

[0025] Disclosed herein, in certain embodiments, is a method of screening for an agent capable of modifying regulation of a gene's expression comprising: identifying a nonsense-mediated RNA decay switch exon (NSE) that limits functional gene expression; identifying one or more splicing regulatory motifs upstream or downstream of the NSE that compete with the NSE for spliceosomal components, said regulatory motifs comprising cryptic splice sites or pseudoexons; targeting the one or more splicing regulatory motifs with antisense polynucleic acid arranged to hybridize to the splicing regulatory motifs through Watson-Crick base pairing; and determining if there is an increased or decreased inclusion of the NSE in a mature RNA transcript of the gene.

[0026] Disclosed herein, in certain embodiments, is a method of modulating gene's expression comprising providing an agent arranged to bind to splicing regulatory motifs, such as cryptic splice sites or pseudoexons, that compete with a nonsense-mediated RNA decay switch exon (NSE) for spliceosomal components.

[0027] Disclosed herein, in certain embodiments, is an agent arranged to bind to a gene splicing regulatory motif, such as a cryptic splice site or a pseudoexon, that competes with a nonsense-mediated RNA decay switch exon (NSE) for spliceosomal components, wherein the splicing regulatory motif controls inclusion of the NSE into a mature RNA transcript of the gene.

[0027a] Disclosed herein, in certain embodiments, is a use of a therapeutic agent for the manufacture of a medicament for the treatment or prevention of a disease or condition in a subject by repressing activation of non-sense mediated RNA decay (NMD), comprising: administering to the subject a pharmaceutical composition comprising: i) a non-sense mediated RNA decay switch exon (NSE)-repressor agent that interacts with a pre-processed mRNA transcript to modulate exclusion of an NSE from a processed mRNA transcript; and ii) a pharmaceutically acceptable excipient and/or a delivery vehicle; wherein the disease or condition is treated or prevented in the subject by the administration of the NSE-repressor agent.

[0027b] Disclosed herein, in certain embodiments, is a use of a therapeutic agent for the manufacture of a medicament for modulating protein expression, comprising: a) contacting a non-sense mediated RNA decay switch exon (NSE)-repressor agent to a target motif within a pre-processed mRNA transcript; b) processing a mRNA transcript from the pre-processed mRNA transcript thereby forming a processed mRNA transcript, wherein the NSE-repressor agent modulates exclusion of an NSE from the processed mRNA transcript; and c) translating the processed mRNA transcript wherein the exclusion of the NSE upregulates protein expression relative to the protein expression of an equivalent mRNA transcript comprising the NSE.

[0028] Disclosed herein, in certain embodiments, is a method, use, composition, vector, or agent substantially described herein, optionally with reference to the accompanying figures.

INCORPORATION BY REFERENCE

[0029] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] Fig. 1A-Fig. 1C illustrate an identification of a U2AF-repressed cryptic exon in ATM intron 28. Fig. 1A shows a schematic of the cryptic exon (termed here NSE for NMD-switch exon) activation. NSE sequence (upper panel) is boxed, asterisk denotes rs609261, and black rectangles show the indicated antisense oligonucleotides. Genome browser views of RNA-Seq data from RNAi- or SSO-mediated depletions of both U2AF35 isoforms (ab-), U2AF35a (a-), U2AF35b (b-) and controls (c) are shown in the lower panel. SSOs targeting 3' ss of U2AF1 exons Ab and 3 and U2AF35 siRNA were as previously described. Y axis, read densities. NSE inclusion/exclusion is schematically shown by dotted lines at the top. ATM exons (gray boxes) are numbered. The 29-nt

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutic agent for the manufacture of a medicament for the treatment or prevention of a disease or condition in a subject by repressing activation of non-sense mediated RNA decay (NMD), comprising:
administering to the subject a pharmaceutical composition comprising:
 - i) a non-sense mediated RNA decay switch exon (NSE)-repressor agent that interacts with a pre-processed mRNA transcript to modulate exclusion of an NSE from a processed mRNA transcript; and
 - ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;wherein the disease or condition is treated or prevented in the subject by the administration of the NSE-repressor agent.
2. The use of claim 1, wherein the expression of a protein translated from the processed mRNA transcript is increased by the exclusion of the NSE.
3. The use of claim 1, wherein the NSE-repressor agent comprises a polynucleic acid polymer.
4. The use of claim 3, wherein the polynucleic acid polymer hybridizes to a target motif within the pre-processed mRNA transcript.
5. The use of claim 4, wherein the target motif is located in an intronic region between two canonical exons.
6. The use of claim 5, wherein the intronic region comprises the NSE.
7. The use of claim 3, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
8. The use of claim 3, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
9. The use of claim 7, wherein the transposed element is Alu or MER51.
10. The use of claim 3, wherein the polynucleic acid polymer is from 10 to 50 nucleotides in length or from 10 to 30 nucleotides in length.

11. The use of claim 3, wherein the polynucleic acid polymer comprises a sequence with at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 23, 26, 37, 39, 51, and 53-55.
12. The use of claim 3, wherein the polynucleic acid polymer hybridizes to the NSE within the sequence
agTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 58);
tcttagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 59); or
tctcagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 60).
13. The use of claim 3, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.
14. The use of claim 3, wherein the polynucleic acid polymer comprises an artificial nucleotide.
15. The use of claim 14, wherein the artificial nucleotide is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), a 1',5'- anhydrohexitol nucleic acid (HNA), a morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.
16. The use of claim 1, wherein the disease or condition is cancer.
17. The use of claim 1, wherein the pre-processed mRNA transcript is an endogenous pre-processed mRNA transcript.
18. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a wild-type protein.
19. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a full-length protein.
20. The use of claim 1, wherein the NSE-repressor agent promotes exclusion of the NSE or a portion of the NSE from the processed mRNA transcript.
21. Use of a therapeutic agent for the manufacture of a medicament for modulating protein expression, comprising:

- a) contacting a non-sense mediated RNA decay switch exon (NSE)-repressor agent to a target motif within a pre-processed mRNA transcript;
 - b) processing a mRNA transcript from the pre-processed mRNA transcript thereby forming a processed mRNA transcript, wherein the NSE-repressor agent modulates exclusion of an NSE from the processed mRNA transcript; and
 - c) translating the processed mRNA transcript wherein the exclusion of the NSE upregulates protein expression relative to the protein expression of an equivalent mRNA transcript comprising the NSE.
22. The use of claim 21, wherein the target motif is located in an intronic region between two canonical exons.
 23. The use of claim 22, wherein the intronic region comprises the NSE.
 24. The use of claim 21, wherein the NSE-repressor agent comprises a polynucleic acid polymer.
 25. The use of claim 24, wherein the polynucleic acid polymer hybridizes to the target motif within the pre-processed mRNA transcript.
 26. The use of claim 24, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, upstream of a transposed element, or downstream of a transposed element.
 27. The use of claim 24, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.
 28. The use of claim 26, wherein the transposed element is Alu or MER51.
 29. The use of claim 24, wherein the polynucleic acid polymer is from 10 to 50 nucleotides in length or from 10 to 30 nucleotides in length.
 30. The use of claim 24, wherein the polynucleic acid polymer comprises a sequence with at least 70% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 23, 26, 37, 39, 51, and 53-55.
 31. The use of claim 24, wherein the polynucleic acid polymer hybridizes to the NSE within the sequence
agTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 58);
tcttagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 59); or
tctcagTCTACAGGTTGGCTGCATAGAAGAAAAAGgtagag (SEQ ID NO: 60).

32. The use of claim 24, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.
33. The use of claim 24, wherein the polynucleic acid polymer comprises an artificial nucleotide.
34. The use of claim 33, wherein the artificial nucleotide is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), a 1',5'- anhydrohexitol nucleic acid (HNA), a morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.
35. The use of claim 21, wherein the NSE-repressor agent promotes exclusion of the NSE or a portion of the NSE from the processed mRNA transcript.