

SUMMARY

In an aspect of the present disclosure, there is provided a modified antisense oligonucleotide (ASO) having 15-40 bases and comprising a base sequence that has at least 95% identity to any one of SEQ ID NOS: 13-90, 92-219, 221- 298, 300-377, and 423-520, and 522-640.

In another aspect of the present disclosure, there is provided a composition comprising the modified ASO as disclosed herein.

In a further aspect of the present disclosure, there is provided use of the modified ASO as disclosed herein in the manufacture of a medicament for reducing expression of a UNC13A cryptic exon splice variant in a cell.

In another aspect of the present disclosure, there is provided a modified ASO as disclosed herein for use in reducing expression of an UNC13A cryptic exon splice variant in a cell.

In one example, the present disclosure provides a method of reducing expression of a UNC13A cryptic exon splice variant in a cell comprising administering a UNC13A cryptic exon splice variant specific inhibitor, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide. In another example, the present disclosure provides a method of reducing phosphorylated TAR-DNA binding protein-43 (TDP-43) in a cell comprising administering a UNC13A cryptic exon splice variant specific inhibitor, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In another example, the present disclosure provides a method of treating TAR-DNA binding protein-43 (TDP-43) proteinopathy in a subject comprising administering a UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense

oligonucleotide.

In yet another example, the present disclosure provides a method of treating a subject that has been identified as having a UNC13A gene mutation in intron 20-21 comprising administering an UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In examples, the cryptic exon comprises the base sequence of SEQ ID NO:5 or SEQ ID NO:6.

CLAIMS

1. A modified antisense oligonucleotide (ASO) having 15-40 bases and comprising a base sequence that has at least 95% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-520, and 522-640.
2. The modified ASO of claim 1, wherein the antisense oligonucleotide has 20-30 bases.
3. The modified ASO of claim 1 or claim 2, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.
4. The modified ASO of any one of claims 1-3, comprises a base sequence set forth in any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-520, and 522-640.
5. The modified ASO of any one of claims 1-4, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 423-432, 439-443, 491-498, 502-507, and 513-514.
6. The modified ASO of any one of claims 1-5, wherein the antisense oligonucleotide has 18-25 bases.
7. The modified ASO of claim 6, wherein the antisense oligonucleotide has 18-22 bases.
8. The modified ASO of any one of claims 1-5, wherein the antisense oligonucleotide has 20-30 bases.

9. A composition comprising the modified ASO of any one of claims 1-8.
10. Use of the modified ASO of any one of claims 5-8 in the manufacture of a medicament for reducing expression of a UNC13A cryptic exon splice variant in a cell.
11. A modified ASO of any one of claims 5-8 for use in reducing expression of an UNC13A cryptic exon splice variant in a cell.