[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), wherein the disease or condition is characterised by an impaired production of a protein and comprises an autosomal dominant disorder, X-linked dominant disorder, X-linked recessive disorder, Y-linked disorder, mitochondrial disease, or multifactorial or polygenic disorder, wherein the subject has a nonsense-mediated RNA decay switch exon (NSE) in a pre-processed mRNA transcript of a gene that encodes the protein, wherein the NSE is an exon that activates the NMD if included in a mature RNA transcript, wherein the therapeutic agent comprises a NSE-repressor agent that interacts with the pre-processed mRNA transcript to promote exclusion of the NSE from the pre-processed mRNA transcript, wherein the NSE is within an intronic region between two canonical exons, and wherein the NSE-repressor agent comprises a polynucleic acid polymer that hybridizes to a target motif within the pre-processed mRNA transcript.

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),

wherein the disease or condition is characterised by an impaired production of a protein and comprises an autosomal dominant disorder, X-linked dominant disorder, X-linked recessive disorder, Y-linked disorder, mitochondrial disease, or multifactorial or polygenic disorder, wherein the subject has a nonsense-mediated RNA decay switch exon (NSE) in a pre-processed mRNA transcript of a gene that encodes the protein, wherein the NSE is an exon that activates the NMD if included in a mature RNA transcript,

wherein the therapeutic agent comprises a NSE-repressor agent that interacts with the pre-processed mRNA transcript to promote exclusion of the NSE from the pre-processed mRNA transcript,

wherein the NSE is within an intronic region between two canonical exons, and

wherein the NSE-repressor agent comprises a polynucleic acid polymer that hybridizes to a target motif within the pre-processed mRNA transcript.

2. The use of claim 1, wherein the expression of a protein translated from a processed mRNA transcript that is processed from the pre-processed mRNA transcript in the cell is increased by the exclusion of the NSE.

3. The use of claim 1, wherein the target motif is located in the intronic region between two canonical exons.

4. The use of claim 1, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, and wherein the transposed element is Alu or MER51.

5. The use of claim 1, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.

6. The use of claim 1, wherein the polynucleic acid polymer is from 10 to 50 nucleotides in length or from 10 to 30 nucleotides in length.

7. The use of claim 1, wherein the polynucleic acid polymer comprises a sequence selected from the group consisting of SEQ ID NOs: 23, 26, 37, 39, 51, and 53-55.

8. The use of claim 1, 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).

9. The use of claim 1, 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.

10. The use of claim 1, wherein the polynucleic acid polymer comprises an artificial nucleotide.

11. The use of claim 10, 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.

12. The use of claim 1, wherein the disease or condition is an autosomal dominant disorder.

13. The use of claim 1, wherein the pre-processed mRNA transcript is an endogenous pre-processed mRNA transcript.

14. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a wild-type protein.

15. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a full-length protein.

16. The use of claim 1, wherein the pre-processed mRNA transcript is a wild-type pre-processed mRNA transcript.