

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a therapeutic agent or a vector encoding the therapeutic agent, wherein the therapeutic agent comprises an antisense oligomer that comprises a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299, and a pharmaceutically acceptable excipient.
2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises the therapeutic agent, and wherein the antisense oligomer comprises a backbone modification, a sugar moiety modification, or a combination thereof.
3. The pharmaceutical composition of claim 2, wherein the antisense oligomer comprises a phosphorothioate linkage or a phosphorodiamidate linkage.
4. The pharmaceutical composition of claim 3, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl moiety, a 2'-Fluoro moiety, or a 2'-O-methoxyethyl moiety; preferably, wherein the antisense oligomer comprises a 2'-O-methoxyethyl moiety; more preferably, wherein each nucleotide of the antisense oligomer comprises a 2'-O-methoxyethyl moiety.
5. The pharmaceutical composition of any one of claims 1-4, wherein the antisense oligomer consists of from 8 to 50 nucleotides, preferably from 12 to 20 nucleotides, more preferably 18 nucleotides.
6. The pharmaceutical composition of any one of claims 1-5, wherein the composition comprises the vector, and wherein the vector comprises a viral vector encoding the therapeutic agent.
7. The pharmaceutical composition of claim 6, wherein the viral vector comprises an adenoviral vector, adeno-associated viral (AAV) vector, lentiviral vector, Herpes Simplex Virus (HSV) viral vector, or retroviral vector.
8. The pharmaceutical composition of any one of claims 1-7, wherein the therapeutic agent promotes exclusion of a non-sense mediated RNA decay-inducing exon (NMD exon) and/or a coding exon from a pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA, and wherein the pre-mRNA is transcribed from an *OPAI* gene and that comprises the NMD exon and/or the coding exon.
9. The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises:
 - (i) a sequence selected from the group consisting of SEQ ID NOs: 36, 227-242, 250, 267, and 280-299;
 - (ii) a sequence selected from the group consisting of SEQ ID NOs: 36, 227-230, 232-242, 280-283 and 288-295;

(iii) a sequence selected from the group consisting of SEQ ID NOs: 227-230, 232-242, 280-286, 288-299; or

(iv) a sequence selected from the group consisting of SEQ ID NOs: 227-230, 232-242, 280-283, and 288-295.

10. The pharmaceutical composition of claim 1, wherein the antisense oligomer comprises a sequence selected from the group consisting of 36, 236, 242, 250, or 267.

11. The pharmaceutical composition of any one of claims 1-10, further comprising a gene editing molecule or a polynucleotide encoding the gene editing molecule.

12. The pharmaceutical composition of claim 11, wherein the gene editing molecule comprises CRISPR-Cas9.

13. The pharmaceutical composition of any one of claims 1-12, wherein the composition is formulated for intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection; preferably, for intravitreal injection.

14. A composition comprising:

(a) an antisense oligomer that comprises a sequence selected from the group consisting of SEQ ID NOs: 6-275 and 280-299, wherein the antisense oligomer comprises a backbone modification, a sugar moiety modification, or a combination thereof; or

(b) a vector encoding the antisense oligomer.

15. The pharmaceutical composition of any one of claims 1-13 or the composition of claim 14 for use in treating or preventing a disease or condition.

16. Use of the pharmaceutical composition of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for the treatment of a disease or condition, wherein the disease or condition

(i) is associated with a loss-of-function mutation in an OPA1 gene; or

(ii) is associated with haploinsufficiency of the OPA1 gene, and wherein the subject has a first allele encoding a functional OPA1 protein, and a second allele from which the OPA1 protein is not produced or produced at a reduced level, or a second allele encoding a nonfunctional OPA1 protein or a partially functional OPA1 protein.

17. The use of claim 16, wherein the disease or condition comprises Optic atrophy type 1 or autosomal dominant optic atrophy (ADOA).

18. Use of the pharmaceutical composition of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for modulating expression of an OPA1 protein in a cell

having a pre-mRNA that is transcribed from an OPA1 gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD exon), wherein the use comprises

contacting the composition or the pharmaceutical composition to the cell, whereby the therapeutic agent modulates splicing of the NMD exon from the pre-mRNA, thereby modulating a level of processed mRNA that is processed from the pre-mRNA, and modulating the expression of the OPA1 protein in the cell.

19. Use of a therapeutic agent or a vector encoding the therapeutic agent in the manufacture of a medicament for modulating expression of an OPA1 protein in a cell having a pre-mRNA that is transcribed from an OPA1 gene, wherein the pre-mRNA comprises a coding exon, wherein the use comprises

contacting the therapeutic agent or the vector encoding the therapeutic agent to the cell, whereby the therapeutic agent promotes exclusion of the coding exon from the pre-mRNA, thereby increasing a level of a processed mRNA that is processed from the pre-mRNA and that lacks the coding exon in the cell.

20. The use of claim 19, wherein the coding exon comprises a sequence with at least 80%, at least 90%, or 100% sequence identity to SEQ ID NO: 277.

21. The use of claim 19 or 20, wherein the therapeutic agent:

- (a) binds to a targeted portion of the pre-mRNA;
- (b) modulates binding of a factor involved in splicing of the coding exon; or
- (c) a combination of (a) and (b).

22. The use of claim 21, wherein the targeted portion of the pre-mRNA comprises an exon-intron junction of exon GRCh38/ hg38: chr3 193626092 to 193626202.

23. The use of claim 21 or 22, wherein the targeted portion of the pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of SEQ ID NO: 277.

24. The use of any one of claims 19-23, wherein the therapeutic agent comprises an antisense oligomer.