₇,R₆₈=are independently N or absent;

R₅₉= A,C,U or absent;

R₁,R₁₀,R₁₄,R₁₅,R₂₇,R₅₆=are independently A,G or absent;

R₂₀,R₂₅=are independently A,G,U or absent;

R₅₇,R₇₂=are independently A,U or absent;

R₃₈,R₃₉,R₆₀=are independently C or absent;

R₅₂= C,G or absent;

R₂,R₁₉,R₃₇,R₅₄,R₅₅,R₆₁,R₆₂,R₆₉,R₇₀=are independently C,G,U or absent;

R₁₁,R₁₃,R₁₇,R₂₈,R₃₅,R₃₆,R₇₁=are independently C,U or absent;

R₈,R₁₈,R₂₃,R₅₃=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-

R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₂₄,R₂₇,R₄₀,R₇₂=are independently A or absent;

R₂₆= A,C or absent;

R₃,R₇,R₆₈=are independently A,C,G or absent;

R₅,R₃₀,R₄₁,R₄₂,R₄₄,R₄₉,R₆₇=are independently A,C,G,U or absent;

R₃₁,R₃₂,R₃₄=are independently A,C,U or absent;

R₉,R₁₀,R₁₄,R₁₅,R₃₃,R₅₀,R₅₆=are independently A,G or absent;

R₁₂,R₁₆,R₂₂,R₂₅,R₂₉,R₄₆=are independently A,G,U or absent;

R₅₇= A,U or absent;

R₁₇,R₃₈,R₃₉,R₆₀,R₆₁,R₇₁=are independently C or absent;

R₆,R₅₂,R₆₄,R₆₆=are independently C,G or absent;

R₂,R₄,R₃₇,R₄₈,R₅₅,R₆₅=are independently C,G,U or absent;

R₁₃,R₃₅,R₄₃,R₆₂,R₆₉=are independently C,U or absent;

R₁,R₁₉,R₂₀,R₅₁,R₇₀=are independently G or absent;

R₂₁,R₄₅,R₆₃=are independently G,U or absent;

R₈,R₁₁,R₂₈,R₃₆,R₅₃,R₅₄,R₅₈,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₂₄,R₂₇,R₄₀,R₇₂=are independently A or absent;

R₂₆= A,C or absent;

R₃,R₇,R₄₉,R₆₈=are independently A,C,G or absent;

R₅,R₃₀,R₄₁,R₄₄,R₆₇=are independently N or absent;

R₃₁,R₃₂,R₃₄=are independently A,C,U or absent;

R₉,R₁₀,R₁₄,R₁₅,R₃₃,R₅₀,R₅₆=are independently A,G or absent;

R₁₂,R₂₅,R₂₉,R₄₂,R₄₆=are independently A,G,U or absent;

R₁₆,R₅₇=are independently A,U or absent;

R₁₇,R₃₈,R₃₉,R₆₀,R₆₁,R₇₁=are independently C or absent;

R₆,R₅₂,R₆₄,R₆₆=are independently C,G or absent;

R₃₇,R₄₈,R₆₅=are independently C,G,U or absent;

R₂,R₄,R₁₃,R₃₅,R₄₃,R₅₅,R₆₂,R₆₉=are independently C,U or absent;

R₁,R₁₉,R₂₀,R₅₁,R₇₀=are independently G or absent;

R₂₁,R₂₂,R₄₅,R₆₃=are independently G,U or absent;

R₈,R₁₁,R₂₈,R₃₆,R₅₃,R₅₄,R₅₈,R₅₉=are independently U or absent;

[R₄₇]_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.

Histidine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{HIS} (SEQ ID NO: 586),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₂₃=absent;

R₁₄,R₂₄,R₅₇=are independently A or absent;

R₇₂= A,C or absent;

R₉,R₂₇,R₄₃,R₄₈,R₆₉=are independently A,C,G or absent;

R₃,R₄,R₅,R₆,R₁₂,R₂₅,R₂₆,R₂₉,R₃₀,R₃₁,R₃₄,R₄₂,R₄₅,R₄₆,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₆,R₆₇,R₆₈=are independently N or absent;

R₁₃,R₂₁,R₄₁,R₄₄,R₆₅=are independently A,C,U or absent;

R₄₀,R₅₁,R₅₆,R₇₀=are independently A,G or absent;

R₇,R₃₂=are independently A,G,U or absent;

R₅₅,R₆₀=are independently C or absent;

R₁₁,R₁₆,R₃₃,R₆₄=are independently C,G,U or absent;

R₂,R₁₇,R₂₂,R₂₈,R₃₅,R₅₃,R₅₉,R₆₁,R₇₁=are independently C,U or absent;

R₁,R₁₀,R₁₅,R₁₉,R₂₀,R₃₇,R₃₉,R₅₂=are independently G or absent;

R₀= G,U or absent;

R₈,R₁₈,R₃₆,R₃₈,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₃=are absent;

R₇,R₁₂,R₁₄,R₂₄,R₂₇,R₄₅,R₅₇,R₅₈,R₆₃,R₆₇,R₇₂=are independently A or absent;

R₃= A,C,U or absent;

R₄,R₄₃,R₅₆,R₇₀=are independently A,G or absent;

R₄₉= A,U or absent;

R₂,R₂₈,R₃₀,R₄₁,R₄₂,R₄₄,R₄₈,R₅₅,R₆₀,R₆₆,R₇₁=are independently C or absent;

R₂₅= C,G or absent;

R₉= C,G,U or absent;

R₈,R₁₃,R₂₆,R₃₃,R₃₅,R₅₀,R₅₃,R₆₁,R₆₈=are independently C,U or absent;

R₁,R₆,R₁₀,R₁₅,R₁₉,R₂₀,R₃₂,R₃₄,R₃₇,R₃₉,R₄₀,R₄₆,R₅₁,R₅₂,R₆₂,R₆₄,R₆₉=are independently G or absent;

R₁₆= G,U or absent;

R₅,R₁₁,R₂₁,R₂₂,R₂₉,R₃₁,R₃₆,R₃₈,R₅₄,R₅₉,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₃=are absent

R₇,R₁₂,R₁₄,R₂₄,R₂₇,R₄₅,R₅₇,R₅₈,R₆₃,R₆₇,R₇₂=are independently A or absent;

R₃= A,C or absent;

R₄,R₄₃,R₅₆,R₇₀=are independently A,G or absent;

R₄₉= A,U or absent;

R₂,R₂₈,R₃₀,R₄₁,R₄₂,R₄₄,R₄₈,R₅₅,R₆₀,R₆₆,R₇₁=are independently C or absent;

R₈,R₉,R₂₆,R₃₃,R₃₅,R₅₀,R₆₁,R₆₈=are independently C,U or absent;

R₁,R₆,R₁₀,R₁₅,R₁₉,R₂₀,R₂₅,R₃₂,R₃₄,R₃₇,R₃₉,R₄₀,R₄₆,R₅₁,R₅₂,R₆₂,R₆₄,R₆₉=are independently G or absent;

R₅,R₁₁,R₁₃,R₁₆,R₂₁,R₂₂,R₂₉,R₃₁,R₃₆,R₃₈,R₅₃,R₅₄,R₅₉,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₂₃=absent;

R₃₈,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₁,R₂₆=are independently A,C,G or absent;

R₀,R₃,R₄,R₆,R₁₆,R₃₁,R₃₂,R₃₄,R₃₇,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₅₉,R₆₂,R₆₃,R₆₄,R₆₆,R₆₇,R₆₈,R₆₉=are independently N or absent;

R₂₂,R₆₁,R₆₅=are independently A,C,U or absent;

R₉,R₁₄,R₁₅,R₂₄,R₂₇,R₄₀=are independently A,G or absent;

R₇,R₂₅,R₂₉,R₅₁,R₅₆=are independently A,G,U or absent;

R₁₈,R₅₄=are independently A,U or absent;

R₆₀= C or absent;

R₂,R₅₂,R₇₀=are independently C,G or absent;

R₅,R₁₂,R₂₁,R₃₀,R₃₃,R₇₁=are independently C,G,U or absent;

R₁₁,R₁₃,R₁₇,R₂₈,R₃₅,R₅₃,R₅₅=are independently C,U or absent;

R₁₀,R₁₉,R₂₀=are independently G or absent;

R₈,R₃₆,R₃₉=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₂₄,R₃₈,R₄₀,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₂₆,R₆₅=are independently A,C or absent;

R₅₈,R₅₉,R₆₇=are independently N or absent;

R₂₂= A,C,U or absent;

R₆,R₉,R₁₄,R₁₅,R₂₉,R₃₄,R₄₃,R₄₆,R₄₈,R₅₀,R₅₁,R₆₃,R₆₉=are independently A,G or absent;

R₃₇,R₅₆=are independently A,G,U or absent;

R₅₄= A,U or absent;

R₂₈,R₃₅,R₆₀,R₆₂,R₇₁=are independently C or absent;

R₂,R₅₂,R₇₀=are independently C,G or absent;

R₅= C,G,U or absent;

R₃,R₄,R₁₁,R₁₃,R₁₇,R₂₁,R₃₀,R₄₂,R₄₄,R₄₅,R₄₉,R₅₃,R₅₅,R₆₁,R₆₄,R₆₆=are independently C,U or absent;

R₁,R₁₀,R₁₉,R₂₀,R₂₅,R₂₇,R₃₁,R₆₈=are independently G or absent;

R₇,R₁₂,R₃₂=are independently G,U or absent;

R₈,R₁₆,R₃₃,R₃₆,R₃₉=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-

R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₄,R₂₄,R₃₈,R₄₀,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₂₆,R₆₅=are independently A,C or absent;

R₂₂,R₅₉=are independently A,C,U or absent;

R₆,R₉,R₁₅,R₃₄,R₄₃,R₄₆,R₅₁,R₅₆,R₆₃,R₆₉=are independently A,G or absent;

R₃₇= A,G,U or absent;

R₁₃,R₂₈,R₃₅,R₄₄,R₅₅,R₆₀,R₆₂,R₇₁=are independently C or absent;

R₂,R₅,R₇₀=are independently C,G or absent;

R₅₈,R₆₇=are independently C,G,U or absent;

R₃,R₄,R₁₁,R₁₇,R₂₁,R₃₀,R₄₂,R₄₅,R₄₉,R₅₃,R₆₁,R₆₄,R₆₆=are independently C,U or absent;

R₁,R₁₀,R₁₉,R₂₀,R₂₅,R₂₇,R₂₉,R₃₁,R₃₂,R₄₈,R₅₀,R₅₂,R₆₈=are independently G or absent;

R₇,R₁₂=are independently G,U or absent;

R₈,R₁₆,R₃₃,R₃₆,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₂₃=are absent;

R₁₄,R₃₈,R₄₀,R₅₇=are independently A or absent;

R₆₀= A,C or absent;

R₃₃,R₄₈,R₇₀=are independently A,C,G or absent;

R₁,R₃,R₄,R₅,R₆,R₁₁,R₁₂,R₁₆,R₁₇,R₂₁,R₂₂,R₂₆,R₂₇,R₂₉,R₃₀,R₃₁,R₃₂,R₄₂,R₄₄,R₄₅,R₄₆,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₆,R₆₇,R₆₈,R₆₉,R₇₁=are independently N or absent;

R₁₈,R₃₅,R₄₁,R₅₉,R₆₅=are independently A,C,U or absent;

R₉,R₁₅,R₅₁=are independently A,G or absent;

R₇,R₂₄,R₂₅,R₃₄,R₅₃,R₅₆=are independently A,G,U or absent;

R₇₂= A,U or absent;

R₃₇= C or absent;

R₁₀,R₅₅=are independently C,G or absent;

R₂,R₁₃,R₂₈,R₄₃,R₆₄=are independently C,G,U or absent;

R₃₆,R₆₁=are independently C,U or absent;

R₁₉,R₂₀,R₅₂=are independently G or absent;

R₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₂,R₂₃=are absent

R₁₄,R₂₄,R₃₈,R₄₀,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₅₉,R₆₀,R₆₂,R₆₅=are independently A,C or absent;

R₆,R₄₅,R₆₇=are independently A,C,G or absent;

R₄= N or absent;

R₂₁,R₄₂=are independently A,C,U or absent;

R₁,R₉,R₂₇,R₂₉,R₃₂,R₄₆,R₅₁=are independently A,G or absent;

R₁₇,R₄₉,R₅₃,R₅₆,R₅₈=are independently A,G,U or absent;

R₆₃=A,U or absent;

R₃,R₁₃,R₃₇=are independently C or absent;

R₄₈,R₅₅,R₆₄,R₇₀=are independently C,G or absent;

R₂,R₅,R₆₆,R₆₈=are independently C,G,U or absent;

R₁₁,R₁₆,R₂₆,R₂₈,R₃₀,R₃₁,R₃₅,R₃₆,R₄₃,R₄₄,R₆₁,R₇₁=are independently C,U or absent;

R₁₀,R₁₂,R₁₅,R₁₉,R₂₀,R₂₅,R₃₃,R₅₂,R₆₉=are independently G or absent;

R₇,R₃₄,R₅₀=are independently G,U or absent;

R₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₂,R₂₃=are absent

R₁₄,R₂₄,R₃₈,R₄₀,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₅₉,R₆₂,R₆₅=are independently A,C or absent;

R₆,R₆₇=are independently A,C,G or absent;

R₄,R₂₁=are independently A,C,U or absent;

R₁,R₉,R₂₇,R₂₉,R₃₂,R₄₅,R₄₆,R₅₁=are independently A,G or absent;

R₁₇,R₅₆,R₅₈=are independently A,G,U or absent;

R₄₉,R₅₃,R₆₃=are independently A,U or absent;

R₃,R₁₃,R₂₆,R₃₇,R₄₃,R₆₀=are independently C or absent;

R₂,R₄₈,R₅₅,R₆₄,R₇₀=are independently C,G or absent;

R₅,R₆₆=are independently C,G,U or absent;

R₁₁,R₁₆,R₂₈,R₃₀,R₃₁,R₃₅,R₃₆,R₄₂,R₄₄,R₆₁,R₇₁=are independently C,U or absent;

R₁₀,R₁₂,R₁₅,R₁₉,R₂₀,R₂₅,R₃₃,R₅₂,R₆₉=are independently G or absent;

R₇,R₃₄,R₅₀,R₆₈=are independently G,U or absent;

R₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent;

R₃₈,R₅₇=are independently A or absent;

R₆₀= A,C or absent;

R₁,R₁₃,R₂₇,R₄₈,R₅₁,R₅₆=are independently A,C,G or absent;

R₂,R₃,R₄,R₅,R₆,R₇,R₉,R₁₀,R₁₁,R₁₂,R₁₆,R₂₃,R₂₆,R₂₈,R₂₉,R₃₀,R₃₁,R₃₂,R₃₃,R₃₄,R₃₇,R₄₁,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₅,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₁₇,R₁₈,R₂₁,R₂₂,R₂₅,R₃₅,R₅₅=are independently A,C,U or absent;

R₁₄,R₁₅,R₃₉,R₇₂=are independently A,G or absent;

R₂₄,R₄₀=are independently A,G,U or absent;

R₅₂,R₆₁,R₆₄,R₇₁=are independently C,G,U or absent;

R₃₆,R₅₃,R₅₉=are independently C,U or absent;

R₁₉= G or absent;

R₂₀= G,U or absent;

R₈,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀ =absent

R₃₈,R₅₇,R₇₂=are independently A or absent;

R₆₀= A,C or absent;

R₄,R₅,R₄₈,R₅₀,R₅₆,R₆₉=are independently A,C,G or absent;

R₆,R₃₃,R₄₁,R₄₃,R₄₆,R₄₉,R₅₈,R₆₃,R₆₆,R₇₀=are independently N or absent;

R₁₁,R₁₂,R₁₇,R₂₁,R₂₂,R₂₈,R₃₁,R₃₇,R₄₄,R₅₅=are independently A,C,U or absent;

R₁,R₉,R₁₄,R₁₅,R₂₄,R₂₇,R₃₄,R₃₉=are independently A,G or absent;

R₇,R₂₉,R₃₂,R₄₀,R₄₅=are independently A,G,U or absent;

R₂₅= A,U or absent;

R₁₃= C,G or absent;

R₂,R₃,R₁₆,R₂₆,R₃₀,R₅₂,R₆₂,R₆₄,R₆₅,R₆₇,R₆₈=are independently C,G,U or absent;

R₁₈,R₃₅,R₄₂,R₅₃,R₅₉,R₆₁,R₇₁=are independently C,U or absent;

R₁₉,R₅₁=are independently G or absent;

R₁₀,R₂₀=are independently G,U or absent;

R₈,R₂₃,R₃₆,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀ =absent

R₃₈,R₅₇,R₇₂=are independently A or absent;

R₆₀= A,C or absent;

R₄,R₅,R₄₈,R₅₀,R₅₆,R₅₈,R₆₉=are independently A,C,G or absent;

R₆,R₃₃,R₄₃,R₄₆,R₄₉,R₆₃,R₆₆,R₇₀=are independently N or absent;

R₁₁,R₁₂,R₁₇,R₂₁,R₂₂,R₂₈,R₃₁,R₃₇,R₄₁,R₄₄,R₅₅=are independently A,C,U or absent;

R₁,R₉,R₁₄,R₁₅,R₂₄,R₂₇,R₃₄,R₃₉=are independently A,G or absent;

R₇,R₂₉,R₃₂,R₄₀,R₄₅=are independently A,G,U or absent;

R₂₅= A,U or absent;

R₁₃= C,G or absent;

R₂,R₃,R₁₆,R₃₀,R₅₂,R₆₂,R₆₄,R₆₇,R₆₈=are independently C,G,U or absent;

R₁₈,R₃₅,R₄₂,R₅₃,R₅₉,R₆₁,R₆₅,R₇₁=are independently C,U or absent;

R₁₉,R₅₁=are independently G or absent;

R₁₀,R₂₀,R₂₆=are independently G,U or absent;

R₈,R₂₃,R₃₆,R₅₄=are independently U or absent;

[R₄₇]_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.

Lysine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{LYS} (SEQ ID NO: 598),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent

R₁₄= A or absent;

R₄₀,R₄₁=are independently A,C or absent;

R₃₄,R₄₃,R₅₁=are independently A,C,G or absent;

R₁,R₂,R₃,R₄,R₅,R₆,R₇,R₁₁,R₁₂,R₁₆,R₂₁,R₂₆,R₃₀,R₃₁,R₃₂,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₅,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₁₃,R₁₇,R₅₉,R₇₁=are independently A,C,U or absent;

R₉,R₁₅,R₁₉,R₂₀,R₂₅,R₂₇,R₅₂,R₅₆=are independently A,G or absent;

R₂₄,R₂₉,R₇₂=are independently A,G,U or absent;

R₁₈,R₅₇=are independently A,U or absent;

R₁₀,R₃₃=are independently C,G or absent;

R₄₂,R₆₁,R₆₄=are independently C,G,U or absent;

R₂₈,R₃₅,R₃₆,R₃₇,R₅₃,R₅₅,R₆₀=are independently C,U or absent;

R₈,R₂₂,R₂₃,R₃₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=are absent

R₁₄= A or absent;

R₄₀,R₄₁,R₄₃=are independently A,C or absent;

R₃,R₇=are independently A,C,G or absent;

R₁,R₆,R₁₁,R₃₁,R₄₅,R₄₈,R₄₉,R₆₃,R₆₅,R₆₆,R₆₈=are independently N or absent;

R₂,R₁₂,R₁₃,R₁₇,R₄₄,R₆₇,R₇₁=are independently A,C,U or absent;

R₉,R₁₅,R₁₉,R₂₀,R₂₅,R₂₇,R₃₄,R₅₀,R₅₂,R₅₆,R₇₀,R₇₂=are independently A,G or absent;

R₅,R₂₄,R₂₆,R₂₉,R₃₂,R₄₆,R₆₉=are independently A,G,U or absent;

R₅₇= A,U or absent;

R₁₀,R₆₁=are independently C,G or absent;

R₄,R₁₆,R₂₁,R₃₀,R₅₈,R₆₄=are independently C,G,U or absent;

R₂₈,R₃₅,R₃₆,R₃₇,R₄₂,R₅₃,R₅₅,R₅₉,R₆₀,R₆₂=are independently C,U or absent;

R₃₃,R₅₁=are independently G or absent;

R₈=G,U or absent;

R₂₂,R₃₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₉,R₁₄,R₃₄,R₄₁=are independently A or absent;

R₄₀= A,C or absent;

R₁,R₃,R₇,R₃₁=are independently A,C,G or absent;

R₄₈,R₆₅,R₆₈=are independently N or absent;

R₂,R₁₃,R₁₇,R₄₄,R₆₃,R₆₆=are independently A,C,U or absent;

R₅,R₁₅,R₁₉,R₂₀,R₂₅,R₂₇,R₂₉,R₅₀,R₅₂,R₅₆,R₇₀,R₇₂=are independently A,G or absent;

R₆,R₂₄,R₃₂,R₄₉=are independently A,G,U or absent;

R₁₂,R₂₆,R₄₆,R₅₇=are independently A,U or absent;

R₁₁,R₂₈,R₃₅,R₄₃=are independently C or absent;

R₁₀,R₄₅,R₆₁=are independently C,G or absent;

R₄,R₂₁,R₆₄=are independently C,G,U or absent;

R₃₇,R₅₃,R₅₅,R₅₉,R₆₀,R₆₂,R₆₇,R₇₁=are independently C,U or absent;

R₃₃,R₅₁=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;

R₇,R₅₁=are independently A,G,U or absent;

R₂₂,R₂₄=are independently A,U or absent;

R₅₅,R₆₀=are independently C or absent;

R₂,R₃,R₂₁,R₃₃,R₄₃,R₅₀,R₆₄=are independently C,G,U or absent;

R₁₁,R₁₂,R₁₃,R₁₇,R₂₈,R₃₅,R₃₆,R₅₉=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₂₅,R₃₇,R₅₂=are independently G or absent;

R₁= G,U or absent;

R₈,R₁₈,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₁₄,R₂₄,R₃₈,R₃₉,R₅₇,R₇₂=are independently A or absent;

R₄₆,R₇₁=are independently A,C or absent;

R₄,R₇₀=are independently A,C,G or absent;

R₄₅= A,C,U or absent;

R₆,R₇,R₁₅,R₂₆,R₂₇,R₃₂,R₃₄,R₄₀,R₄₁,R₅₆,R₆₉=are independently A,G or absent;

R₂₉= A,G,U or absent;

R₅,R₉,R₆₇=are independently A,U or absent;

R₃₅,R₄₉,R₅₅,R₆₀=are independently C or absent;

R₂₁,R₄₃,R₆₂=are independently C,G or absent;

R₂,R₃₃,R₆₈=are independently C,G,U or absent;

R₃,R₁₁,R₁₂,R₁₃,R₂₈,R₃₀,R₃₆,R₄₂,R₄₄,R₄₈,R₅₈,R₅₉,R₆₁,R₆₆=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₂₅,R₃₇,R₅₁,R₅₂,R₆₃,R₆₄=are independently G or absent;

R₁,R₃₁,R₅₀=are independently G,U or absent;

R₈,R₁₆,R₁₇,R₂₂,R₅₃,R₅₄,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₂,R₂₃=absent

R₅,R₇,R₁₄,R₂₄,R₂₆,R₃₂,R₃₄,R₃₈,R₃₉,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₄₆= A,C or absent;

R₇₀= A,C,G or absent;

R₄,R₆,R₁₅,R₅₆,R₆₉=are independently A,G or absent;

R₉,R₄₅=are independently A,U or absent;

R₂,R₁₁,R₁₃,R₃₅,R₄₃,R₄₉,R₅₅,R₆₀,R₆₈,R₇₁=are independently C or absent;

R₃₃= C,G or absent;

R₃,R₂₈,R₃₆,R₄₈,R₅₈,R₅₉,R₆₁=are independently C,U or absent;

R₁,R₁₀,R₁₉,R₂₀,R₂₁,R₂₅,R₂₇,R₂₉,R₃₇,R₄₀,R₅₁,R₅₂,R₆₂,R₆₃,R₆₄=are independently G or absent;

R₈,R₁₂,R₁₆,R₁₇,R₃₀,R₃₁,R₄₂,R₄₄,R₅₀,R₅₃,R₅₄,R₆₅,R₆₆,R₆₇=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-

R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀ =absent

R₁₄,R₅₇=are independently A or absent;

R₇₀,R₇₂=are independently A,C or absent;

R₉,R₂₆,R₂₇=are independently A,C,G or absent;

R₄,R₅,R₆,R₁₆,R₂₁,R₂₉,R₃₀,R₃₁,R₃₂,R₃₃,R₃₄,R₃₇,R₄₁,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₆₁,R₆₂,
R₆₃,R₆₄,R₆₆,R₆₇,R₆₈=are independently N or absent;

R₃₅,R₆₅=are independently A,C,U or absent;

R₂₄,R₄₀,R₅₆=are independently A,G or absent;

R₇,R₂₅,R₅₁=are independently A,G,U or absent;

R₅₅,R₆₀=are independently C or absent;

R₁,R₃,R₇₁=are independently C,G or absent;

R₁₁,R₁₂,R₂₀,R₆₉=are independently C,G,U or absent;

R₁₃,R₁₇,R₁₈,R₂₂,R₂₃,R₂₈,R₅₉=are independently C,U or absent;

R₁₀,R₁₅,R₁₉,R₃₈,R₃₉,R₅₂=are independently G or absent;

R₂= are independently G,U or absent;

R₈,R₃₆,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₂,R₂₃=absent;

R₁₄,R₄₅,R₅₆,R₅₇,R₅₈,R₆₅,R₆₈=are independently A or absent;

R₆₁= A,C,G or absent;

R₄₃=N or absent;

R₃₇= A, C,U or absent;

R₂₄,R₂₇,R₃₃,R₄₀,R₄₄,R₆₃=are independently A,G or absent;

R₃,R₁₂,R₃₀,R₃₂,R₄₈,R₅₅,R₆₀,R₇₀,R₇₁,R₇₂=are independently C or absent;

R₅,R₃₄,R₄₂,R₆₆=are independently C,G or absent;

R₂₀= C,G,U or absent;

R₃₅,R₄₁,R₄₉,R₆₂=are independently C,U or absent;

R₁,R₂,R₆,R₉,R₁₀,R₁₅,R₁₉,R₂₆,R₃₈,R₃₉,R₄₆,R₅₀,R₅₁,R₅₂,R₆₄,R₆₇,R₆₉=are independently G or absent;

R₁₁,R₁₆=are independently G,U or absent;

R₄,R₇,R₈,R₁₃,R₂₁,R₂₅,R₂₈,R₂₉,R₃₁,R₃₆,R₅₃,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₇,R₁₈,R₂₂,R₂₃=absent

R₁₄,R₄₅,R₅₆,R₅₇,R₅₈,R₆₅,R₆₈=are independently A or absent;

R₃₇= A,C,U or absent;

R₂₄,R₂₇,R₄₀=are independently A,G or absent;

R₃,R₅,R₁₂,R₃₀,R₃₂,R₄₈,R₄₉,R₅₅,R₆₀,R₆₁,R₆₂,R₆₆,R₇₀,R₇₁,R₇₂=are independently C or absent;

R₃₄,R₄₂=are independently C,G or absent;

R₄₃= C,G,U or absent;

R₄₁= C,U or absent;

R₁,R₂,R₆,R₉,R₁₀,R₁₅,R₁₉,R₂₀,R₂₆,R₃₃,R₃₈,R₃₉,R₄₄,R₄₆,R₅₀,R₅₁,R₅₂,R₆₃,R₆₄,R₆₇,R₆₉=are independently G or absent;

R₁₆= G,U or absent;

R₄,R₇,R₈,R₁₁,R₁₃,R₂₁,R₂₅,R₂₈,R₂₉,R₃₁,R₃₅,R₃₆,R₅₃,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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.

Serine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{SER} (SEQ ID NO: 607),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀=absent;

R₁₄,R₂₄,R₅₇=are independently A or absent;

R₄₁= A,C or absent;

R₂,R₃,R₄,R₅,R₆,R₇,R₉,R₁₀,R₁₁,R₁₂,R₁₃,R₁₆,R₂₁,R₂₅,R₂₆,R₂₇,R₂₈,R₃₀,R₃₁,R₃₂,R₃₃,R₃₄,R₃₇,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₆₂,R₆₃,R₆₄,R₆₅,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₁₈= A,C,U or absent;

R₁₅,R₄₀,R₅₁,R₅₆=are independently A,G or absent;

R₁,R₂₉,R₅₈,R₇₂=are independently A,G,U or absent;

R₃₉= A,U or absent;

R₆₀= C or absent;

R₃₈= C,G or absent;

R₁₇,R₂₂,R₂₃,R₇₁=are independently C,G,U or absent;

R₈,R₃₅,R₃₆,R₅₅,R₅₉,R₆₁=are independently C,U or absent;

R₁₉,R₂₀=are independently G or absent;

R₅₂= G,U or absent;

R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₂₃=absent

R₁₄,R₂₄,R₄₁,R₅₇=are independently A or absent;

R₄₄= A,C or absent;

R₂₅,R₄₅,R₄₈=are independently A,C,G or absent;

R₂,R₃,R₄,R₅,R₃₇,R₅₀,R₆₂,R₆₆,R₆₇,R₆₉,R₇₀=are independently N or absent;

R₁₂,R₂₈,R₆₅=are independently A,C,U or absent;

R₉,R₁₅,R₂₉,R₃₄,R₄₀,R₅₆,R₆₃=are independently A,G or absent;

R₇,R₂₆,R₃₀,R₃₃,R₄₆,R₅₈,R₇₂=are independently A,G,U or absent;

R₃₉= A,U or absent;

R₁₁,R₃₅,R₆₀,R₆₁=are independently C or absent;

R₁₃,R₃₈=are independently C,G or absent;

R₆,R₁₇,R₃₁,R₄₃,R₆₄,R₆₈=are independently C,G,U or absent;

R₃₆,R₄₂,R₄₉,R₅₅,R₅₉,R₇₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₂₇,R₅₁=are independently G or absent;

R₁,R₁₆,R₃₂,R₅₂=are independently G,U or absent;

R₈,R₁₈,R₂₁,R₂₂,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₂₃=absent

R₁₄,R₂₄,R₄₁,R₅₇,R₅₈=are independently A or absent;

R₄₄= A,C or absent;

R₂₅,R₄₈=are independently A,C,G or absent;

R₂,R₃,R₅,R₃₇,R₆₆,R₆₇,R₆₉,R₇₀=are independently N or absent;

R₁₂,R₂₈,R₆₂=are independently A,C,U or absent;

R₇,R₉,R₁₅,R₂₉,R₃₃,R₃₄,R₄₀,R₄₅,R₅₆,R₆₃=are independently A,G or absent;

R₄,R₂₆,R₄₆,R₅₀=are independently A,G,U or absent;

R₃₀,R₃₉=are independently A,U or absent;

R₁₁,R₁₇,R₃₅,R₆₀,R₆₁=are independently C or absent;

R₁₃,R₃₈=are independently C,G or absent;

R₆,R₆₄=are independently C,G,U or absent;

R₃₁,R₄₂,R₄₃,R₄₉,R₅₅,R₅₉,R₆₅,R₆₈,R₇₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₂₇,R₅₁,R₅₂=are independently G or absent;

R₁,R₁₆,R₃₂,R₇₂=are independently G,U or absent;

R₈,R₁₈,R₂₁,R₂₂,R₃₆,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁- R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-

R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₂₃=absent

R₁₄,R₄₁,R₅₇=are independently A or absent;

R₅₆,R₇₀=are independently A,C,G or absent;

R₄,R₅,R₆,R₇,R₁₂,R₁₆,R₂₆,R₃₀,R₃₁,R₃₂,R₃₄,R₃₇,R₄₂,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₄,R₆₅,R₆₆,R₆₇,R₆₈,R₇₂=are independently N or absent;

R₁₃,R₁₇,R₂₁,R₃₅,R₆₁=are independently A,C,U or absent;

R₁,R₉,R₂₄,R₂₇,R₂₉,R₆₉=are independently A,G or absent;

R₁₅,R₂₅,R₅₁=are independently A,G,U or absent;

R₄₀,R₅₃=are independently A,U or absent;

R₃₃,R₄₃=are independently C,G or absent;

R₂,R₃,R₅₉=are independently C,G,U or absent;

R₁₁,R₁₈,R₂₂,R₂₈,R₃₆,R₅₄,R₅₅,R₆₀,R₇₁=are independently C,U or absent;

R₁₀,R₂₀,R₃₈,R₅₂=are independently G or absent;

R₁₉= G,U or absent;

R₈,R₃₉=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₁₄,R₄₁,R₅₇=are independently A or absent;

R₉,R₄₂,R₄₄,R₄₈,R₅₆,R₇₀=are independently A,C,G or absent;

R₄,R₆,R₁₂,R₂₆,R₄₉,R₅₈,R₆₃,R₆₄,R₆₆,R₆₈=are independently N or absent;

R₁₃,R₂₁,R₃₁,R₃₇,R₆₂=are independently A,C,U or absent;

R₁,R₁₅,R₂₄,R₂₇,R₂₉,R₄₆,R₅₁,R₆₉=are independently A,G or absent;

R₇,R₂₅,R₄₅,R₅₀,R₆₇=are independently A,G,U or absent;

R₄₀,R₅₃=are independently A,U or absent;

R₃₅= C or absent;

R₃₃,R₄₃=are independently C,G or absent;

R₂,R₃,R₅,R₁₆,R₃₂,R₃₄,R₅₉,R₆₅,R₇₂=are independently C,G,U or absent;

R₁₁,R₁₇,R₂₂,R₂₈,R₃₀,R₃₆,R₅₅,R₆₀,R₆₁,R₇₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₃₈,R₅₂=are independently G or absent;

R₈,R₃₉,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₁₄,R₄₀,R₄₁,R₅₇=are independently A or absent;

R₄₄= A,C or absent;

R₉,R₄₂,R₄₈,R₅₆=are independently A,C,G or absent;

R₄,R₆,R₁₂,R₂₆,R₅₈,R₆₄,R₆₆,R₆₈=are independently N or absent;

R₁₃,R₂₁,R₃₁,R₃₇,R₄₉,R₆₂=are independently A,C,U or absent;

R₁,R₁₅,R₂₄,R₂₇,R₂₉,R₄₆,R₅₁,R₆₉=are independently A,G or absent;

R₇,R₂₅,R₄₅,R₅₀,R₆₃,R₆₇=are independently A,G,U or absent;

R₅₃= A,U or absent;

R₃₅= C or absent;

R₂,R₃₃,R₄₃,R₇₀=are independently C,G or absent;

R₅,R₁₆,R₃₄,R₅₉,R₆₅=are independently C,G,U or absent;

R₃,R₁₁,R₂₂,R₂₈,R₃₀,R₃₆,R₅₅,R₆₀,R₆₁,R₇₁=are independently C,U or absent;

R₁₀,R₁₉,R₂₀,R₃₈,R₅₂=are independently G or absent;

R₃₂= G,U or absent;

R₈,R₁₇,R₃₉,R₅₄,R₇₂=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀= absent;

R₂₄,R₃₉,R₄₁,R₅₇=are independently A or absent;

R₂,R₃,R₂₆,R₂₇,R₄₀,R₄₈=are independently A,C,G or absent;

R₄,R₅,R₆,R₂₉,R₃₀,R₃₁,R₃₂,R₃₄,R₄₂,R₄₄,R₄₅,R₄₆,R₄₉,R₅₁,R₅₈,R₆₃,R₆₆,R₆₇,R₆₈=are independently N or absent;

R₁₃,R₁₄,R₁₆,R₁₈,R₂₁,R₆₁,R₆₅,R₇₁=are independently A,C,U or absent;

R₁,R₉,R₁₀,R₁₅,R₃₃,R₅₀,R₅₆=are independently A,G or absent;

R₇,R₂₅,R₇₂=are independently A,G,U or absent;

R₃₇,R₃₈,R₅₅,R₆₀=are independently C or absent;

R₁₂,R₃₅,R₄₃,R₆₄,R₆₉,R₇₀=are independently C,G,U or absent;

R₁₁,R₁₇,R₂₂,R₂₈,R₅₉,R₆₂=are independently C,U or absent;

R₁₉,R₂₀,R₅₂=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;

R₃₂,R₄₃,R₆₈=are independently C,G,U or absent;

R₁₁,R₁₆,R₂₈,R₃₁,R₄₉,R₅₉,R₆₅,R₇₀=are independently C,U or absent;

R₁,R₉,R₁₀,R₁₉,R₂₀,R₅₀,R₅₂,R₆₉=are independently G or absent;

R₅,R₈,R₂₉,R₃₀,R₄₂,R₅₁,R₆₄,R₆₆=are independently G,U or absent;

R₁₇,R₃₆,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₂,R₂₃=absent

R₁₄,R₂₄,R₃₉,R₄₁,R₅₇,R₇₂=are independently A or absent;

R₃,R₄,R₁₃,R₆₁,R₇₁=are independently A,C or absent;

R₆,R₄₄=are independently A,C,G or absent;

R₂₁= A,C,U or absent;

R₂,R₇,R₁₅,R₂₅,R₃₃,R₃₄,R₄₅,R₅₆,R₆₃=are independently A,G or absent;

R₅₈= A,G,U or absent;

R₄₆= A,U or absent;

R₃₇,R₃₈,R₅₅,R₆₀,R₆₂=are independently C or absent;

R₁₂,R₂₆,R₂₇,R₃₅,R₄₀,R₄₈,R₆₇=are independently C,G or absent;

R₃₂,R₄₃,R₆₈=are independently C,G,U or absent;

R₁₁,R₁₆,R₂₈,R₃₁,R₄₉,R₅₉,R₆₅,R₇₀=are independently C,U or absent;

R₁,R₉,R₁₀,R₁₉,R₂₀,R₅₀,R₅₂,R₆₉=are independently G or absent;

R₅,R₈,R₂₉,R₃₀,R₄₂,R₅₁,R₆₄,R₆₆=are independently G,U or absent;

R₁₇,R₃₆,R₅₃,R₅₄=are independently U or absent;

[R₄₇]_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.

Tyrosine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{TYR} (SEQ ID NO: 616),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-
R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-
R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-
R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀ =absent

R₁₄,R₃₉,R₅₇=are independently A or absent;

R₄₁,R₄₈,R₅₁,R₇₁=are independently A,C,G or absent;

R₃,R₄,R₅,R₆,R₉,R₁₀,R₁₂,R₁₃,R₁₆,R₂₅,R₂₆,R₃₀,R₃₁,R₃₂,R₄₂,R₄₄,R₄₅,R₄₆,R₄₉,R₅₀,R₅₈,R₆₂,R₆₃,R₆₆,
R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₂₂,R₆₅=are independently A,C,U or absent;

R₁₅,R₂₄,R₂₇,R₃₃,R₃₇,R₄₀,R₅₆=are independently A,G or absent;

R₇,R₂₉,R₃₄,R₇₂=are independently A,G,U or absent;

R₂₃,R₅₃=are independently A,U or absent;

R₃₅,R₆₀=are independently C or absent;

R₂₀= C,G or absent;

R₁,R₂,R₂₈,R₆₁,R₆₄=are independently C,G,U or absent;

R₁₁,R₁₇,R₂₁,R₄₃,R₅₅=are independently C,U or absent;

R₁₉,R₅₂=are independently G or absent;

R₈,R₁₈,R₃₆,R₃₈,R₅₄,R₅₉=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₇,R₉,R₁₄,R₂₄,R₂₆,R₃₄,R₃₉,R₅₇=are independently A or absent;

R₄₄,R₆₉=are independently A,C or absent;

R₇₁= A,C,G or absent;

R₆₈= N or absent;

R₅₈= A,C,U or absent;

R₃₃,R₃₇,R₄₁,R₅₆,R₆₂,R₆₃=are independently A,G or absent;

R₆,R₂₉,R₇₂=are independently A,G,U or absent;

R₃₁,R₄₅,R₅₃=are independently A,U or absent;

R₁₃,R₃₅,R₄₉,R₆₀=are independently C or absent;

R₂₀,R₄₈,R₆₄,R₆₇,R₇₀=are independently C,G or absent;

R₁,R₂,R₅,R₁₆,R₆₆=are independently C,G,U or absent;

R₁₁,R₂₁,R₂₈,R₄₃,R₅₅,R₆₁=are independently C,U or absent;

R₁₀,R₁₅,R₁₉,R₂₅,R₂₇,R₄₀,R₅₁,R₅₂=are independently G or absent;

R₃,R₄,R₃₀,R₃₂,R₄₂,R₄₆=are independently G,U or absent;

R₈,R₁₂,R₁₇,R₂₂,R₃₆,R₃₈,R₅₀,R₅₄,R₅₉,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₇,R₉,R₁₄,R₂₄,R₂₆,R₃₄,R₃₉,R₅₇,R₇₂=are independently A or absent;

R₄₄,R₆₉=are independently A,C or absent;

R₇₁= A,C,G or absent;

R₃₇,R₄₁,R₅₆,R₆₂,R₆₃=are independently A,G or absent;

R₆,R₂₉,R₆₈=are independently A,G,U or absent;

R₃₁,R₄₅,R₅₈=are independently A,U or absent;

R₁₃,R₂₈,R₃₅,R₄₉,R₆₀,R₆₁=are independently C or absent;

R₅,R₄₈,R₆₄,R₆₇,R₇₀=are independently C,G or absent;

R₁,R₂=are independently C,G,U or absent;

R₁₁,R₁₆,R₂₁,R₄₃,R₅₅,R₆₆=are independently C,U or absent;

R₁₀,R₁₅,R₁₉,R₂₀,R₂₅,R₂₇,R₃₃,R₄₀,R₅₁,R₅₂=are independently G or absent;

R₃,R₄,R₃₀,R₃₂,R₄₂,R₄₆=are independently G,U or absent;

R₈,R₁₂,R₁₇,R₂₂,R₃₆,R₃₈,R₅₀,R₅₃,R₅₄,R₅₉,R₆₅=are independently U or absent;

[R₄₇]_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),

R₀-R₁-R₂-R₃-R₄-R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂-R₄₃-R₄₄-R₄₅-R₄₆-[R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₂₃=absent;

R₂₄,R₃₈,R₅₇=are independently A or absent;

R₉,R₇₂=are independently A,C,G or absent;

R₂,R₄,R₅,R₆,R₇,R₁₂,R₁₅,R₁₆,R₂₁,R₂₅,R₂₆,R₂₉,R₃₁,R₃₂,R₃₃,R₃₄,R₃₇,R₄₁,R₄₂,R₄₃,R₄₄,R₄₅,R₄₆,R₄₈,R₄₉,R₅₀,R₅₈,R₆₁,R₆₂,R₆₃,R₆₄,R₆₅,R₆₆,R₆₇,R₆₈,R₆₉,R₇₀=are independently N or absent;

R₁₇,R₃₅,R₅₉=are independently A,C,U or absent;

R₁₀,R₁₄,R₂₇,R₄₀,R₅₂,R₅₆=are independently A,G or absent;

R₁,R₃,R₅₁,R₅₃=are independently A,G,U or absent;

R₃₉= C or absent;

R₁₃,R₃₀,R₅₅=are independently C,G,U or absent;

R₁₁,R₂₂,R₂₈,R₆₀,R₇₁=are independently C,U or absent;

R₁₉= G or absent;

R₂₀= 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;

R₂,R₄,R₁₃,R₄₈,R₅₅,R₆₁=are independently C,G,U or absent;

R₁₁,R₂₂,R₂₈,R₃₀,R₃₅,R₆₀,R₇₁=are independently C,U or absent;

R₁₉= G or absent;

R₁,R₃,R₂₀,R₄₂=are independently G,U or absent;

R₈,R₂₁,R₃₆,R₅₄=are independently U or absent;

[R₄₇]_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),

R₀- R₁-R₂- R₃-R₄ -R₅-R₆-R₇-R₈-R₉-R₁₀-R₁₁-R₁₂-R₁₃-R₁₄-R₁₅-R₁₆-R₁₇-R₁₈-R₁₉-R₂₀-R₂₁-R₂₂-R₂₃-R₂₄-R₂₅-R₂₆-R₂₇-R₂₈-R₂₉-R₃₀-R₃₁-R₃₂-R₃₃-R₃₄-R₃₅-R₃₆-R₃₇-R₃₈-R₃₉-R₄₀-R₄₁-R₄₂- R₄₃- R₄₄-R₄₅-R₄₆- [R₄₇]_x-R₄₈-R₄₉-R₅₀-R₅₁-R₅₂-R₅₃-R₅₄-R₅₅-R₅₆-R₅₇-R₅₈-R₅₉-R₆₀-R₆₁-R₆₂-R₆₃-R₆₄-R₆₅-R₆₆-R₆₇-R₆₈-R₆₉-R₇₀-R₇₁-R₇₂

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

R₀,R₁₈,R₂₃=absent

R₂₄,R₃₈,R₄₀,R₅₇,R₇₂=are independently A or absent;

R₂₉,R₆₄,R₇₀=are independently A,C,G or absent;

R₄₉,R₅₀,R₆₂=are independently N or absent;

R₁₆,R₂₆,R₃₁,R₃₂,R₃₇,R₄₁,R₄₃,R₅₉,R₆₅=are independently A,C,U or absent;

R₉,R₁₄,R₂₇,R₄₆,R₅₂,R₅₆,R₆₆=are independently A,G or absent;

R₇,R₁₂,R₂₅,R₃₃,R₄₄,R₄₅,R₅₃,R₅₈,R₆₃,R₆₈=are independently A,G,U or absent;

R₆₉= A,U or absent;

R₃₉= C or absent;

R₅,R₆₇=are independently C,G or absent;

R₂,R₄,R₁₃,R₁₅,R₄₈,R₅₅=are independently C,G,U or absent;

R₆,R₁₁,R₂₂,R₂₈,R₃₀,R₃₄,R₃₅,R₆₀,R₆₁,R₇₁=are independently C,U or absent;

R₁₀,R₁₉,R₅₁=are independently G or absent;

R₁,R₃,R₂₀,R₄₂=are independently G,U or absent;

R₈,R₁₇,R₂₁,R₃₆,R₅₄=are independently U or absent;

[R₄₇]_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 R₄₇. 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	CAGGCGGGTTCTGCCCCGCGC
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	TAAC TAGATACTTTCAGAT
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	TATAGGGTCAAAAACCTCTATC
47	498	TATGCAGAAATACCTGCATC
48	499	TCCCCATACGGGGGC
49	500	TCCCGAAGGGGTTC
50	501	TCTACGTATGTGGGC
51	502	TCTCATAGGAGTTC
52	503	TCTCCTCTGGAGGC
53	504	TCTTAGCAATAAGGT
54	505	TCTTG TAGGAGTTC
55	506	TGAACGTAAGTTCGC
56	507	TGAACTGCGAGGTTC
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	TGGGCGTTTCGCCCCG
82	533	TGGGCTTCGCCCCG
83	534	TGGGGGATAACCCCGT
84	535	TGGGGGTTTCCCGT
85	536	TGGT
86	537	TGGTGGCAACACCGT
87	538	TGGTTTATAGCCGT
88	539	TGTACGGTAATACCGTACC
89	540	TGTCCGCAAGGACGT
90	541	TGTCCTAACGGACGT
91	542	TGTCCTATTACGGACGT
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	TTCCCTTCGGGAGC
102	553	TTCTAGCAATAGAGT
103	554	TTCTCCACTGGGGAGC
104	555	TTCTCGAGAGGGAGC
105	556	TTCTCGTATGAGAGC
106	557	TTTAAGGTTTCCCTTAAC
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 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 bases 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 TTTGCATGTATGAGGCCCGGGTTCGATCCC CGGCACCTCCA
1203	Arg	ACG	GGGCCAGTGGCGCAATGGATAACGCGTCTG ACTACGGATCAGAAGATTCCAGGTTCGACTC CTGGCTGGCTCG
1204	Arg	CCG	GGCCGCGTGGCCTAATGGATAAAGGCGTCTG ATTCCGGATCAGAAGATTGAGGGTTCGAGTC CCTTCGTGGTCTG
1205	Arg	CCT	GCCCCAGTGGCCTAATGGATAAAGGCACTGG CCTCCTAAGCCAGGGATTGTGGGTTCGAGTC CCACCTGGGGTA
1206	Arg	TCG	GACCGCGTGGCCTAATGGATAAAGGCGTCTG ACTTCGGATCAGAAGATTGAGGGTTCGAGTC CCTCCGTGGTCTG
1207	Arg	TCT	GGCTCTGTGGCGCAATGGATNAGCGCATTG GACTTCTAATTCAAAGGTTGCGGGTTCGAGT CCCNCCAGAGTCG
1208	Asn	GTT	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTAAACCGNAAAGGTTGGTGGTTCGAGC CCACCCAGGGACG
1209	Asp	GTC	TCCTCGTTAGTATAGTGGTGAGTATCCCCGC CTGTCACGCGGGAGACCGGGTTCGATTCCC CGACGGGGAG
1210	Cys	GCA	GGGGGTATAGCTCAGNGGGTAGAGCATTG ACTGCAGATCAAGAGGTCCCCGGTTCAAATC CGGGTGCCCCCT
1211	Gln	CTG	GGTTCCATGGTGTAAATGGTNAGCACTCTGGA CTCTGAATCCAGCGATCCGAGTTCAAAGTCTC GGTGGAACCT
1212	Gln	TTG	GGTCCCATGGTGTAAATGGTTAGCACTCTGGA CTTTGAATCCAGCGATCCGAGTTCAAATCTC GGTGGGACCT
1213	Glu	CTC	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCG CTCTCACC GCCGCGGCCCGGGTTCGATTCCC GGTCAGGGAA
1214	Glu	TTC	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCG CTTTCACCGCNGCGGCCCGGGTTCGATTCCC GGTCAGGGAA
1215	Gly	CCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCC TCCCACGCNGGAGACCCGGGTTCGATTCCCG GCCAATGCA
1216	Gly	GCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCC TGCCACGCGGGAGGCCCGGGTTCGATTCCCG GCCAATGCA

1217	Gly	TCC	GCGTTGGTGGTATAGTGGTGAGCATAGCTGC CTTCCAAGCAGTTGACCCGGGTTTCGATTCCC GGCCAACGCA
1218	Ile	AAT	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGT GCTAATAACGCCAAGGTCGCGGGTTCGATCC CCGTACGGGCCA
1219	Ile	TAT	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGT ACTTATAATGCCGAGGTTGTGAGTTCGAGCC TCACCTGGAGCA
1220	Leu	AAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTG GATTAAGGCTCCAGTCTCTTCGGGGGCGTGG GTTCTGAATCCCACCGCTGCCA
1221	Leu	CAA	GTCAGGATGGCCGAGTGGTCNTAAGGCGCC AGACTCAAGTTCTGGTCTCCGNATGGAGGCG TGGGTTCTGAATCCCACCTTCTGACA
1222	Leu	CAG	GTCAGGATGGCCGAGCGGTCTAAGGCGCTG CGTTCAGGTCGCAGTCTCCCCTGGAGGCGTG GGTTCGAATCCCACCTCCTGACA
1223	Leu	TAA	ACCAGGATGGCCGAGTGGTTAAGGCGTTGG ACTTAAGATCCAATGGACAGATGTCCGCGTG GGTTCGAACCCCACTCCTGGTA
1224	Leu	TAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTG GATTTAGGCTCCAGTCTCTTCGGNGGCGTGG GTTCTGAATCCCACCGCTGCCA
1225	Lys	CTT	GCCCGGCTAGCTCAGTCGGTAGAGCATGAG ACTCTTAATCTCAGGGTCGTGGGTTTCGAGCC CCACGTTGGGCGNNN
1226	Lys	TTT	GCCTGGATAGCTCAGTCGGTAGAGCATCAG ACTTTTAATCTGAGGGTCCAGGGTTCAAGTC CCTGTTTCAGGCG
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 GTTTGAATCCTGCCGACTACG
1233	Ser	CGA	GCTGTGATGGCCGAGTGGTTAAGGCGTTGG ACTCGAAATCCAATGGGGTCTCCCCGCGCAG GTTTGAATCCTGCTCACAGCG
1234	Ser	GCT	GACGAGGNNTGGCCGAGTGGTTAAGGCGAT GGACTGCTAATCCATTGTGCTCTGCACGCGT GGGTTCGAATCCCATCCTCGTCG
1235	Ser	TGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGG ACTTGAAATCCATTGGGGTCTCCCCGCGCAG GTTTGAATCCTGCCGCTACG
1236	Thr	AGT	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC CCAGCGGGGCCT
1237	Thr	CGT	GGCNCTGTGGCTNAGTNGGNTAAAGCGCCG GTCTCGTAAACNNGGAGATCNTGGGTTCGA ATCCANCNNGGCCT
1238	Thr	TGT	GGCTCCATAGCTCAGNNGGTTAGAGCACTG GTCTTGTAACAGGGGTCGCGAGTTCAAAT CTCGCTGGGGCCT
1239	Trp	CCA	GACCTCGTGGCGCAACGGTAGCGCGTCTGA CTCCAGATCAGAAGGTTGCGTGTTCAAATCA CGTCGGGGTCA
1240	Tyr	GTA	CCTTCGATAGCTCAGCTGGTAGAGCGGAGG ACTGTAGATCCTTAGGTCGCTGGTTCGATTC CGGCTCGAAGGA
1241	Val	AAC	GTTTCCGTAGTGTAGTGGTTATCACGTTTCG CTAACACGCGAAAGGTCCCCGGTTCGAAAC CGGGCGGAAACA
1242	Val	CAC	GTTTCCGTAGTGTAGTGGTTATCACGTTTCG CTCACACGCGAAAGGTCCCCGGTTCGAAAC CGGGCGGAAACA
1243	Val	TAC	GGTTCCATAGTGTAGTGGTTATCACGTCTGC TTTACACGCGAGAAGGTCCTGGGTTCGAGCCC CAGTGAACCA
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
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1245	Ala	AGC	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGC TTAGCATGCAAGAGGTAGTGGGATCGATGCC CACATTCTCCANN
1246	Ala	CGC	GGGGATGTAGCTCAGTGGTAGAGCGCATGCT TCGCATGTATGAGGTCCCGGGTTCGATCCCC GGCATCTCCANN
1247	Ala	TGC	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCT TTGCATGTATGAGGCCCGGGTTCGATCCCC GGCACCTCCANN
1248	Arg	ACG	GGGCCAGTGGCGCAATGGATAACGCGTCTGA CTACGGATCAGAAGATTCCAGGTTCGACTCC TGGCTGGCTCGNN
1249	Arg	CCG	GGCCGCGTGGCCTAATGGATAAGGCGTCTGA TTCCGGATCAGAAGATTGAGGGTTCGAGTCC CTTCGTGGTCGNN
1250	Arg	CCT	GCCCCAGTGGCCTAATGGATAAGGCACTGGC CTCCTAAGCCAGGGATTGTGGGTTCGAGTCC CACCTGGGGTANN
1251	Arg	TCG	GACCGCGTGGCCTAATGGATAAGGCGTCTGA CTTCGGATCAGAAGATTGAGGGTTCGAGTCC CTCCGTGGTCGNN
1252	Arg	TCT	GGCTCTGTGGCGCAATGGATNAGCGCATTGG ACTTCTAATTCAAAGGTTGCGGGTTCGAGTC CCNCCAGAGTCGNN
1253	Asn	GTT	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCG GCTGTAAACCGNAAAGGTTGGTGGTTCGAGC CCACCCAGGGACGNN
1254	Asp	GTC	TCCTCGTTAGTATAGTGGTAGATCCCCGCC TGTCACGCGGGAGACCGGGGTTGATTCCCC GACGGGGAGNN
1255	Cys	GCA	GGGGGTATAGCTCAGNGGGTAGAGCATTGGA CTGCAGATCAAGAGGTCCCCGGTCAAATCC GGGTGCCCCCTNN
1256	Gln	CTG	GGTTCCATGGTGTAAATGGTNAGCACTCTGGA CTCTGAATCCAGCGATCCGAGTTCAAAGTCTC GGTGGAACCTNN
1257	Gln	TTG	GGTCCCATGGTGTAAATGGTTAGCACTCTGGA CTTTGAATCCAGCGATCCGAGTTCAAATCTC GGTGGGACCTNN
1258	Glu	CTC	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCG CTCTACCGCCGCGGCCCGGGTTCGATTCCC GGTCAGGGAANN
1259	Glu	TTC	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCG CTTTCACCGCNGCGGCCCGGGTTCGATTCCC GGTCAGGGAANN

1260	Gly	CCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCT CCCACGCNGGAGACCCGGGTTTCGATTCCCGG CCAATGCANN
1261	Gly	GCC	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCT GCCACGCGGGAGGCCCGGGTTTCGATTCCCGG CCAATGCANN
1262	Gly	TCC	GCGTTGGTGGTATAGTGGTAGCATAGCTGC CTTCCAAGCAGTTGACCCGGGTTTCGATTCCC GGCCAACGCANN
1263	Ile	AAT	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGT GCTAATAACGCCAAGGTCGCGGGTTTCGATCC CCGTACGGGCCANN
1264	Ile	TAT	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGT ACTTATAATGCCGAGGTTGTGAGTTCGAGCC TCACCTGGAGCANN
1265	Leu	AAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTAAGGCTCCAGTCTCTTCGGGGGCGTGGG TTCGAATCCCACCGCTGCCANN
1266	Leu	CAA	GTCAGGATGGCCGAGTGGTCNTAAGGCGCCA GACTCAAGTTCTGGTCTCCGNATGGAGGCGT GGGTTTCGAATCCCCTCTGACANN
1267	Leu	CAG	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGC GTTTCAGGTCGCAGTCTCCCCTGGAGGCGTGG GTTTCGAATCCCCTCTGACANN
1268	Leu	TAA	ACCAGGATGGCCGAGTGGTTAAGGCGTTGGA CTTAAGATCCAATGGACAGATGTCCGCGTGG GTTTCGAACCCCACTCCTGGTANN
1269	Leu	TAG	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGG ATTTAGGCTCCAGTCTCTTCGGNNGCGTGGG TTCGAATCCCACCGCTGCCANN
1270	Lys	CTT	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGA CTCTTAATCTCAGGGTCGTGGGTTTCGAGCCCC ACGTTGGGCGNNNNN
1271	Lys	TTT	GCCTGGATAGCTCAGTCGGTAGAGCATCAGA CTTTTAATCTGAGGGTCCAGGGTTCAAGTCCC TGTTTCAGGCGNNN
1272	Met	CAT	GCCCTCTTAGCGCAGTNGGCAGCGCGTCAGT CTCATAATCTGAAGGTCCTGAGTTCGAGCCT CAGAGAGGGCANN
1273	Phe	GAA	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGA CTGAAGATCNTAAAGGTCCTGGTTCAATCC CGGGTTTCGGCANN
1274	Pro	AGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT AGGATGCGAGAGGTCCCGGGTCAAATCCCG GACGAGCCCN

1275	Pro	CGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT CGGGTGCGAGAGGTCCCAGGGTTCAAATCCCG GACGAGCCCN
1276	Pro	TGG	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTT TGGGTGCGAGAGGTCCCAGGGTTCAAATCCCG GACGAGCCCN
1277	Ser	AGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGA CTAGAAATCCATTGGGGTTTCCCCGCGCAGG TTCGAATCCTGCCGACTACGNN
1278	Ser	CGA	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGA CTCGAAATCCAATGGGGTCTCCCCGCGCAGG TTCGAATCCTGCTCACAGCGNN
1279	Ser	GCT	GACGAGGNNTGGCCGAGTGGTTAAGGCGAT GGACTGCTAATCCATTGTGCTCTGCACGCGT GGGTTCGAATCCCATCCTCGTCGNN
1280	Ser	TGA	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGA CTTGAATCCATTGGGGTCTCCCCGCGCAGG TTCGAATCCTGCCGGCTACGNN
1281	Thr	AGT	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTG TCTAGTAAACAGGAGATCCTGGGTTCGAATC CCAGCGGGGCCTNN
1282	Thr	CGT	GGCNCTGTGGCTNAGTNGGNTAAAGCGCCGG TCTCGTAAACCNGGAGATCNTGGGTTCGAAT CCANCNNGGCCTNN
1283	Thr	TGT	GGCTCCATAGCTCAGNGGGTTAGAGCACTGG TCTTGTAACCAGGGGTCGCGAGTTCAAATC TCGCTGGGGCCTNN
1284	Trp	CCA	GACCTCGTGGCGCAACGGTAGCGCGTCTGAC TCCAGATCAGAAGGTTGCGTGTTCAAATCAC GTCGGGGTCANNN
1285	Tyr	GTA	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGA CTGTAGATCCTTAGGTCGCTGGTTCGATTCCG GCTCGAAGGANNN
1286	Val	AAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCCGC TAACACGCGAAAGGTCCCCGGTTCGAAACCG GGCGGAAACANNN
1287	Val	CAC	GTTTCCGTAGTGTAGTGGTTATCACGTTCCGC 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

Method of making TREMs, TREM core fragments, and TREM fragments

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 phase synthesis or liquid phase synthesis.

In an embodiment, a TREM, a TREM core fragment or a TREM fragment made according to a synthetic 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 synthetic TREM via 5'-Silyl-2'-Orthoester (2'-ACE) chemistry is provided in Example 3. The method provided in Example 3 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 1×10^6 TREM molecules, at least 1×10^7 TREM molecules, at least 1×10^8 TREM molecules or at least 1×10^9 TREM molecules.

In an embodiment, a TREM composition comprises at least 1×10^6 TREM core fragment molecules, at least 1×10^7 TREM core fragment molecules, at least 1×10^8 TREM core fragment molecules or at least 1×10^9 TREM core fragment molecules.

In an embodiment, a TREM composition comprises at least 1×10^6 TREM fragment molecules, at least 1×10^7 TREM fragment molecules, at least 1×10^8 TREM fragment molecules or at least 1×10^9 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 amoebocyte 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, 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 leukemia-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 1-(monomethoxy-polyethyleneglycol)-2,3- dimyristoylglycerol (PEG-DMG)), PEG-dialkylxypropyl (DAA), PEG-phospholipid, PEG- ceramide (Cer), a pegylated phosphatidylethanolamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG)

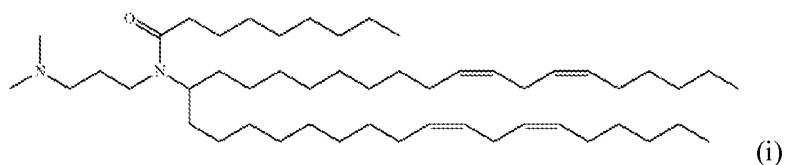
(such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-1-0-(w- methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypopylcarbam, N- (carbonyl-methoxypoly ethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, and those described in Table 2 of WO2019051289 (incorporated 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.

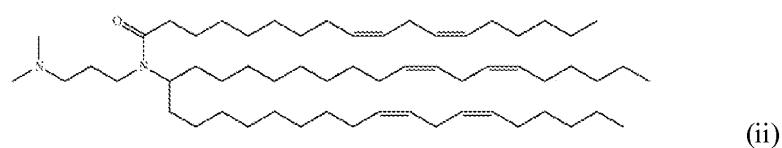
In some embodiments, the lipid particle comprises an ionizable lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a sterol. The amounts of these components can be varied independently and to achieve desired properties. For example, in some embodiments, the lipid 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.

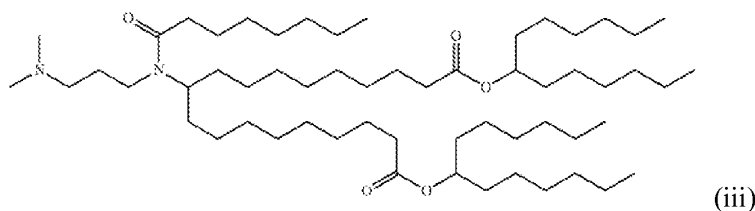
Some non-limiting example of lipid compounds that may be used (e.g., in combination with other lipid components) to form lipid nanoparticles for the delivery of compositions described herein, e.g., nucleic acid (e.g., RNA) described herein includes,



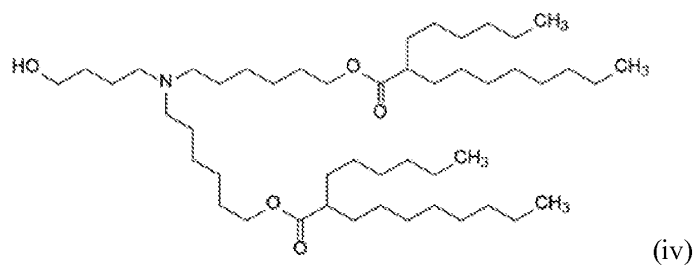
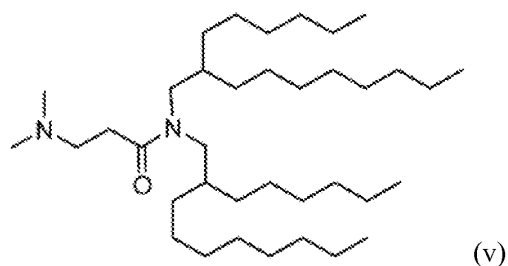
In some embodiments an LNP comprising Formula (i) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



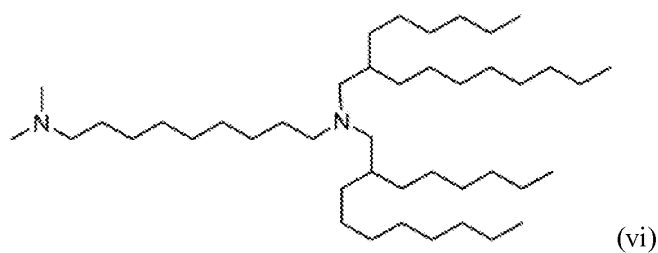
In some embodiments an LNP comprising Formula (ii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



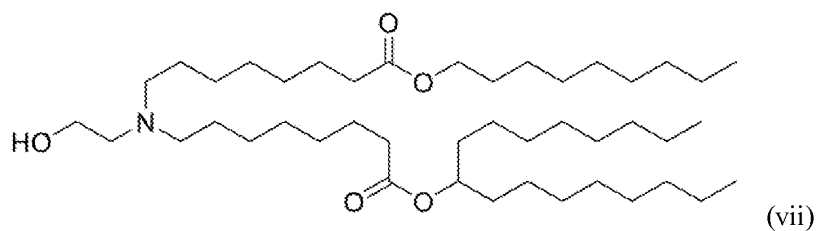
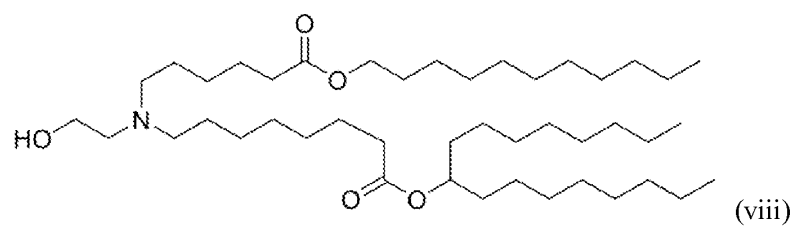
In some embodiments an LNP comprising Formula (iii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



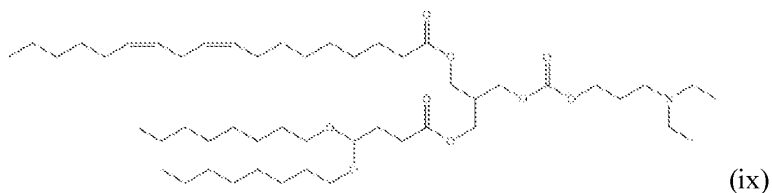
In some embodiments an LNP comprising Formula (v) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



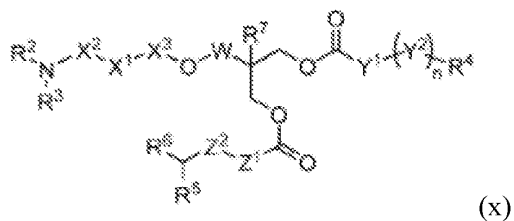
In some embodiments an LNP comprising Formula (vi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



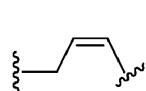
In some embodiments an LNP comprising Formula (viii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



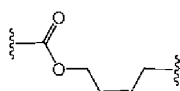
In some embodiments an LNP comprising Formula (ix) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



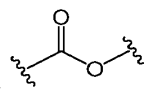
wherein X^1 is O, NR^1 , or a direct bond, X^2 is C2-5 alkylene, X^3 is $C(=O)$ or a direct bond, R^1 is H or Me, R^3 is C1-3 alkyl, R^2 is C1-3 alkyl, or R^2 taken together with the nitrogen atom to which it is attached and 1-3 carbon atoms of X^2 form a 4-, 5-, or 6-membered ring, or X^1 is NR^1 , 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



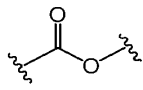
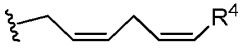
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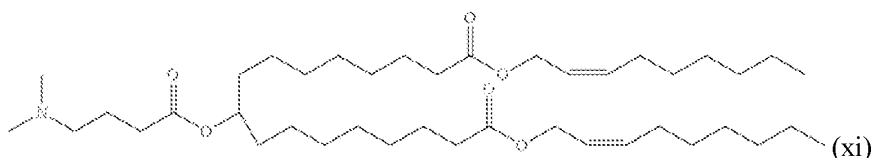
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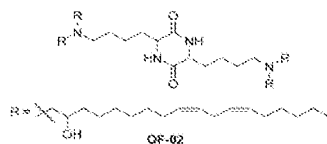
(in either

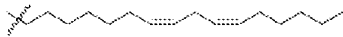
n is 0 to 3, R^4 is C1-15 alkyl, Z^1 is C1-6 alkylene or a direct bond, Z^2 is , (in either orientation) or absent, provided that if Z^1 is a direct bond, Z^2 is absent; R^5 is C5-9 alkyl or C6-10 alkoxy, R^6 is C5-9 alkyl or C6-10 alkoxy, W is methylene or a direct bond, and R^7 is H or Me, or a salt 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 $C(=O)$, Y^1 is linear C n 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 C x alkoxy.

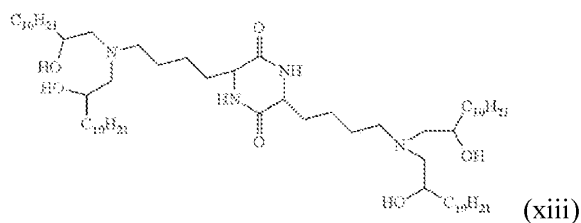
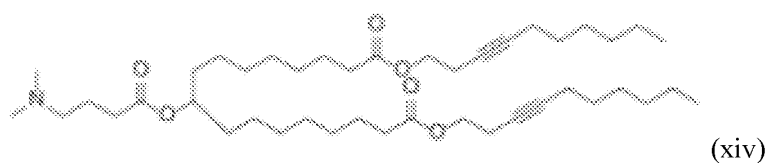
In some embodiments an LNP comprising Formula (xii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



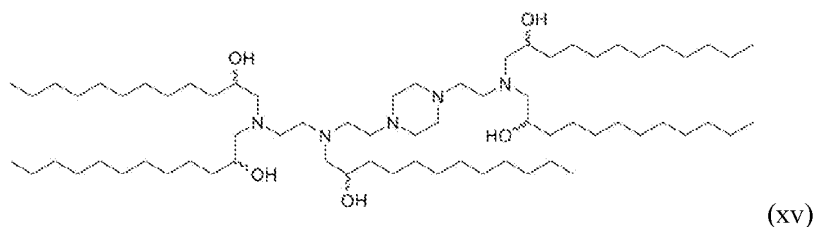
In some embodiments an LNP comprising Formula (xi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



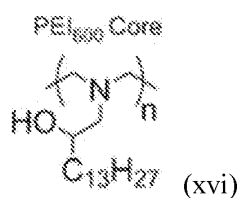
where $R =$  (xii)



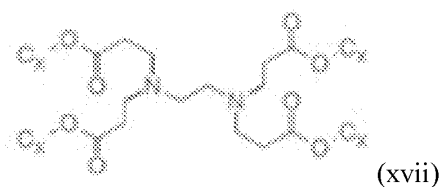
In some embodiments an LNP comprises a compound of Formula (xiii) and a compound of Formula (xiv).

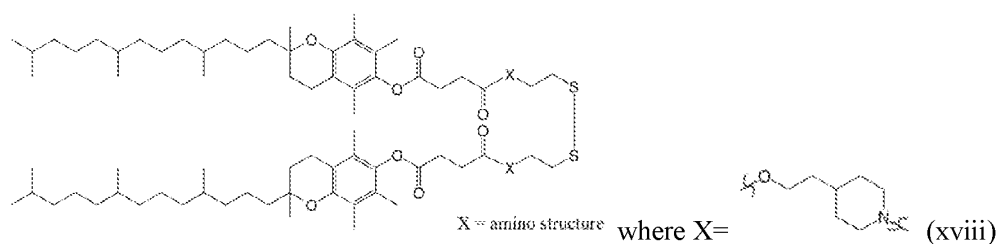


In some embodiments, an LNP comprising Formula (xv) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

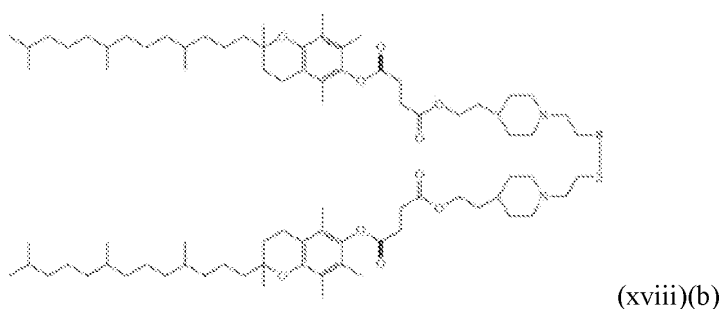
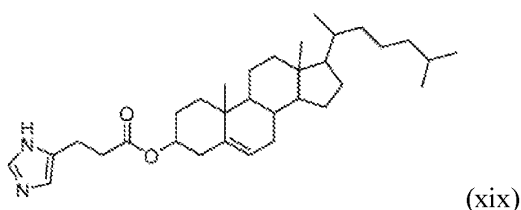


In some embodiments an LNP comprising a formulation of Formula (xvi) is used to deliver a TREM composition described herein to the lung endothelial cells.

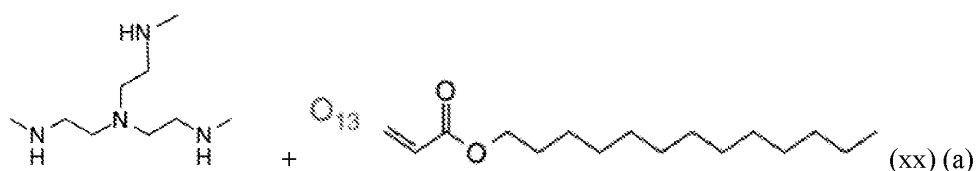




(a)



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:



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-1H- 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), (iii), (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 WO2013/016058; A of WO2012/162210; 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 WO2009/132131; 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 1Z)-heptatriaconta-6,9,28,3 1-tetraen-19-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 (13Z,16Z)-A,A-dimethyl-3- nonyldocosa-13, 16-dien-1-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), 18-1-trans PE, 1-stearoyl-2-oleoyl- phosphatidylethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierycoylphosphatidylcholine (DEPC), palmitoyloleoylphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidic acid, 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, palmitoyl, 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](https://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, dodecylamine, hexadecylamine, acetyl palmitate, glycerol ricinoleate, hexadecyl stearate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethoxylated 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.

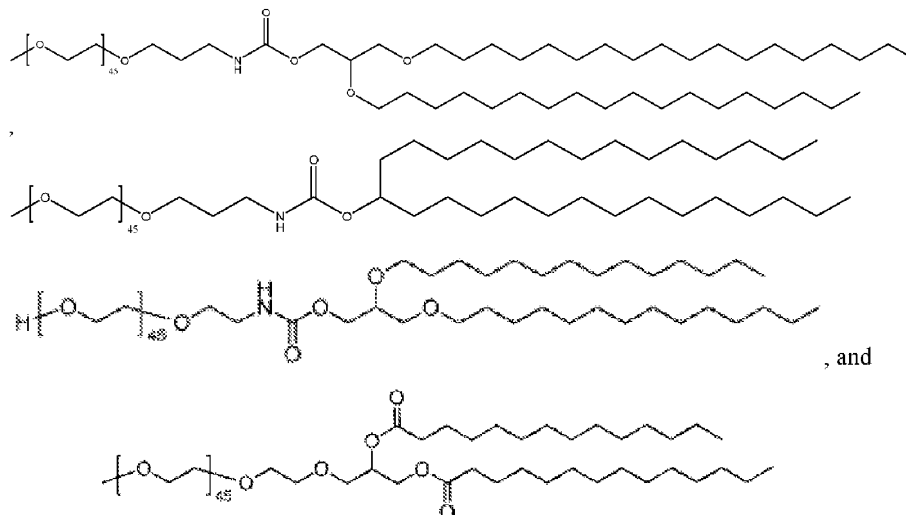
In some aspects, the lipid nanoparticle can further comprise a component, such as a sterol, to provide membrane integrity. One exemplary sterol that can be used in the lipid nanoparticle is cholesterol and derivatives thereof. Non-limiting examples of cholesterol derivatives include polar analogues such as 5 α -cholestanol, 5 β -coprostanol, choiesterolyl-(2'-hydroxy)-ethyl ether, choiesterolyl-(4'-hydroxy)-butyl ether, and 6-ketocholestanol; non-polar analogues such as 5 α -cholestane, cholestenone, 5 α -cholestanone, 5 β -cholestanone, and choiesterolyl decanoate; and mixtures thereof. In some embodiments, the cholesterol derivative is a polar analogue, e.g., choiesterolyl-(4'-hydroxy)-butyl 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 1-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (PEG-DMG)), PEG-dialkylxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanolamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-1-0-(w-methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypylcarbam, N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-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-dipalmitoyloxypropyl, or PEG-distearoyloxypropyl. The PEG-lipid can be one or more of PEG-DMG, PEG-dilaurylglycerol, PEG-dipalmitoylglycerol, PEG- disteryllycerol, PEG-dilaurylglycamide, PEG-dimyristylglycamide, PEG- dipalmitoylglycamide, PEG-disterylglycamide, PEG-cholesterol (1-[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:



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,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-(((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-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 1 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 tablet 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 ONPATTRA.

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 composition comprising a TREM comprising an ASGPR binding moiety (*e.g.*, a pharmaceutical TREM composition described herein) can modulate a function in a cell, tissue or subject. In embodiments, a composition comprising a TREM comprising an ASGPR binding moiety (*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).

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 a 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 disorder 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.

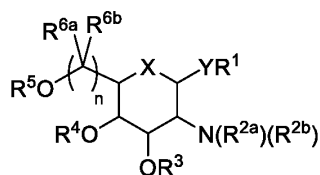
All references and publications cited herein are hereby incorporated by reference.

ENUMERATED EMBODIMENTS

1. A tRNA effector molecule (TREM) comprising an asialoglycoprotein receptor (ASGPR) binding moiety, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide of the TREM, or at a terminus (e.g., the 5' or 3' terminus) of the TREM, or within the internucleotide linkage of a TREM.
2. The TREM of embodiment 1, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide of the TREM.

3. The TREM of any one of embodiments 1-2, wherein the ASGPR binding moiety is bound to a terminus (e.g., the 5' or 3' terminus) of the TREM.
4. The TREM of any one of embodiments 1-3, wherein the ASGPR binding moiety is present within the internucleotide linkage of a TREM.
5. A TREM comprising:
 - (i) a sequence of Formula A comprising:
[L1]_y-[ASt Domain1]_x-[L2]_x-[DH Domain]_x-[L3]_x-[ACH Domain]_x-[VL Domain]_y-[TH Domain]_x-[L4]_x-[ASt Domain2]_x, (A); and
 - (ii) an asialoglycoprotein receptor (ASGPR) binding moiety (e.g., a GalNAc moiety, e.g., GalNAc);wherein y is 0 or 1 and x is 1.
6. The TREM of embodiment 5, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the ASt Domain 1.
7. The TREM of any one of embodiments 1-6, wherein the ASGPR binding moiety is bound to a nucleobase at any one of positions 1-9 within the TREM.
8. The TREM of embodiment 5, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the DH Domain.
9. The TREM of claim 1-8, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of positions 10-26 within the TREM.
10. The TREM of embodiment 5, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the ACH Domain.
11. The TREM of any one of embodiments 1-10, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of positions 27-43.

12. The TREM of embodiment 5, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide within the TH Domain.
13. The TREM of any one of embodiments 1-12, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of positions 50-64.
14. The TREM of embodiment 5, wherein the ASGPR binding moiety is bound to a nucleobase within the ASt Domain 2.
15. The TREM of any one of embodiments 1-14, wherein the ASGPR binding moiety is bound to a nucleobase at any one of positions 65-76 within the TREM.
16. The TREM of any one of embodiments 1-15, wherein the ASGPR binding moiety (e.g., a GalNAc moiety, e.g., GalNAc) is coupled to the nucleobase moiety of a nucleotide of the TREM molecule via a covalent linkage (e.g., at a nitrogen or carbon atom in the nucleobase moiety).
17. The TREM of any one of embodiments 1-16, wherein the nucleobase is a naturally occurring nucleobase or a non-naturally occurring nucleobase.
18. The TREM of any one of embodiments 1-17, wherein the nucleobase comprises uracil, adenine, guanine, cytosine, thymine, or a variant thereof.
19. The TREM molecule of any one of embodiments 1-18, wherein the ASGPR binding moiety comprises a GalNAc moiety (e.g., a GalNAc or a GalNAc analog).
20. The TREM molecule of any one of embodiments 1-19, wherein the ASGPR binding moiety comprises a plurality of GalNAc moieties.
21. The TREM molecule of any one of embodiments 1-20, wherein the ASGPR binding moiety comprises a structure of Formula (I):



(I) or a salt thereof, wherein:

each of X and Y is independently O, N(R⁷), or S;

each of R¹, R³, R⁴, and R⁵ are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁸;

or R³ and R⁴ are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R⁸;

R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃);

each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁹;

R⁷ is hydrogen, alkyl, or C(O)-alkyl;

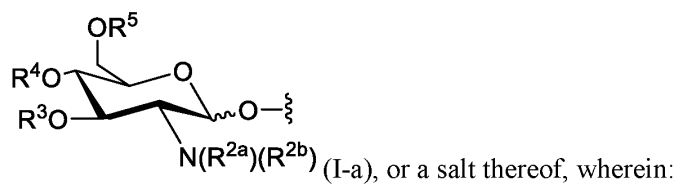
each of R⁸ and R⁹ is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl;

R^A is hydrogen, or alkyl, alkenyl, alkynyl, and n is an integer between 0 and 6, wherein the structure of Formula (I) may be connected to a linker or TREM.

22. The TREM of embodiment 21, wherein the GalNAc moiety comprises a plurality of structures of Formula (I).

23. The TREM of any one of embodiments 21-22, wherein the GalNAc moiety further comprises a linker.

24. The TREM of any one of embodiments 1-23, wherein the ASGPR binding moiety comprises a structure of Formula (I-a):



R^{2a} is hydrogen or alkyl;

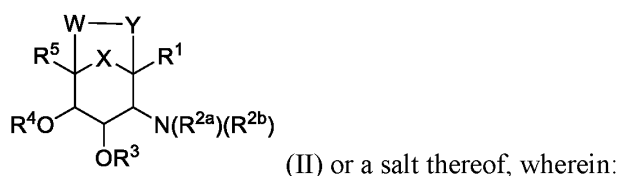
R^{2b} is $-C(O)alkyl$ (e.g., $C(O)CH_3$);

each of R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, $C(O)alkyl$, $C(O)alkenyl$, $C(O)alkynyl$, $C(O)heteroalkyl$, $C(O)haloalkyl$, $C(O)aryl$, $C(O)heteroaryl$, $C(O)cycloalkyl$, or $C(O)heterocyclyl$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ; and

R^8 is hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl,

wherein the “~” represents a bond in any configuration, and “ ξ ” represents an attachment point to a linker or a TREM.

25. The TREM of any one of embodiments 1-24, wherein the ASGPR binding moiety comprises a structure of Formula (II):



X is O, $N(R^7)$, or S;

each of W or Y is independently O or $C(R^{10a})(R^{10b})$, wherein one of W and Y is O;

each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, $C(O)alkyl$, $C(O)alkenyl$, $C(O)alkynyl$, $C(O)heteroalkyl$, $C(O)haloalkyl$, $C(O)aryl$, $C(O)heteroaryl$, $C(O)cycloalkyl$, or $C(O)heterocyclyl$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ;

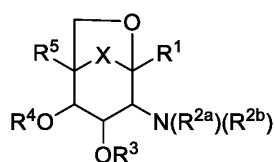
or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ;

R^{2a} is hydrogen or alkyl; R^{2b} is $-C(O)alkyl$ (e.g., $C(O)CH_3$);

each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, $-OR^A$, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ; R^7 is hydrogen, alkyl, or $C(O)-alkyl$;

each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; each of R^{10a} and R^{10b} is independently hydrogen, heteroalkyl, haloalkyl, or halo; and R^A is hydrogen, or alkyl, alkenyl, alkynyl, wherein the structure of Formula (I) may be connected to a linker or a TREM.

26. The TREM of any one of embodiments 1-25, wherein the ASGPR binding moiety comprises a structure of Formula (II):



(II-a) or a salt thereof, wherein X is O, $N(R^7)$, or S;

each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, $C(O)-alkyl$, $C(O)-alkenyl$, $C(O)-alkynyl$, $C(O)-heteroalkyl$, $C(O)-haloalkyl$, $C(O)-aryl$, $C(O)-heteroaryl$, $C(O)-cycloalkyl$, or $C(O)-heterocyclyl$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^8 ;

or R^3 and R^4 are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R^8 ;

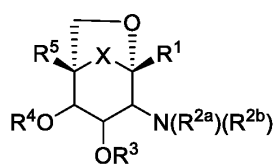
R^{2a} is hydrogen or alkyl; R^{2b} is $-C(O)alkyl$ (e.g., $C(O)CH_3$); each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, $-OR^A$, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9 ;

R^7 is hydrogen, alkyl, or $C(O)-alkyl$;

each of R^8 and R^9 is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; and R^A is hydrogen, or alkyl, alkenyl, alkynyl,

wherein the structure of Formula (I) may be connected to a linker or a TREM.

27. The TREM of any one of embodiments 1-26, wherein the ASGPR binding moiety comprises a structure of Formula (II-b):



(II-b) or a salt thereof, wherein :

X is O, N(R⁷), or S;

each of R¹, R³, R⁴, and R⁵ are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl, C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁸;

or R³ and R⁴ are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R⁸;

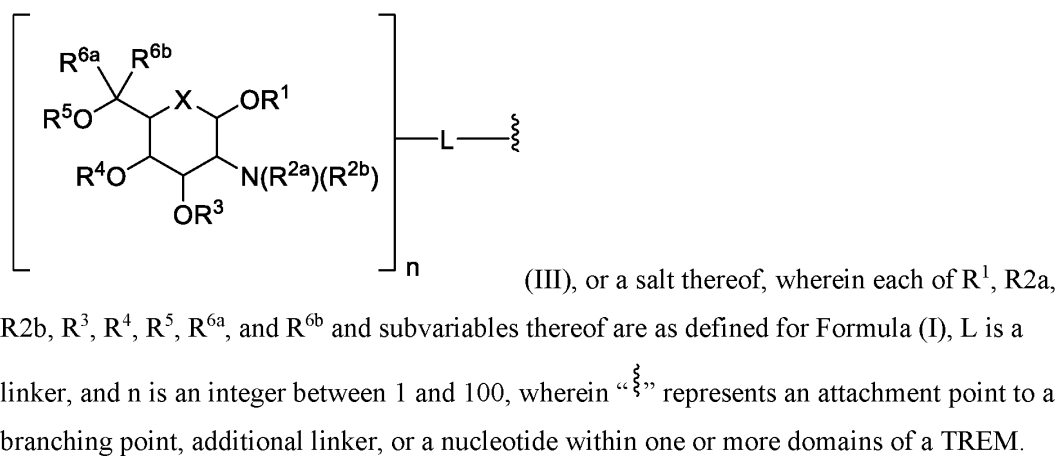
R^{2a} is hydrogen or alkyl; R^{2b} is -C(O)alkyl (e.g., C(O)CH₃);

each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁹;

R⁷ is hydrogen, alkyl, or C(O)-alkyl; each of R⁸ and R⁹ is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl; and

R^A is hydrogen, or alkyl, alkenyl, alkynyl, wherein the structure of Formula (I) may be connected to a linker or a TREM.

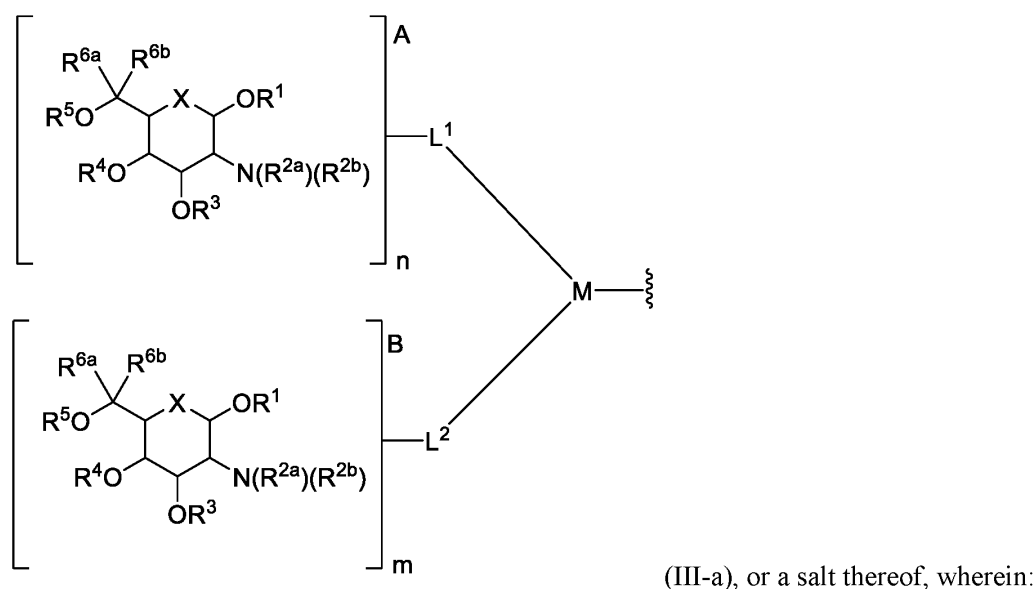
28. The TREM of any one of embodiments 1-27, wherein the ASGPR binding moiety comprises a structure of Formula (III):



29. The TREM of embodiment 28, wherein L comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.

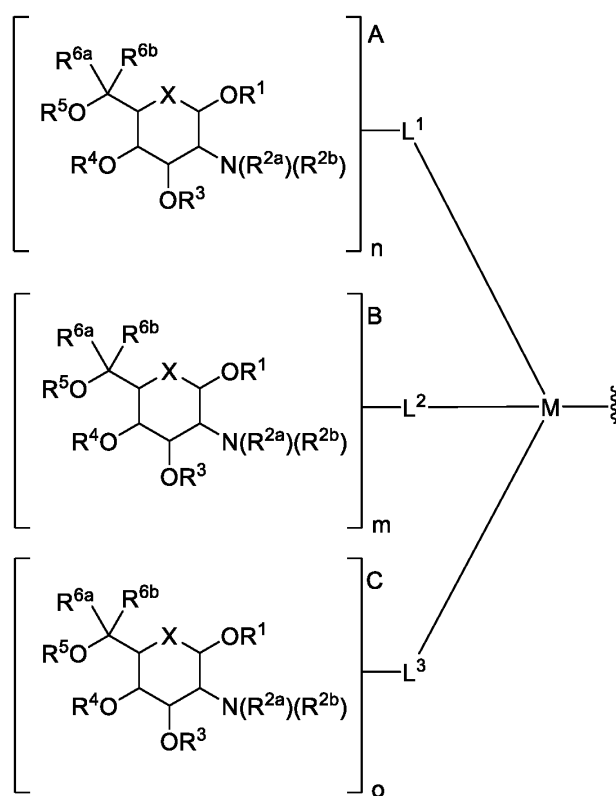
30. The TREM of any one of embodiments 28-29, wherein L comprises a carbonyl, amide, amine, or ester moiety.

31. The TREM of any one of embodiments 1-30, wherein the ASGPR binding moiety comprises a structure of Formula (III-a):



each of R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} and subvariables thereof are as defined for Formula (I), each of L^1 and L^2 is independently a linker, each of m and n is independently an integer between 1 and 100, and M is a linker, wherein “ ξ ” represents an attachment point to a branching point, additional linker, or a nucleotide within one or more domains of a TREM.

32. The TREM of any one of embodiments 1-31, wherein the ASGPR binding moiety comprises a structure of Formula (II-b):



(II-b), or a salt thereof, wherein:

each of R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^{6a} , and R^{6b} and subvariables thereof are as defined for Formula (I);

each of L^1 , L^2 , and L^3 is independently a linker;

each of m , n , and o is independently an integer between 1 and 100;

and M is a branching point, wherein “ ξ ” represents an attachment point to a branching point, additional linker, or a nucleotide within one or more domains of a TREM.

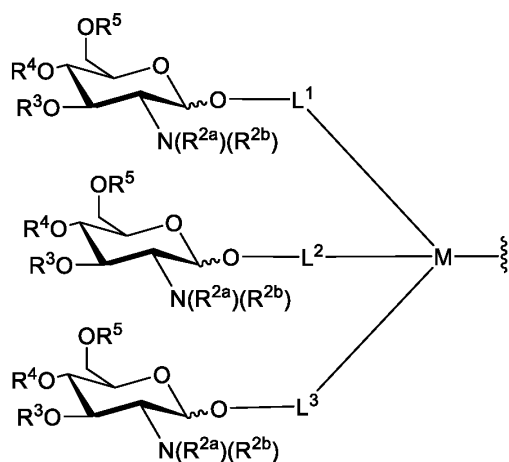
33. The TREM of any one of embodiments 31-32, wherein each of L^1 , L^2 , and optionally L^3 independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.

34. The TREM of any one of embodiments 31-33, wherein each of L^1 , L^2 , and optionally L^3 independently comprises a carbonyl, amide, amine, or ester moiety.

35. The TREM of any one of embodiments 31-34, wherein M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.

36. The TREM of any one of embodiments 31-35, wherein M comprises a carbonyl, amide, amine, or ester moiety.

37. The TREM of any one of embodiments 1-36, wherein the ASGPR binding moiety comprises a structure of Formula (II-c):



(II-c), or a salt thereof, wherein:

each of R^{2a} , R^{2b} , R^3 , R^4 , R^5 , and subvariables thereof are as defined for Formula (I);
each of L^1 , L^2 , and L^3 is independently a linker; and

M is a branching point, wherein “ $\frac{\xi}{\xi}$ ” represents an attachment point to a branching point, additional linker, or a nucleotide within one or more domains of a TREM.

38. The TREM of embodiment 37, each of L^1 , L^2 , and L^3 independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.
39. The TREM of any one of embodiments 37-38, wherein each of L^1 , L^2 , and L^3 independently comprises a carbonyl, amide, amine, or ester moiety.
40. The TREM of any one of embodiments 37-39, wherein M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.
41. The TREM of any one of embodiments 37-40, wherein M comprises a carbonyl, amide, amine, or ester moiety.
42. The TREM of any one of embodiments 1-41, wherein the TREM is selected from a TREM provided in Table 12, e.g., any one of Compounds 99-131.
43. The TREM of any one of embodiments 1-42, wherein the ASGPR binding moiety is selected from any one of Compounds (X-i)-(X-xxiii), and/or a salt or protected form thereof.
44. The TREM of any one of embodiments 1-43, wherein the ASGPR binding moiety is selected from any one of Compounds (X-i), Compound (X-xxii), and Compound (X-xxiii), and/or a salt or protected form thereof.
45. The TREM of any one of embodiments 1-44, wherein the ASGPR binding moiety is Compound (X-i) and/or a salt or protected form thereof.
45. The TREM of any one of embodiments 1-44, wherein the ASGPR binding moiety is Compound (X-xxii) and/or a salt or protected form thereof.
46. The TREM of any one of embodiments 1-44, wherein the ASGPR binding moiety is Compound (X-xxiii) and/or a salt or protected form thereof.

47. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 1, 16, 17, 19, 20, 21, 46, 47, or 50.

48. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at a plurality of TREM positions selected from 1, 2, 3, 4, 5, 6, 7, 8, or 9.

49. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26.

50. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at a plurality of TREM positions selected from 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26.

51. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43.

52. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at a plurality of TREM positions selected from 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43.

53. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, or 64.

54. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at a plurality of TREM positions selected from 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, or 64.

55. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76.

56. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at a plurality of TREM positions selected from 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, or 76.

57. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 1, 16, 17, 19, 20, 21, 46, 47, or 50, e.g., of a TREM comprising one of SEQ ID NO.: 1-654.

58. The TREM of any one of embodiments 1-46, wherein the ASGPR binding moiety is bound to a nucleobase within a nucleotide at any one of TREM positions 1, 16, 17, 19, 20, 21, 46, 47, or 50, e.g., of a TREM comprising one of SEQ ID NOs.: 1-654.

59. The TREM of any one of embodiments 1-58, wherein the TREM comprises a sequence selected from any one of SEQ ID NOs: 1-654.

60. The TREM of any one of embodiments 1-59, wherein the TREM comprises a sequence selected from any one of the TREMs provided in Table 12, e.g., SEQ ID NOs: 622-654.

61. The TREM of any one of embodiments 1-60, wherein the TREM comprises a sequence selected from SEQ ID NO. 622, SEQ ID NO: 650, and SEQ ID NO: 653.

62. The TREM of any one of embodiments 1-61, wherein the TREM comprises a sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of a TREM provided in Table 12, e.g., any one of SEQ ID NOs. 622-654 provided in Table 12.

63. The TREM of any one of embodiments 1-62, wherein the TREM comprises a sequence that is at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 provided in Table 12.

64. The TREM of any one of embodiments 1-63, wherein the TREM 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, 60 nt, 65 nt, 70 nt, or 75 nt (but less than the full length) of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

65. The TREM of any one of embodiments 1-64, wherein the TREM comprises at least 60 nt, 65 nt, 70 nt, or 75 nt of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

66. The TREM of any one of embodiments 1-65, wherein the TREM 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, 60 nt, 65 nt, 70 nt, or 75 nt (but less than the full length) of a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

67. The TREM of any one of embodiments 1-66, wherein the TREM comprises at least 60 nt, 65 nt, 70 nt, or 75 nt of a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

68. The TREM of any one of claims 1-67, wherein the TREM comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-652 provided in Table 12.

69. The TREM of any one of embodiments 1-68, wherein the TREM is selected from SEQ ID NO. 622, SEQ ID NO. 650, and SEQ ID NO. 653.

70. The TREM of any one of embodiments 1-69, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 622.

71. The TREM of any one of embodiments 1-69, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 650.

72. The TREM of any one of embodiments 1-69, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 653.

73. The TREM of any one of embodiments 1-72, wherein the TREM is a compound provided in Table 12, e.g., any one of Compound Nos. 99-131.

74. The TREM of any of embodiments 1-40, wherein the TREM retains the ability to support protein synthesis, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.

75. The TREM of any of embodiments 1-74, wherein the TREM retains the ability to be charged by a synthetase, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.

76. The TREM of any of embodiments 1-75, wherein the TREM retains the ability to be bound by an elongation factor, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.

77. The TREM of any of embodiments 1-76, wherein the TREM retains the ability to introduce an amino acid into a peptide chain, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.

78. The TREM of any of embodiments 1-77, wherein the TREM retains the ability to support elongation or support initiation, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
79. The TREM of any of embodiments 1-78, wherein the TREM has a binding affinity to an ASGPR of between 0.01 nM and 100 mM.
80. The TREM of any of embodiments 1-79, wherein the TREM comprises a chemical modification, e.g., a chemical modification described herein, e.g., in any one of Tables 5-8.
81. A pharmaceutical composition comprising a TREM of any one of the preceding embodiments.
82. The pharmaceutical composition of embodiment 81, further comprising a pharmaceutically acceptable component, e.g., an excipient.
83. A lipid nanoparticle formulation comprising a TREM of any one of embodiments 1-80.
84. A lipid nanoparticle formulation comprising a pharmaceutical composition of any one of claims 81-82.
86. A method of delivery of a TREM of any one of embodiments 1-80, or a pharmaceutical composition of any one of 81-82, or a lipid nanoparticle of any one of embodiments 83-84, to a subject or cell.
87. A method of treating a subject having a disease or disorder associated with a PTC comprising administering to the subject a of any one of embodiments 1-80, or a pharmaceutical composition of any one of 81-82, or a lipid nanoparticle of any one of embodiments 83-84, thereby treating the subject having the disease or disorder.

EXAMPLES

The following examples are provided to further illustrate some embodiments of the present disclosure, 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.

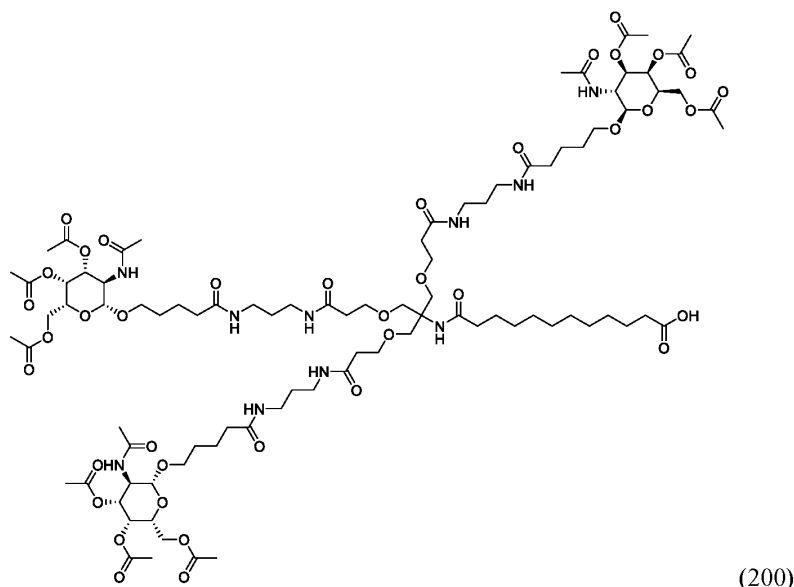
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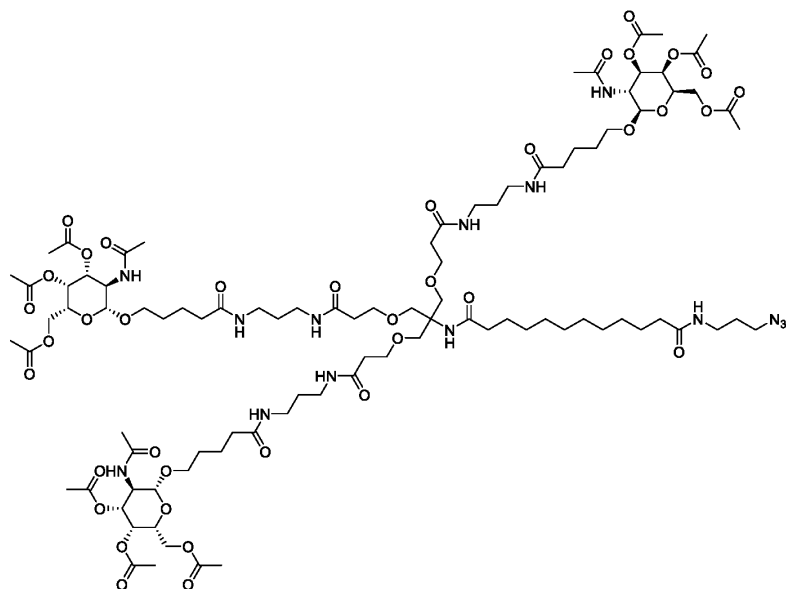
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Example 1: Preparation of Selected ASGPR Binding Moieties

Compound 200: 11-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-16,16-bis((3-((3-(5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanamido)-propyl)amino)-3-oxopropoxy)methyl)-5,11,18-trioxo-14-oxa-6,10,17-triazanonacosan-29-oic acid (Compound 100) may be prepared according to the procedures provided by Nair K. et al. (2014) *J. Am. Chem. Soc.*, 134(49), 16958-16961, which is incorporated herein by reference in its entirety.

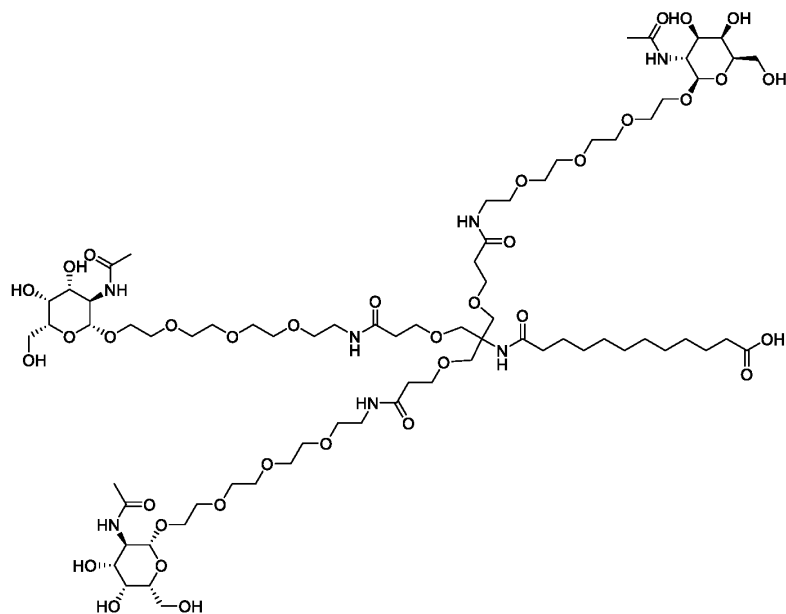


Compound 201: Trebler GalNAc azide (N-(N-propargyldodecanoylamido)-tris{2-oxa-6,10-diaza-5,11-dioxo-15-[3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyloxy]pentadecyl}methane) is commercially available (e.g., from Primetich; catalog #0079).



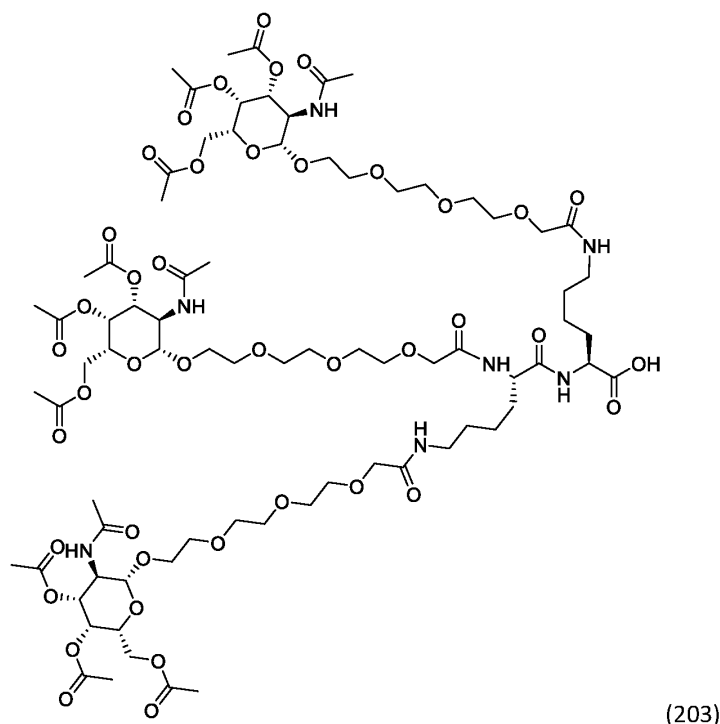
(201)

Compound 202: 1-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-18,18-bis(17-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-5-oxo-2,9,12,15-tetraoxa-6-azaheptadecyl)-13,20-dioxo-3,6,9,16-tetraoxa-12,19-diazahentriacontan-31-oic acid



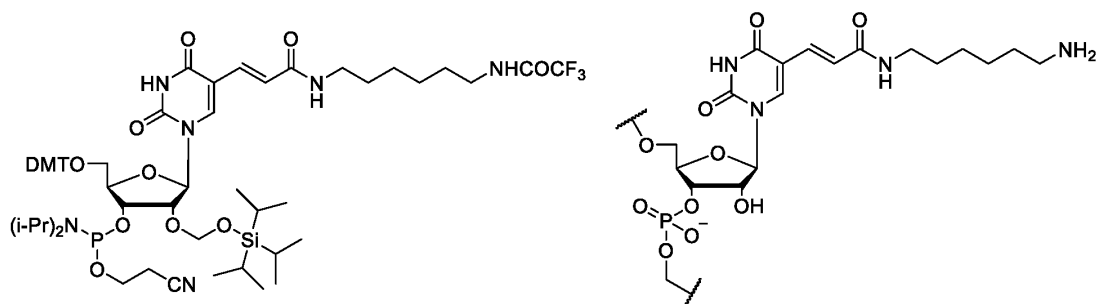
(202)

Compound 203: (17S,20S)-1-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-20-(1-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-11-oxo-3,6,9-trioxa-12-azahexadecan-16-yl)-17-(2-(2-(2-(2-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethoxy)ethoxy)acetamido)-11,18-dioxo-3,6,9-trioxa-12,19-diazahenicosan-21-oic acid was prepared according the procedures outlined in U.S. Patent No. 9,796,756, which is incorporated herein by reference in its entirety.



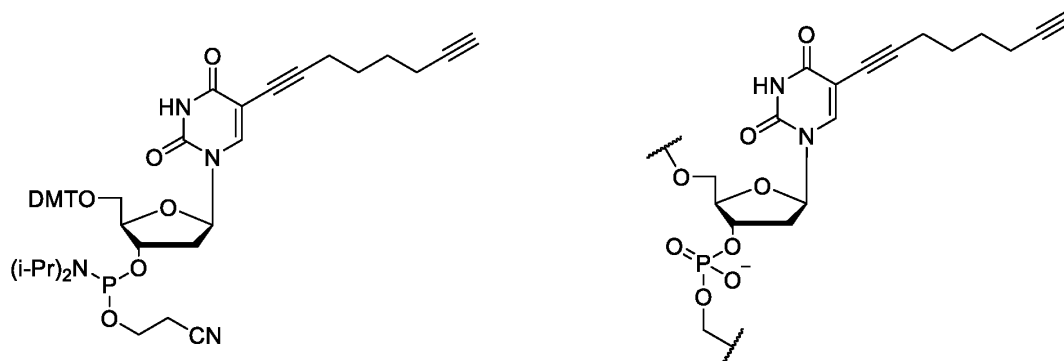
Example 2: Preparation of Selected Nucleotides

Amino Nucleobase 1: Modified nucleotides comprising an amine handle at the nucleobase, such as AN1 (C6-U phosphoramidite (5'-Dimethoxytrityl-5-[N-(trifluoroacetylaminohexyl)-3-acrylimido]-Uridine, 2'-O-triisopropylsilyloxymethyl-3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite)), may be purchased from Glen Research; catalog # 10-3039. Briefly, Amino-Modifier C6-U phosphoramidite was purchased with the primary amine protected as trifluoroacetate and incorporated into a TREM to afford the amino nucleobase AN1.



(AN1)

Alkyne Nucleobase 2: Modified nucleotides comprising an alkyne handle at the nucleobase, such as AN2 (C8-alkyne-dT-CE phosphoramidite (5'-dimethoxytrityl-5-(octa-1,7-diynyl)-2'-deoxyuridine, 3'-[(2-cyanoethyl)-(N,N-diisopropyl)]-phosphoramidite)) may be purchased from Glen Research; catalog # 10-1540. C8-Alkyne-dT-CE Phosphoramidite is incorporated into TREM molecules via standard phosphoramidite chemistry to afford the amino nucleobase AN2.



(AN2)

Example 3: Synthesis of Exemplary TREMs

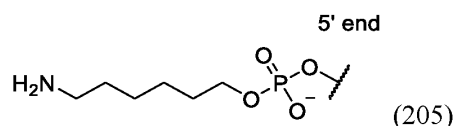
The example describes the synthesis of exemplary TREMs. The TREMs may be chemically synthesized and purified by HPLC according to standard solid phase synthesis methods and phosphoramidite chemistry (see, e.g., Scaringe S. et al. (2004) *Curr Protoc Nucleic Acid Chem*, 2.10.1-2.10.16; Usman N. et al. (1987) *J. Am. Chem. Soc.*, 109, 7845-7854). Exemplary nucleotide phosphoramidites used in the syntheses include 5'-O-dimethoxytrityl-N6-(benzoyl)-2'-O-t-butyl dimethylsilyl-adenosine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, 5'-O-dimethoxytrityl-N4-(acetyl)-2'-O-t-butyl dimethylsilyl-cytidine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, 5'-O-dimethoxytrityl-N2-(isobutyryl)-2'-

O-t-butyl dimethylsilyl-guanosine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite, and 5'-O-dimethoxytrityl-2'-O-t-butyl dimethylsilyl-uridine-3'-O-(2-cyanoethyl-N,N-diisopropylamino) phosphoramidite,

A large number of TREMs were synthesized in this manner, including, *inter alia*, (1) an arginine non-cognate TREM (e.g., TREM-Arg-TGA) that contains the sequence of ARG-UCU-TREM but with the anticodon sequence corresponding to UCA instead of UCU (i.e., SEQ ID NO: 622); (2) a serine non-cognate TREM named TREM-Ser-TAG that contains the sequence of SER-GCU-TREM but with the anticodon sequence corresponding to CUA instead of GCU (i.e., SEQ ID NO: 653); and (3) a glutamine non-cognate TREM named TREM-Gln-TAA that contains the sequence of GLN-CUG-TREM but with the anticodon sequence corresponding to UUA instead of CUG (i.e., SEQ ID NO: 650).

Example 4: Synthesis of TREMs with a terminal amino linker

This example describes the synthesis of TREM molecules with an amino linker at the 5' terminus. The amino linker is added to the 5' end of the oligonucleotides via phosphoramidite chemistry on a synthesizer. For example, TFA-amino C6 CED phosphoramidite (may be incorporated at the 5' end of oligonucleotide (Compound 205). Similar chemistry may be employed to couple the amino linker to the 3' terminus.

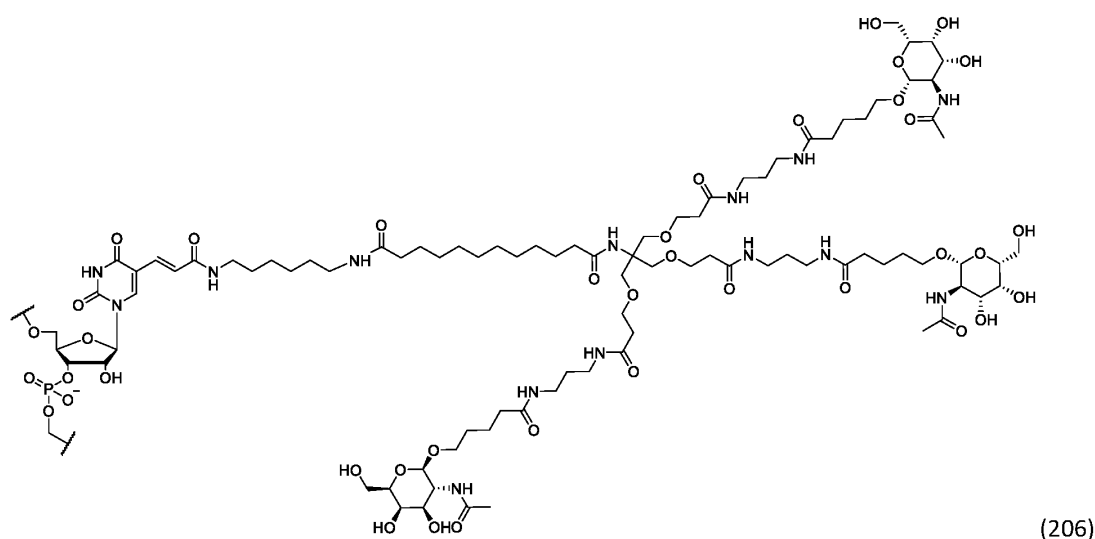


Additionally, the amino linker may be incorporated into the TREM sequence by using a phosphoramidite comprising an aminohexyl linker. In these cases, a compound such as 6-(4-monomethoxytritylamino)hexyl-(2-cyanoethyl)-(N,N-diisopropyl)phosphoramidite may be used, which is commercially available from ChemGenes; catalog # CLP-1563.

Example 5: Synthesis of TREMs comprising an ASGPR binding moiety

The example describes the synthesis of an exemplary TREM comprising an ASGPR binding moiety. Several methods of coupling the ASGPR binding moieties to the TREM may be used, including employing amide formation and triazole-based click chemistry may be used. For example, the carboxylic acid triantennary GalNAc molecule (Compound 200) in Example 1 was coupled with oligonucleotides bearing amino linkers via an amide bond formation reaction. Briefly, a solution of Compound 200 (2 equivalents), HATU (1.8 equivalents) and

diisopropylethylamine (8 equivalents) in dry acetonitrile (or dry DMF) was vortexed for 2 minutes. To this solution was added an aqueous solution of a TREM bearing an amino linker (1 equivalent), such as the TREM bearing an amino linker outlined in Example 4. The reaction mixture was vortexed for 2 minutes and kept at room temperature for 60 minutes, at which point the solvent was removed under vacuum, diluted with water, and purified by reversed phase column chromatography or ion exchange chromatography. In cases where GalNAc moieties contain protecting groups, these protecting groups were removed by appropriate treatment. For example, when the free hydroxyl groups in the GalNAc moieties were protected with acetyl groups, ammonium hydroxide treatment was performed for 6 h at room temperature, followed by purification to afford the final GalNAc-TREM conjugate (206).



ASGPR binding moieties bearing a free carboxylate, such as Compounds 200, 202, and 203 were also first activated to pentafluorophenyl esters (PFPs), followed by coupling a free amine on the TREM, either at the 3' or 5' terminus or internally on a nucleobase amine (for example, a linker on a nucleobase).

Additionally, TREMs were coupled to various ASGPR binding moieties by converting certain ASGPR binding moieties bearing free carboxylates, such as Compounds 200, 202, and 203, to N-hydroxysuccinimide (NHS)-activated compounds. Briefly, the carboxylate-bearing ASGPR binding moieties were dissolved in dimethylformamide (DMF) and N-hydroxysuccinimide (NHS, 1.1 equiv) and N,N-diisopropylcarbodiimide (1.1 equiv) were added. The solution was stirred at room temperature for 18 hours and coupled directly to a TREM

without further purification. A TREM bearing a free amine group, such as a TREM with a terminal amino linker or a TREM bearing a modified nucleotide (e.g., AN1 or AN2), was dissolved in mixture of 50 mM sodium carbonate/bicarbonate buffer pH 9.6 and dimethylsulfoxide (DMSO) 4:6 v/v. To this solution was added 1.2 molar equivalents of the NHS ester-activated ASGPR binding moiety solution in DMF. The reaction was carried out at room temperature for 1 hour, after which another 1.2 molar equivalent of the NHS ester-activated ASGPR binding moiety in DMF was added. After 1 hour, the reaction was diluted 15-fold with water, filtered through a 1.2 μ m filter, and purified by reversed-phase HPLC (Xbridge C18 Prep 19 x 50 mm, using a 100 mM triethylamine acetate pH 7 / 95% acetonitrile buffer system). Any protecting groups on the ASGPR binding moieties were then removed, for example, by treatment with 3M sodium acetate pH 5.2 and 80% ethanol.

Alternatively, TREM molecules bearing an alkyne group were conjugated to ASGPR binding moieties bearing an azide group, such as Trebler GalNAc azide (Compound 201). The reaction was carried out via copper catalyzed azide-alkyne cycloaddition (Saneyoshi H. et al. (2017) *Bioorg. Med. Chem.*, 25, 3350-3356; incorporated herein by reference in its entirety), and purified using standard techniques to yield triazolyl-containing moieties such as Compound 207 below.

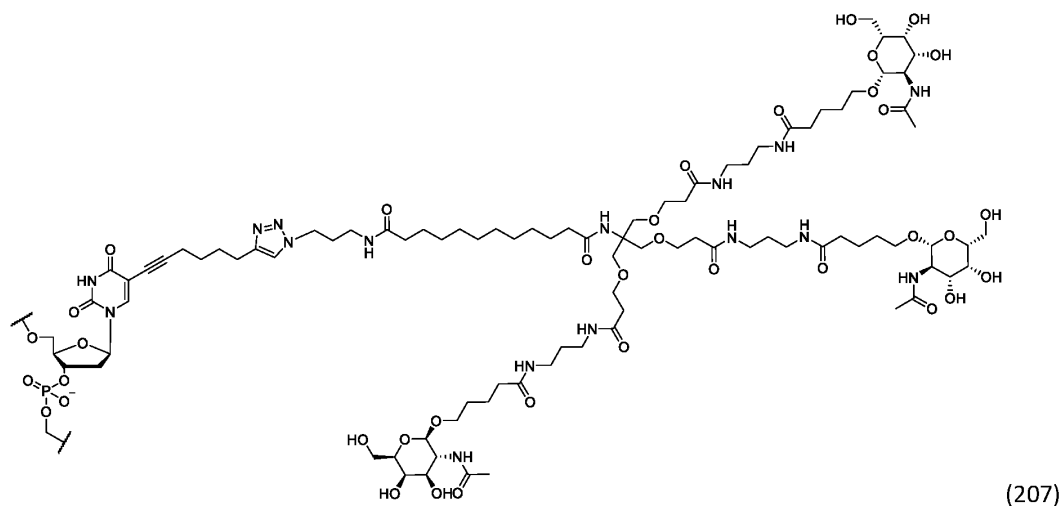


Table 12 summarizes a list of TREMs prepared containing an ASGPR binding moiety, according to the protocols provided herein. Each TREM in the sequence is either unconjugated (e.g., a control) or conjugated to either i) a ASGPR binding moiety described herein (abbreviated

as “GalNAc” in the table); ii) a fluorophore such as Cy3; and/or iii) a linker (abbreviated as “5-LC-N” in the table. The molecular weight of each TREM was confirmed by LC-MS, wherein the determined molecular weight was found to be within +/- 0.04% of the calculated molecular weight for each TREM.

Table 12: Exemplary TREMs comprising an ASGPR binding moiety

Compound No.	SEQ ID NO.	Descriptor	Sequence	Calculated MW
99	622	Arg-TGA (Unconjugated)	GGCUCCGUGGCGCAAUGGAUAGCGCAUUGGACUUCAAAUUCAAA GGUUCCGGGUUCGAGUCCCGGC GGAGUCGCCA	
100	623	Arg-TGA (1-G-GalNAc – linkage on 5' terminus)	[GalNAc]-[TE]- GGGUCCGUGGCGCAAUGGAUA GCGCAUUGGACUUCAAAUUCAA AGGUUCCGGGUUCGAGUCCCGG CGGAGUCGCCA	26,355.7
101	624	Arg-TGA (16-U-GalNAc)	GGCUCCGUGGCGCAAU[GalNAc] GGAUAGCGCAUUGGACUUCAAA UUCAAAGGUUCCGGGUUCGAGU CCCGGCGGAGUCGCCA	26,343.8
102	625	Arg-TGA (20-U-GalNAc)	GGCUCCGUGGCGCAAUGGAU[GalNAc] AGCGCAUUGGACUUCAAA UUCAAAGGUUCCGGGUUCGAGU CCGGCGGAGUCGCCA	26,343.8
103	626	Arg-TGA (47-U-GalNAc)	GGCUCCGUGGCGCAAUGGAUAGCGCAUUGGACUUCAAA UUCAAA GGU[GalNAc]UCCGGGUUCGAGU CCGGCGGAGUCGCCA	26,343.8
104	627	Arg-TGA (16-U-GalNAc) & 5'-Cy3	[Cy3]GGCUCCGUGGCGCAAU[GalNAc] GGAUAGCGCAUUGGACUUC AAUUCAAAGGUUCCGGGUUCGA GUCCCGGCGGAGUCGCCA	26,851.0
105	628	Arg-TGA (20-U-GalNAc) & 5'-Cy3	[Cy3]GGCUCCGUGGCGCAAUGGAU[GalNAc] AGCGCAUUGGACUUC AAUUCAAAGGUUCCGGGUUCGA GUCCCGGCGGAGUCGCCA	26,851.0
106	629	Arg-TGA (47-U-GalNAc) & 5'-Cy3	[Cy3]GGCUCCGUGGCGCAAUGGAUAGCGCAUUGGACUUCAAA UUC AAAGGU[GalNAc]UCCGGGUUCGA GUCCCGGCGGAGUCGCCA	26,851.0
107	630	Arg-TGA (16-linker)	GGCUCCGUGGCGCAAU[5-LC-N] GGAUAGCGCAUUGGACUUCAAA UUCAAAGGUUCCGGGUUCGAGU CCCGGCGGAGUCGCCA	24,676.9

108	631	Arg-TGA (20-linker)	GGCUCCGUGGCGCAAUGGAU[5-LC-N]AGCGCAUUGGACUUCAAA UUCAAAGGUUCCGGGUUCGAGU CCCGGCGGAGUCGCCA	24,676.9
109	632	Arg-TGA (47-linker)	GGCUCCGUGGCGCAAUGGAUAG CGCAUUGGACUUCAAAUUCAAA GGU[5-LC-N]UCCGGGUUCGAGUCCC GGCGGAGUCGCCA	24,676.9
110	633	Gln-TAA (16-U-GalNAc)	GGUUCCAUGGUGUAAU[GalNAc]G GUAAGCACUCUGGACUUUAAAU CCAGCGAUCCGAGUUCGAGUCUC GGUGGAACCUCCA	25,890.5
111	634	Gln-TAA (19-U-GalNAc)	GGUUCCAUGGUGUAAUGGU[GalNAc] AAGCACUCUGGACUUUAAAU CCAGCGAUCCGAGUUCGAGUCUC GGUGGAACCUCCA	25,890.5
112	635	Gln-TAA (16-U-GalNAc) & 5'-Cy3	[Cy3]GGUUCCAUGGUGUAAU[GalNAc] GGUAAGCACUCUGGACUUU AAAUCCAGCGAUCCGAGUUCGA GUCUCGGUGGAACCUCCA	26,397.7
113	636	Gln-TAA (19-U-GalNAc) & 5'-Cy3	[Cy3]GGUUCCAUGGUGUAAUGGU [GalNAc]AAGCACUCUGGACUUUA AAUCCAGCGAUCCGAGUUCGAG UCUCGGUGGAACCUCCA	26,397.7
114	637	Gln-TAA (47-U-GalNAc) & 5'-Cy3	[Cy3]GGUUCCAUGGUGUAAUGGU AAGCACUCUGGACUUUAAAUCC AGCGAU[GalNAc]CCGAGUUCGAG UCUCGGUGGAACCUCCA	26,397.7
115	638	Gln-TAA (16-linker)	GGUUCCAUGGUGUAAU[5-LC-N] GGUAAGCACUCUGGACUUUAA AUCCAGCGAUCCGAGUUCGAGU CUCGGUGGAACCUCCA	24,223.6
116	639	Gln-TAA (19-linker)	GGUUCCAUGGUGUAAUGGU[5-LC-N] AAGCACUCUGGACUUUAAAUCC CAGCGAUCCGAGUUCGAGUCUC GGUGGAACCUCCA	24,223.6
117	640	Gln-TAA (47-linker)	GGUUCCAUGGUGUAAUGGUAAG CACUCUGGACUUUAAAUCCAGC GA U[5-LC-N]CCGAGUUCGAGU CUCGGUGGAACCUCCA	24,223.6
118	641	Ser-TAG (1-G-GalNAc – linkage on 5'terminus)	[GalNAc]-[TE]- GACGAGGUGGCCGAGUGGUUAA GGCGAUGGACUCUAAAUCCA GUGCUCUGCACGCGUGGGUUCG AAUCCCAUCCUCGUCGCCA	29,170.4
119	642	Ser-TAG (16-U-GalNAc)	GACGAGGUGGCCGAGU[GalNAc]G GUUAAGGCGAUGGACUCUAAAU CCAUGGUGCUCUGCACGCGUGG	29,158.4

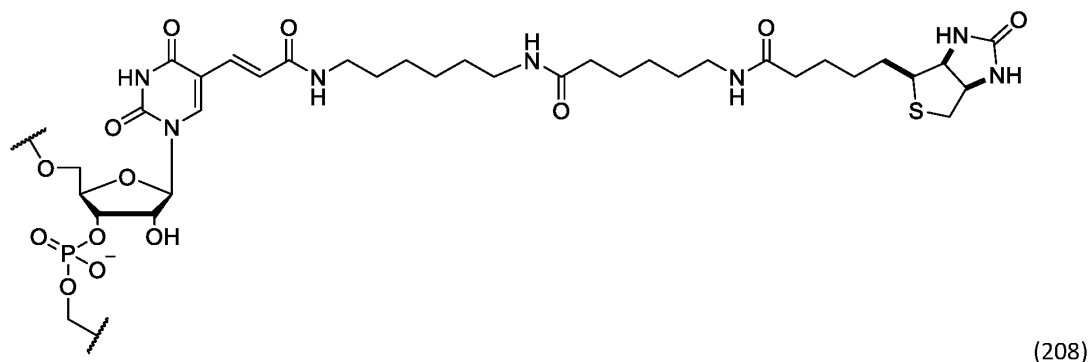
			GUUCGAAUCCCAUCCUCGUCGCC A	
120	643	Ser-TAG (20- U-GalNAc)	GACGAGGUGGCCGAGUGGUU[Gal NAc]AAGGCGAUGGACUCUAAA UCCAUUGUGCUCUGCACGCGUGG GUUCGAAUCCCAUCCUCGUCGCC A	29,158.4
121	644	Ser-TAG (46- U-GalNAc)	GACGAGGUGGCCGAGUGGUUAA GGCGAUGGACUCUAAAUCCAUU GU[GalNAc]GCUCUGCACGCGUGG GUUCGAAUCCCAUCCUCGUCGCC A	29,158.4
122	645	Ser-TAG (20- U-GalNAc) & 5'-Cy3	[Cy3]GACGAGGUGGCCGAGUGGU U[GalNAc]AAGGCGAUGGACUCUA AAUCCAUUGUGCUCUGCACGCG UGGGUUCGAAUCCCAUCCUCGUC GCCA	29,665.7
123	646	Ser-TAG (46- U-GalNAc) & 5'-Cy3	[Cy3]GACGAGGUGGCCGAGUGGU UAAGGCGAUGGACUCUAAAUCC AUUGU[GalNAc]GCUCUGCACGCG UGGGUUCGAAUCCCAUCCUCGUC GCCA	29,665.7
124	647	Ser-TAG (16- linker)	GACGAGGUGGCCGAGU[5-LC- N]GGUUAAGGCGAUGGACUCUAA AUCCAUUGUGCUCUGCACGCGU GGGUUCGAAUCCCAUCCUCGUCG CCA	27,491.6
125	648	Ser-TAG (20- linker)	GACGAGGUGGCCGAGUGGUU[5- LC-N]AAGGCGAUGGACUCUAA AUCCAUUGUGCUCUGCACGCGU GGGUUCGAAUCCCAUCCUCGUCG CCA	27,491.6
126	649	Ser-TAG (46- linker)	GACGAGGUGGCCGAGUGGUUAA GGCGAUGGACUCUAAAUCCAUU GU[5-LC- N]GCUCUGCACGCGUGGGU UCGAAUCCCAUCCUCGUCGCCA	27,491.6
127	650	Gln-TAA (Unconjugated)	GGUUGCAUGGUGUAAUGGUAAG CACUCUGGACUUUAAAUCCAGC GAUCCGAGUUCGAGUCUCGGUG GAACCUCCA	
128	651	Gln-TAA-1-G- GalNAc	[GalNAc]-[TE]- GGUUGCAUGGUGUAAUGGUAAG CACUCUGGACUUUAAAUCCAGC GAUCCGAGUUCGAGUCUCGGUG GAACCUCCA	
129	652	Gln-TAA-47- U-GalNAc	GGUUGCAUGGUGUAAUGGUAAG CACUCUGGACUUUAAAUCCAGC GAU[GalNAc]CCGAGUUCGAGUCU CGGUGGAACCUCCA	

130	653	Ser-TAG (Unconjugated)	GACGAGGUGGCCGAGUGGUUAA GGCGAUGGACUCUAAAUCCA UUGUCUCUGCACGCGUGGGUUCG AAUCCCAUCCUCGUCGCCA	
131	654	Ser-TAG (16- U-GalNAc) & 5'-Cy3	[Cy3]GACGAGGUGGCCGAGU[Gal NAc]GGUUAAGGCGAUGGACUCU AAAUCCAUGUGUCUCUGCACGC GUGGGUUCGAAUCCCAUCCUCG UCGCCA	

Example 6: Synthesis of biotin conjugated TREM molecules as probes

This example describes the synthesis of biotin conjugated TREM molecule. These molecules may be utilized as GalNAc-TREM conjugate mimics, for example, and be useful for investigation of which positions along the TREM sequence are suitable for labeling (+)-Biotin N-hydroxysuccinimide ester may be purchased from Sigma-Aldrich (catalog # H1759). The TREM molecules bearing a free amine may be synthesized as described previously, e.g., Example 4, then coupled with (+)-Biotin N-hydroxysuccinimide ester to form an amide bond, according to the method, e.g., as outlined in Bengstrom M. et al. (1990) *Nucleos. Nucleot. Nucl.* 9, 123-127. Briefly, a solution of TREM molecules with amino base modification and excess (+)-Biotin N-hydroxysuccinimide ester may be mixed together and vortexed for several hours at 37°C. LCMS analysis is used to determine whether the reaction is complete. The solvent is removed under vacuum, and the resulting residue is diluted with water then subjected to purification using reversed phase column chromatography to afford the final compound (e.g., Compound 208)

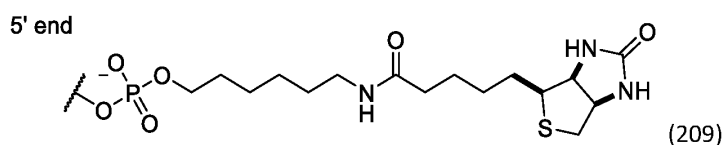
For example, the the biotin moiety was installed on the arginine non-cognate TREM molecules at position 20 and position 47 named as TREM-Arg-TGA-Biotin-20 and TREM-Arg-TGA-Biotin-47 respectively. The arginine non-cognate TREM molecules contain the sequence of ARG-UCU-TREM body but with the anticodon sequence corresponding to UCA instead of UCU.



Example 7: Synthesis of biotin conjugated TREM molecules as probes

This example describes the synthesis of TREM molecules conjugated with biotin at the 5' terminus. (+)-Biotin N-hydroxysuccinimide ester may be purchased from Sigma-Aldrich (catalog # H1759). The TREM molecules with amino linker at the 5' end may be prepared, e.g., as described in Example 4. The amino-modified TREM is then coupled with (+)-Biotin N-hydroxysuccinimide ester to form an amide bond, according to the method, e.g., outlined in Bengstrom M. et al. (1990) *Nucleos. Nucleot. Nucl.* 9, 123-127. Briefly, a solution of the amino-modified TREM and excess (+)-Biotin N-hydroxysuccinimide ester are mixed together and vortexed for several hours at 37°C. LCMS analysis is used to determine whether the reaction is complete. The solvent is removed under vacuum, and the resulting residue is diluted with water then subjected to purification using reversed phase column chromatography to afford the final compound (e.g., Compound 209).

For example, the biotin moiety was installed on the arginine non-cognate TREM molecule, referred to as TREM-Arg-TGA-5'-Biotin. The arginine non-cognate TREM molecules contain the sequence of ARG-UCU-TREM body but with the anticodon sequence corresponding to UCA instead of UCU.



Example 8: Analysis of GalNAc-TREMs via HPLC

The example describes the analysis of GalNAc-TREM molecules via HPLC. GalNAc-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 μ m) may be used for this analysis. Samples may be prepared by dissolving 0.5 nmol of the oligonucleotide in 75 μ L of water and injecting 2 μ L of the solution. The buffers used may be 50 mM dimethylhexylammonium acetate with 10% CH₃CN (acetonitrile) as buffer A and 50 mM dimethylhexylammonium acetate with 75% CH₃CN as buffer B (gradient 25-75% buffer B over 5 mins), with a flow rate of 0.5 mL/min at 60 °C.

Example 9: Analysis of GalNAc-TREMs via mass spectrometry

The example describes the mass spectrometry analysis of the GalNAc-TREM molecules. ESI-LCMS data for the oligonucleotides may be acquired on a Thermo Ultimate 3000-LTQ-XL mass spectrometer. Samples may be prepared by dissolving 0.5 nmol of the oligonucleotide in 75 μ L of water and injecting 10 μ L of the solution directly onto a Novatia C18 (HTCS-HTC1-4) trap column. Following injection into the trap column, the sample may be eluted directly onto the LTQ-MS with 85% CH₃CN, 50 mM HFIP (hexafluoro-2-propanol), 10 μ M EDTA (ethylenediaminetetraacetic acid), 0.35% DIPEA (N,N-diisopropylethylamine) and the mass to charge ratio (m/z) is determined.

Example 10. In vitro delivery of GalNAc-TREMs to cells expressing the ASGPR

This example describes the *in vitro* delivery of exemplary GalNAc-conjugated TREMs into U2OS cells expressing the ASGPR under gymnotic conditions (without a transfection agent). The methods described in this example can be adopted for evaluating the levels of GalNAc-TREMs in ASGR-expressing cells after delivery.

Host cell modification

A U2OS cell line engineered to stably express the ASGP receptor (ASGPR) was generated using plasmid transfection and selection. Briefly, the cells were co-transfected with a plasmid encoding the ASGPRI gene and a puromycin selection cassette. The next day, cells were selected with puromycin. The remaining cells were expanded and tested for ASGPR expression.

Delivery of GalNAc-TREMs under gymnotic conditions

The ASGPR engineered U2OS cells were harvested and diluted to 4×10^4 cells/mL in complete growth medium, and 100 μ L of the diluted cell suspension was added in a 96-well plate (3904, Corning, USA). The plate was placed in a 37°C 5% CO₂ incubator for cell attachment to the well bottom. After 20-24 hours, various GalNAc-TREMs modified with a fluorophore at the 5' terminus (Cy3) were diluted to a 10-fold concentration (e.g. 1000 nM) into the RNase-free

water and added to the well at a 1:10 dilution. The plate was placed in the 37°C 5% CO₂ incubator for 20–24h before the tRNA quantification assay to determine the intracellular levels of the GalNAc-TREM.

Quantitative tRNA delivery using live imaging

At 20–24h post tRNA delivery, the plate was taken out of the incubator. After aspirating the culture medium (Hoechst 33342; Thermofisher, USA) was diluted to 1:10,000 in the full growth medium and added to the cells. The plate was incubated at room temperature (~25°C) for 10min, then washed with 1X DPBS for 6 times. After the last wash, the plate was added with the full growth medium (100uL per/well). The plate was then imaged under ImageXpress Pico Microscope (Molecular Device, USA) with three channels (Cy3/DAPI/Brightfield) at 20X magnification. The average intensity of Cy3 channel was quantified by the “Cell scoring” function from the microscope software. Free uptake by the ASGPR1-expressing U2OS cells of Gln-TAA conjugated with GalNAc at three different positions (Compounds 112, 113, and 114) along the TREM was detected by visualizing the Cy3 tag with fluorescent microscopy (FIG. 1A–1F). The negative control cells (FIG. 1G–1H) were exposed to unconjugated Gln-TAA TREMs while the positive control (FIG. 1I–1J) was exposed to GalNAc-modified Gln-TAA TREMs with RNAiMAX transfection reagent. FIG. 2 is a quantitation of the average intensity of the microscopy results, demonstrating that free uptake of the TREM was as good as transfection-facilitated uptake of the TREM. Similar results were obtained with Ser-TAG (Compounds 122 and 123; FIG. 3A–3H and FIG. 4) and Arg-TGA (Compounds 104, 105, and 106; FIG. 5A–5J and FIG. 6) modified TREMs.

Example 11. In vitro delivery of GalNAc-TREM to primary human hepatocytes

This example describes the *in vitro* delivery of a GalNAc-conjugated TREM into primary human hepatocytes under gymnotic conditions (without a transfection agent). The methods described in this example can be adopted for evaluating the levels of GalNAc-TREMs in the hepatocytes after delivery.

One cryo-vial of Liverpool, 10 donor human cryoplateable hepatocytes (X008001-P, BioIVT, USA), was carefully thawed and diluted in pre-warmed INVITROGRO CP Medium at 37°C. The total cell count and the number of viable cells were determined using a cell counter. A >70% viability was expected with a successful thawing procedure. The cells were further diluted to 7 × 10⁵ viable cells/mL, and 70uL of the diluted cell suspension was seeded in a collagen-

coated 96-well plate (354649, Corning, USA). The plate was shaken gently in a back-and-forth and side-to-side manner to evenly distribute the cells. The plate was placed in a 37°C 5% CO₂ incubator. After 2 hours, the plate was carefully washed with INVITROGRO CP Medium. GalNAc-TREMs were diluted to a working concentration (e.g. 100 nM) into the growth medium and added to the well. The plate was placed in the 37°C 5% CO₂ incubator for 20–24h before the tRNA quantification assay to determine the intracellular levels of the GalNAc-TREM.

Quantitative tRNA delivery using Cy3 live imaging

At 20-24h post tRNA delivery, the plate was taken out of the incubator. After aspirating the culture medium, Hoechst 33342 (62249, Thermofisher, USA) was diluted to 1:10,000 in the INVITROGRO CP Medium and added to the cells. The plate was incubated at room temperature (~25°C) for 10min, then washed with 1X DPBS for 6 times. After the last wash, the plate was added with INVITROGRO CP medium (100uL per/well). The plate was then imaged under ImageXpress Pico Microscope (Molecular Device, USA) with three channels (Cy3/DAPI/Brightfield) at 20X magnification. The average intensity of Cy3 channel was quantified by the “Cell scoring” function from the microscope software. FIG. 7A-7J depicts fluorescent microscopy images of Cy3-conjugated modified Gln-TAA TREMs. Free uptake of the TREMs by primary human hepatocytes was as efficient as or better than the cells incubated with the TREM and transfection reagent. FIG. 8 is the quantitation of uptake of each TREM as measured by average intensity. Similar results were obtained with Ser-TAG TREMs (FIG. 9A-9H and FIG. 10) and Arg-TGA TREMs (FIG. 11A-11J and FIG. 12).

Example 12. Readthrough of a premature termination codon (PTC) in a reporter protein via administration of TREMs comprising an ASGPRG binding moiety through transfection

This example describes an assay to test the ability of non-cognate TREMs bearing an ASGPR binding moiety (“GalNAc-TREMs”) to readthrough a PTC in a cell expressing a protein having a PTC. This Example describes three different GalNAc-modified TREMs (Gln-TAA, Ser-TAG, or Arg-TGA), though a TREM specifying any one of the other 19 amino acids can also be used. The specific GalNAc TREMs tested are summarized in Table 12 above.

Host cell modification

A cell line engineered to stably express the NanoLuc reporter construct containing a premature termination codon (PTC) was generated using the FlpIn system according to the manufacturer's instructions.

Delivery of non-cognate GalNAc-TREM into host cells through transfection

To ensure proper folding of each TREM, the GalNAc-TREMs were heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes. To deliver the GalNAc-TREM into the NanoLuc reporter cells, a reverse transfection reaction was performed on the NanoLuc reporter cells using lipofectamine RNAiMAX (ThermoFisher Scientific, USA) according to manufacturer instructions. Briefly, 5uL of a 2.5uM solution of GalNAc-TREMs were diluted in a 20uL RNAiMAX/OptiMEM mixture. After 30min gentle mixing at room temperature, the 25uL GalNAc-TREM/transfection mixture was added to a 96-well plate and kept still for 20-30min before adding the cells. The NanoLuc reporter cells were harvested and diluted to 4×10^5 cells/mL in complete growth medium, and 100uL of the diluted cell suspension was added and mixed to the plate containing the GalNAc-TREM. After 24h, 100uL complete growth medium was added to the 96-well plate for cell health.

Translation suppression assay

To monitor the efficacy of the GalNAc-TREMs to readthrough the PTC in the reporter construct 48 hours after GalNAc-TREM delivery into cells, a NanoGlo bioluminescent assay (Promega, USA) was performed according to manufacturer instruction. Briefly, cell media was replaced and allowed to equilibrate to room temperature. NanoGlo reagent was prepared by mixing the buffer with substrate in a 50:1 ratio. 50uL of mixed NanoGlo reagent was added to the 96-well plate and mixed on the shaker at 600rpm for 10min. After 2min, the plate was centrifuged at 1000g, 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 was used. As a negative control, a host cell expressing the NanoLuc reporter construct with a PTC was used, but no GalNAc-TREM was transfected. The efficacy of the GalNAc-TREMs was 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 was expected that if the GalNAc-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 GalNAc-TREM was not functional, the stop mutation was not rescued, and luminescence less or equal to the negative control was detected. Gln-TAA TREMs, each modified with GalNAc at different positions, demonstrated concentration-dependent readthrough ability in ASGPR1-U2OS-nLuc-PTC reporter cells (FIG. 13). Ser-TAG and Arg-TGA TREMs demonstrated similar concentration-dependent readthrough ability (FIG. 14 and 15).

The impacts of including ASGPR binding moieties in the TREM sequence were evaluated and are summarized in Table 13 below. The data for each modified TREM is provided as log₂ fold changes compared with the mock sample, wherein “1” indicates less than a 4.00 log₂ fold change; “2” indicates a log₂ fold change greater than or equal to 4.01 and less than 7.00 log₂ fold change; and “3” indicates greater than or equal to 7.01 log₂ fold change. The results show that the ASGPR binding moieties and other modifications were tolerated at many positions, but particular sites were sensitive to modification or exhibited improved activity when modified.

Table 13: Readthrough ability of exemplary TREMs modified with an ASGPR binding moiety

Compound No.	Results	Compound No.	Results	Compound No.	Results
100	1	109	2	118	1
101	2	110	2	119	3
102	2	111	2	120	1
103	2	112	2	121	1
104	2	113	2	122	1
105	2	114	3	123	1
106	2	115	3	124	3
107	2	116	3	125	3
108	2	117	3	126	3

Example 13: Readthrough of a premature termination codon (PTC) in a reporter protein via administration of a TREM comprising an ASGPR binding moiety in cells expressing the ASGPR

This example describes an assay to test the ability of a non-cognate GalNAc-TREM to readthrough a PTC in a cell line expressing a reporter protein having a PTC. This Example

describes certain TREM sequences, though a non-cognate TREM specifying any one of the 20 amino acids can be used.

Host cell modification

A cell line engineered to stably express the ASGPR and a NanoLuc reporter construct containing a premature termination codon (PTC) is generated using the FlpIn system according to manufacturer's instructions. Briefly, HEK293T (293T ATCC ® CRL-3216) cells were co-transfected with an expression vector containing a NanoLuc reporter with a PTC, 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. Following that expansion step, the cells are co-transfected with a plasmid encoding the ASGRI gene and selection cassette, such as a puromycin cassette. The next day, cells are selected with puromycin. The remaining cells are expanded and tested for ASGPR expression.

Synthesis and preparation of non-cognate GalNAc-TREM

In this example, the arginine non-cognate GalNAc-TREM, is produced such that it contains the sequence of the ARG-UCU-TREM body but with the anticodon sequence corresponding to UCA instead of UCU and is conjugated to the GalNAc moiety. The arginine non-cognate GalNAc-TREM may be synthesized as described previously and its quality controlled using methods as described herein. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Delivery of non-cognate GalNAc-TREM into host cells

100 nM of the arginine non-cognate GalNAc-TREM may be delivered to mammalian cells gymnotically or using transfection reagents, as described herein.

Translation suppression assay

To monitor the efficacy of the arginine non-cognate GalNAc-TREM to readthrough the PTC in the reporter construct, the cells are evaluated roughly 24-48 hours after TREM delivery. The cell media is replaced and the cells are allowed to equilibrate to room temperature. An equal volume to the cell media of ONE-Glo™ EX Reagent is added to the well and mixed on the orbital shaker at 500rpm for 3 min followed by addition of an equal volume of cell media of NanoDLR™ Stop & Glo, followed by and mixing on the orbital shaker at 500rpm for 3 min. The

reaction is incubated at room temperature for 10min and NanoLuc activity is detected by reading the luminescence in a plate reader. 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 GalNAc-TREM is transfected. The efficacy of the GalNAc-TREM may be measured as a ratio of the NanoLuc luminescence in the experimental sample to the NanoLuc luminescence of the positive control. It is expected that if the arginine non-cognate TREM is functional, read-through the stop mutation in the NanoLuc reporter may occur and produce a luminescent reading higher than the luminescent reading measured in the negative control. If the arginine non-cognate TREM is not functional, the stop mutation may not be rescued, and luminescence less or equal to the negative control is detected.

Example 14: Readthrough of a premature termination codon (PTC) in the alpha-galactosidase (GLA) ORF through administration of a TREM comprising an ASGPR binding moiety

This example describes an assay to test the ability of a non-cognate GalNAc-TREM to readthrough a PTC, such as R220X, in the alpha-galactosidase (GLA) open reading frame (ORF) in hepatocytes differentiated from reprogrammed Fabry disease patient-derived cell line. This Example describes an arginine non-cognate GalNAc-TREM, though Aanon-cognate TREM specifying any one of the other 19 amino acids can be used.

Patient-derived cells

Fibroblast cells derived from a patient with Fabry disease having a PTC in the alpha-galactosidase (GLA) open reading frame (ORF), such as R220X, may be obtained from a center or an organization, such as the Coriell Institute (catalog #s GM00881 and GM02769). The patient-derived fibroblast cells are reprogrammed into iPSCs and differentiated into hepatocytes as previously shown (Takahashi, K. & Yamanaka, S. (2006) *Cell* **126**, 663–676 (2006); Park I. et al. (2008) *Nature* **451**, 141–146); Jia, B. et al. (2014) *Life Sci.* **108**, 22-29).

Synthesis and preparation of non-cognate GalNAc-TREM

In this example, the arginine non-cognate GalNAc-TREM is produced such that it contains the sequence of the ARG-UCU-TREM body but with the anticodon sequence corresponding to UCA instead of UCU and is conjugated to the GalNAc moiety. The arginine non-cognate GalNAc-TREM is synthesized as described previously and its quality controlled

using methods as described in Examples 8-9. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Delivery of non-cognate GalNAc-TREM into hepatocytes

100 nM of the arginine non-cognate GalNAc-TREM may be delivered gymnotically, to iPSC-derived hepatocytes cells originating from Fabry patient-derived fibroblasts.

Translation suppression assay

To monitor the efficacy of the arginine non-cognate GalNAc-TREM to readthrough the PTC in the GLA ORF, 24-48 hours after transfection, cell media is replaced, and cells are lysed. Using Western blot detection, the non-cognate GalNAc-TREM efficacy is measured as the level of full-length protein expression, in this example of GLA enzyme, in the reprogrammed hepatocyte cells dosed with the Arg non-cognate TREM, in comparison to the GLA expression levels found in control hepatocyte cells not receiving the TREM. For example, as a control, cells of a person unaffected by the disease (i.e. cells having an ORF with a WT GLA transcript) may be used. It is expected that if the non-cognate GalNAc-TREM is functional, it can readthrough the PTC and the full-length protein level will be detected at higher levels than that found in reprogrammed hepatocyte cells which have not been administered the non-cognate GalNAc-TREM. If the non-cognate GalNAc-TREM is not functional, the full-length protein level will be detected at a similar level as detected in patient-derived fibroblast cells or reprogrammed hepatocyte cells which have not been administered the non-cognate GalNAc-TREM.

Example 15: Readthrough of a premature termination codon (PTC) in the alpha-galactosidase (GLA) ORF to produce a functional GLA protein through administration of TREM comprising a ASGPR binding moiety

This example describes an assay to test the ability of a non-cognate GalNAc-TREM to readthrough a PTC, such as R220X, in the alpha-galactosidase (GLA) open reading frame (ORF) in hepatocytes differentiated from reprogrammed Fabry disease patient-derived cell line to generate the production of a functional GLA protein. This Example describes an arginine non-cognate GalNAc-TREM, though a non-cognate TREM specifying any one of the other 19 amino acids can be used. Fibroblast cells derived from a patient with Fabry disease having a PTC in the alpha-galactosidase (GLA) open reading frame (ORF), such as R220X, may be obtained from a center or an organization, such as the Coriell Institute (catalog #s GM00881 and GM02769). The

cells can be reprogrammed and differentiated according to the exemplary protocols provided in Example 14.

To monitor the functionality of the GLA protein produced as a result of arginine non-cognate GalNAc-TREM-mediated PTC readthrough, a GLA protein activity assay may be performed using the Alpha Galactosidase Activity Assay Kit (Abcam) according to manufacturer instructions. Alternatively, GLA activity may be determined using the artificial substrate 4-methylumbelliferyl- α -D-galactoside as described previously in Desnick RJ, *et al. J Lab Clin Med.* 1973; 81:157–71.

Example 16: Correction of a missense mutation in an ORF with administration of a GalNAc-TREM

This example describes the administration of a GalNAc-TREM to correct a missense mutation. In this example, a GalNAc-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 prevents GFP excitation at the 470 nm and 390 nm wavelengths, may be 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 lipofectamine 2000 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.

Transfection of non-cognate GalNAc-TREM into host cells

To deliver the GalNAc-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 GalNAc-TREM to correct the missense mutation in the reporter construct, 24-48 hours after gymnotic delivery of the GalNAc-TREM, cell media is replaced and cell fluorescence is measured. A TREM that is not conjugated to a GalNAc moiety is used as a negative control in the experiment, and cells expressing WT GFP are used as a positive control for the assay. If the GalNAc-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 GalNAc-TREM is not functional, the GFP protein produced fluoresces only when excited with a 470 nm wavelength, as is observed in the negative control, indicating that the missense mutation was not corrected.

Example 17: Evaluation of protein expression levels of SMC-containing ORF with administration of a GalNAc-TREM

This example describes administration of a GalNAc-TREM to alter expression levels of an SMC-containing ORF.

To create a system to study the effects of GalNAc-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.

Evaluation of protein level of SMC-containing ORF

A GalNAc-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 PNPL3A ORF sequence. In this example, the GalNAc-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 18: Modulation of protein translation rate of SMC-containing ORF with GalNAc-TREM administration

This example describes administration of a GalNAc-TREM to alter the rate of protein translation of an SMC-containing ORF.

To monitor the effects of GalNAc-TREM addition on translation elongation rates in vitro translation system, in this example the RRL system (Promega), is used, in which the fluorescence change over time of a reporter gene (GFP), is a surrogate for translation rates.

Evaluation of protein translation rate of SMC-containing ORF

First, a mammalian lysate depleted of the endogenous tRNA using an antisense oligonucleotide targeting the sequence between the anticodon and variable loop may be 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
GGGGAUGUAGCUCAGUGGUAGAGCGCAUGCUUUGCAUGUAUGAGGUCCCCGGGUU
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 $\lambda_{\text{ex}}485/\lambda_{\text{em}}528$ with data points collected every 30 seconds over a period of 1 hour. 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 GalNAc-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 GalNAc-TREM.

CLAIMS

1. A tRNA effector molecule (TREM) comprising:
(i) a sequence of Formula A comprising:
[L1]_y-[ASt Domain1]_x-[L2]_x-[DH Domain]_x-[L3]_x-[ACH Domain]_x-[VL Domain]_y-[TH Domain]_x-[L4]_x-[ASt Domain2]_x, (A);
wherein, independently, [L1] and [VL Domain], are optional;
each y is independently 0 or 1; and
each x is 0 or 1; and
(ii) an asialoglycoprotein receptor (ASGPR) binding moiety (e.g., a GalNAc moiety, e.g., GalNAc),
wherein the ASGPR binding moiety is conjugated to a nucleobase within a nucleotide of the TREM, or at a terminus (e.g., the 5' or 3' terminus) of the TREM, or within the internucleotide linkage of a TREM.
2. The TREM of claim 1, wherein each x is 1.
3. The TREM of any one of claims 1-2, wherein the ASGPR moiety is present within the L1, ASt Domain1, L2, DH Domain, L3, ACH Domain, VL Domain, TH Domain, L4, or ASt Domain.
4. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within L1.
5. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within ASt Domain1.
6. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within L2.

7. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within DH Domain.
8. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within L3.
9. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within the ACH Domain.
10. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within VL Domain.
11. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within TH Domain.
12. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within L4.
13. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within ASt Domain2.
14. The TREM of any one of claims 1-3, wherein the ASGPR binding moiety is present within one of L1, ASt Domain1, or ASt Domain2.
15. The TREM of any one of claims 1-14, wherein the ASGPR binding moiety is covalently bound to a nucleobase within a nucleotide of the TREM, or at a terminus (e.g., the 5' or 3' terminus) of the TREM, or within the internucleotide linkage of a TREM (e.g., at a nitrogen or carbon atom in the nucleobase moiety).

16. The TREM of any one of claims 1-15, wherein the ASGPR binding moiety (e.g., a GalNAc moiety, e.g., GalNAc) is bound to a nucleobase within a nucleotide of the TREM.
17. The TREM of any one of claims 1-16, wherein the nucleobase is a naturally occurring nucleobase or a non-naturally occurring nucleobase.
18. The TREM of any one of claims 1-17, wherein the nucleobase comprises uracil, adenine, guanine, cytosine, thymine, or a variant thereof.
19. The TREM of any one of claims 1-15, wherein the ASGPR binding moiety (e.g., a GalNAc moiety, e.g., GalNAc) is bound to one or both of the termini within the TREM.
20. The TREM of claim 19, wherein the ASGPR binding moiety (e.g., a GalNAc moiety, e.g., GalNAc) is bound to the 5' terminus of the TREM.
21. The TREM of claim 19, wherein the ASGPR binding moiety (e.g., a GalNAc moiety, e.g., GalNAc) is bound to the 3' terminus of the TREM.
22. The TREM of any one of claims 1-15, wherein the ASGPR binding moiety is present within an internucleotide linkage of the TREM.
23. The TREM of any one of claims 1-22, wherein the TREM comprises the sequence of any one of the TREMs provided in Table 12, e.g., SEQ ID NOs. 622-654.
24. The TREM of any one of claims 1-23, wherein the TREM comprises a sequence that is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of a TREM provided in Table 12, e.g., any one of SEQ ID NOs. 622-654 provided in Table 12.

25. The TREM of any one of claims 1-24, wherein the TREM comprises a sequence that is at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a sequence of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 provided in Table 12.

26. The TREM of any one of claims 1-25, wherein the TREM 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, 60 nt, 65 nt, 70 nt, or 75 nt (but less than the full length) of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

27. The TREM of any one of claims 1-26, wherein the TREM comprises at least 60 nt, 65 nt, 70 nt, or 75 nt of a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

28. The TREM of any one of claims 1-27, wherein the TREM 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, 60 nt, 65 nt, 70 nt, or 75 nt (but less than the full length) of a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

29. The TREM of any one of claims 1-28, wherein the TREM comprises at least 60 nt, 65 nt, 70 nt, or 75 nt of a TREM which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-654 disclosed in Table 12.

30. The TREM of any one of claims 1-29, wherein the TREM comprises a sequence that differs no more than 1 ribonucleotide (nt), 2 nt, 3 nt, 4 nt, 5 nt, 6 nt, 7 nt, 8 nt, 9 nt, 10 nt, 12 nt, 14 nt, 16 nt, 18, nt, or 20 nt from a TREM provided in Table 12, *e.g.*, any one of SEQ ID NOs. 622-652 provided in Table 12.

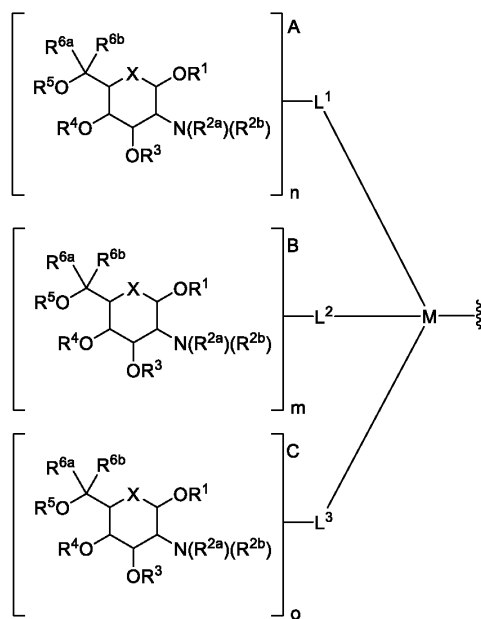
31. The TREM of any one of claims 1-30, wherein the TREM is selected from SEQ ID NO. 622, SEQ ID NO. 650, and SEQ ID NO. 653.

32. The TREM of any one of claims 1-31, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 622.

33. The TREM of any one of claims 1-31, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 650.

34. The TREM of any one of claims 1-31, wherein the TREM is at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO. 653.

35. The TREM of any one of claims 1-34, wherein the ASGPR binding moiety comprises a structure of Formula (III-b):



(III-b), or a salt thereof, wherein:

each X is independently O, $N(R^7)$, or S;

each of R^1 , R^3 , R^4 , and R^5 are independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, C(O)-alkyl, C(O)-alkenyl,

C(O)-alkynyl, C(O)-heteroalkyl, C(O)-haloalkyl, C(O)-aryl, C(O)-heteroaryl, C(O)-cycloalkyl, or C(O)-heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁸;

or R³ and R⁴ are taken together with the oxygen atoms to which they are connected to form a heterocyclyl ring optionally substituted with one or more R⁸;

R^{2a} is hydrogen or alkyl;

R^{2b} is -C(O)alkyl (e.g., C(O)CH₃);

each of R^{6a} and R^{6b} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, cyano, nitro, -OR^A, aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R⁹;

R⁷ is hydrogen, alkyl, or C(O)-alkyl;

each of R⁸ and R⁹ is independently hydrogen, halo, cyano, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, or heterocyclyl;

R^A is hydrogen, or alkyl, alkenyl, alkynyl;

each of L¹, L², and L³ is independently a linker;

each of m, n, and o is independently an integer between 1 and 100;

M is a linker,

wherein “ ξ ” represents an attachment point to a branching point, additional linker, or TREM, e.g., a linker, a nucleobase, internucleotide linkage, or terminus within the TREM sequence.

36. The TREM of claim 35, wherein X is O.

37. The TREM of any one of claims 35-36, each of R¹, R³, R⁴, and R⁵ are independently hydrogen or alkyl (e.g., CH₃).

38. The TREM of any one of claims 35-37, R^{2a} is hydrogen and R^{2b} is C(O)CH₃.

39. The TREM of any one of claims 35-38, wherein each of R^{6a} and R^{6b} is hydrogen.

40. The TREM of any one of claims 35-39, wherein each of m, n, and o is independently an integer between 1 and 10.
41. The TREM of any one of claims 35-40, wherein each of m, n, and o is independently 1.
42. The TREM of any one of claims 35-41, wherein each of L¹, L², and L³ independently comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.
43. The TREM of any one of claims 35-42, wherein each of L¹, L², and L³ independently is cleavable or non-cleavable.
44. The TREM of any one of claims 35-43, wherein each of L¹, L², and L³ independently comprises a polyethylene glycol group.
45. The TREM of any one of claims 35-44, wherein M comprises an alkylene, alkenylene, alkynylene, heteroalkylene, or haloalkylene group.
46. The TREM of any one of claims 35-45, wherein M comprises an ester, amide, disulfide, ether, carbonate, aryl, heteroaryl, cycloalkyl, or heterocyclyl group.
47. The TREM of any one of claims 35-46, wherein M is cleavable or non-cleavable.
48. The TREM of any one of claims 1-47, wherein the ASGPR binding moiety comprises a galactose (Gal), galactosamine (GalNH₂), or N-acetylgalactosamine (GalNAc) moiety.
49. The TREM of any one of claims 1-48, wherein the ASGPR binding moiety comprises a plurality of galactose (Gal), galactosamine (GalNH₂), or N-acetylgalactosamine (GalNAc) moieties.
50. The TREM of any one of claims 1-49, wherein the ASGPR binding moiety comprises an ASGPR carbohydrate and an ASGPR linker.

51. The TREM of any one of claims 1-50, wherein the ASGPR binding moiety comprises a triantennary GalNAc moiety.
52. The TREM of any one of claims 1-51, wherein the TREM is a compound provided in Table 12, e.g., any one of Compound Nos. 99-131.
53. The TREM of any of claims 1-52, wherein the TREM retains the ability to support protein synthesis, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
54. The TREM of any of claims 1-53, wherein the TREM retains the ability to be charged by a synthetase, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
55. The TREM of any of claims 1-54, wherein the TREM retains the ability to be bound by an elongation factor, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
56. The TREM of any of claims 1-55, wherein the TREM retains the ability to introduce an amino acid into a peptide chain, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
57. The TREM of any of claims 1-56, wherein the TREM retains the ability to support elongation or support initiation, e.g., relative to a TREM that does not comprise an ASGPR binding moiety or a naturally occurring tRNA.
58. The TREM of any of claims 1-57, wherein the TREM has a binding affinity to an ASGPR of between 0.01 nM and 100 mM.

59. The TREM of any one of claims 1-58, wherein the TREM further comprises a chemical modification (e.g., a naturally occurring modification or a non-naturally occurring chemical modification).
60. A pharmaceutical composition comprising a TREM of any one of claims 1-59.
61. The pharmaceutical composition of claim 60, further comprising a pharmaceutically acceptable component, e.g., an excipient.
62. A lipid nanoparticle formulation comprising a TREM of any one of claims 1-59.
63. A lipid nanoparticle formulation comprising a pharmaceutical composition of any one of claim 60-61.
64. A method of making a TREM of any one of claims 1-59.
65. A composition for use in treating a subject having a disease or disorder associated with a PTC comprising administering to the subject a TREM comprising an ASGPR binding moiety described herein (e.g., a TREM of any one of claims 1-59) or a pharmaceutical composition of any one of claims 60-61 or a lipid nanoparticle formulation of any one of claims 62-63, thereby treating the subject having the disease or disorder.