

[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, ~~and~~ 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, ~~and~~
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 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.~~3. The use of claim ~~4~~1, wherein the target motif is located in ~~an~~the intronic region between two canonical exons.
- ~~6. The use of claim 5, wherein the intronic region comprises the NSE.~~
- ~~7.~~4. The use of claim ~~3~~1, wherein the polynucleic acid polymer hybridizes to a motif within a transposed element, and wherein the transposed element is Alu or MER51.
- ~~8.~~5. The use of claim ~~3~~1, wherein the polynucleic acid polymer hybridizes to a motif within ATM intron 28.

- ~~9~~.6. The use of claim ~~3~~1, wherein the polynucleic acid polymer is from 10 to 50 nucleotides in length or from 10 to 30 nucleotides in length.
- ~~10~~.7. The use of claim ~~3~~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.
- ~~11~~.8. The use of claim ~~3~~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).
- ~~12~~.9. The use of claim ~~3~~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.
- ~~13~~.10. The use of claim ~~3~~1, wherein the polynucleic acid polymer comprises an artificial nucleotide.
- ~~14~~.11. The use of claim ~~13~~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- dimethylaminoethoxyethyl (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.
- ~~15~~.12. The use of claim 1, wherein the disease or condition is an autosomal dominant disorder.
- ~~16~~.13. The use of claim 1, wherein the pre-processed mRNA transcript is an endogenous pre-processed mRNA transcript.
- ~~17~~.14. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a wild-type protein.
- ~~18~~.15. The use of claim 1, wherein a protein translated from the processed mRNA transcript is a full-length protein.
- ~~19~~.16. The use of claim 1, wherein the pre-processed mRNA transcript is a wild-type pre-processed mRNA transcript.