effective HTRA1 inhibition. The invention also provides effective antisense oligonucleotide sequences and compounds which are capable of inhibiting HTRA1, and their use in treatment of diseases or disorders where HTRA1 is indicated.

SUMMARY

The present disclosure relates to oligonucleotides targeting a mammalian HTRA1 nucleic acid, *i.e.* are capable of inhibiting the expression of HTRA1 and to treat or prevent diseases related to the functioning of the HTRA1. The oligonucleotides targeting HTRA1 are antisense oligonucleotides, *i.e.* are complementary to their HTRA1 nucleic acid target.

The oligonucleotide of the disclosure may be in the form of a pharmaceutically acceptable salt, such as a sodium salt or a potassium salt.

Accordingly, the disclosure provides antisense oligonucleotides which comprise a contiguous nucleotide sequence of 10 - 30 nucleotides in length with at least 90% complementarity, such as fully complementary to a mammalian HTRA1 nucleic acid, such as SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3 or SEQ ID NO 4.

The disclosure provides pharmaceutical compositions comprising the oligonucleotides of the disclosure and pharmaceutically acceptable diluents, carriers, salts and/or adjuvants.

The disclosure provides LNA antisense oligonucleotides, such as LNA gapmer oligonucleotides, which comprise a contiguous nucleotide sequence of 10 - 30 nucleotides in length with at least 90% complementarity, such as fully complementary to a HTRA1 nucleic acid, such as a sequence selected from the group consisting of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3 or SEQ ID NO 4.

In one aspect, the disclosure provides for an antisense oligonucleotide of formula $T_sA_sT_st_st_sa_sc_sc_st_sg_sg_st_sT_sG_sT_sT$ (SEQ ID NO 143), wherein a capital letter represents an LNA nucleoside unit, a lower case letter represents a DNA nucleoside unit, subscript s represents a phosphorothioate internucleoside linkage.

The disclosure provides for an antisense oligonucleotide comprising a contiguous nucleotide region of 10 – 22, such as 12 - 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 147:

SEQ ID NO 147: 5' CCAACAACCAGGTAAATATTTG 3'

The disclosure provides for an antisense oligonucleotide comprising a contiguous nucleotide region of 10 – 17, such as 11, 12, 13, 14, 15, 16, such as 12 – 16 or 12 - 17 nucleotides which are complementarity to a sequence selected from the group consisting of SEQ ID NO 148 - 155.

The disclosure provides for an antisense oligonucleotide comprising a contiguous nucleotide region of 10 – 17, such as 11, 12, 13, 14, 15, 16, such as 12 – 16 or 12 - 17 nucleotides which are complementarity to SEQ ID NO 148 or 155.

5

The disclosure provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 147:

SEQ ID NO 147: 5' CCAACAACCAGGTAAATATTTG 3'

The disclosure provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of at least 10, such as at least 12 contiguous nucleotides which are complementary to a sequence present in a sequence selected from SEQ ID NO 148 – 155.

The disclosure provides for an antisense oligonucleotide of at least 12 nucleotides in length, wherein said antisense oligonucleotide comprises the contiguous sequence of SEQ ID NO 146 SEQ ID NO 146: 5' TTTACCTGGTT 3'.

The disclosure provides for the oligonucleotides provided in the examples. The disclosure provides for the oligonucleotide, such as an antisense oligonucleotide, which comprises at least 10, such as at least 12, present in a sequence selected from the group consisting of SEQ ID NO 5 – 145.

The disclosure provides for a conjugate comprising the oligonucleotide according to the disclosure, and at least one conjugate moiety covalently attached to said oligonucleotide.

The disclosure provides for a pharmaceutically acceptable salt of the oligonucleotide or conjugate of the disclosure. In another aspect, the disclosure provides for a pharmaceutically acceptable salt of the antisense oligonucleotide as defined herein.

In another aspect, the disclosure provides for a pharmaceutical composition comprising the antisense oligonucleotide as defined herein; and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant

The disclosure provides methods for *in vivo* or *in vitro* method for modulation of HTRA1 expression in a cell which is expressing HTRA1, by administering an oligonucleotide, conjugate or composition of the disclosure in an effective amount to said cell. In another aspect, the disclosure provides for an in vitro method for modulating HTRA1 expression in a target cell which is expressing HTRA1, said method comprising administering the antisense oligonucleotide, pharmaceutically acceptable salt, or pharmaceutical composition as defined herein in an effective amount to said cell.

The disclosure provides methods for treating or preventing a disease, disorder or dysfunction associated with *in vivo* activity of HTRA1 comprising administering a therapeutically or prophylactically effective amount of the oligonucleotide of the disclosure, or conjugate thereof, to a subject suffering from or susceptible to the disease, disorder or dysfunction.

The oligonucleotide or composition of the disclosure is used for the treatment or prevention of macular degeneration, and other disorders where HTRA1 is implicated.

In another aspect, the disclosure provides for the antisense oligonucleotide as defined herein, or the pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein, for use in medicine.

The disclosure provides for the oligonucleotide or conjugate of the disclosure, for use in the treatment of a disease or disorder selected from the list comprising of Duchenne muscular dystrophy, arthritis, such as osteoarthritis, familial ischemic cerebral small-vessel disease, Alzhiemer's disease and Parkinson's disease.

In another aspect, the disclosure provides for the antisense oligonucleotide as defined herein, or the pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment or prevention of macular degeneration.

The disclosure provides for the oligonucleotide or conjugate of the disclosure, for use in the treatment of macular degeneration, such as wet or dry age related macular degeneration (e.g. wAMD, dAMD, geographic atrophy, intermediate dAMD) or diabetic retinopathy.

The disclosure provides for the use of the oligonucleotide, conjugate or composition of the disclosure, for the manufacture of a medicament for the treatment of macular degeneration, such as wet or dry age related macular degeneration (*e.g.* wAMD, dAMD, geographic atrophy, intermediate dAMD) or diabetic retinopathy.

In another aspect, the disclosure provides for use of the antisense oligonucleotide as defined herein, or the pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein, for the preparation of a medicament for treatment or prevention of macular degeneration.

The disclosure provides for the use of the oligonucleotide, conjugate or composition of the disclosure, for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of Duchenne muscular dystrophy, arthritis, such as osteoarthritis, familial ischemic cerebral small-vessel disease, Alzhiemer's disease and Parkinson's disease.

The disclosure provides for a method of treatment of a subject suffering from a disease or disorder selected from the group consisting of Duchenne muscular dystrophy, arthritis, such as osteoarthritis, familial ischemic cerebral small-vessel disease, Alzhiemer's disease and Parkinson's disease, said method comprising the step of administering an effective amount of the oligonucleotide, conjugate or composition of the disclosure to the subject.

The disclosure provides for a method of treatment of a subject suffering from an ocular disease, such as macular degeneration, such as wet or dry age related macular degeneration (*e.g.* wAMD, dAMD, geographic atrophy, intermediate dAMD) or diabetic retinopathy, said method comprising the step of administering an effective amount of the oligonucleotide, conjugate or composition of the disclosure to the subject.

The disclosure provides for a method of treatment of a subject suffering from an ocular disease, such as macular degeneration, such as wet or dry age related macular degeneration (*e.g.* wAMD, dAMD, geographic atrophy, intermediate dAMD) or diabetic retinopathy, said method comprising administering at least two dosages of the oligonucleotide of the disclosure, or pharmaceutically acceptable salt thereof, in an intraocular injection in a dosage of from about 10µg - 200 µg, wherein the dosage interval between administration consecutive is at least 4 weeks or at least monthly.

CLAIMS

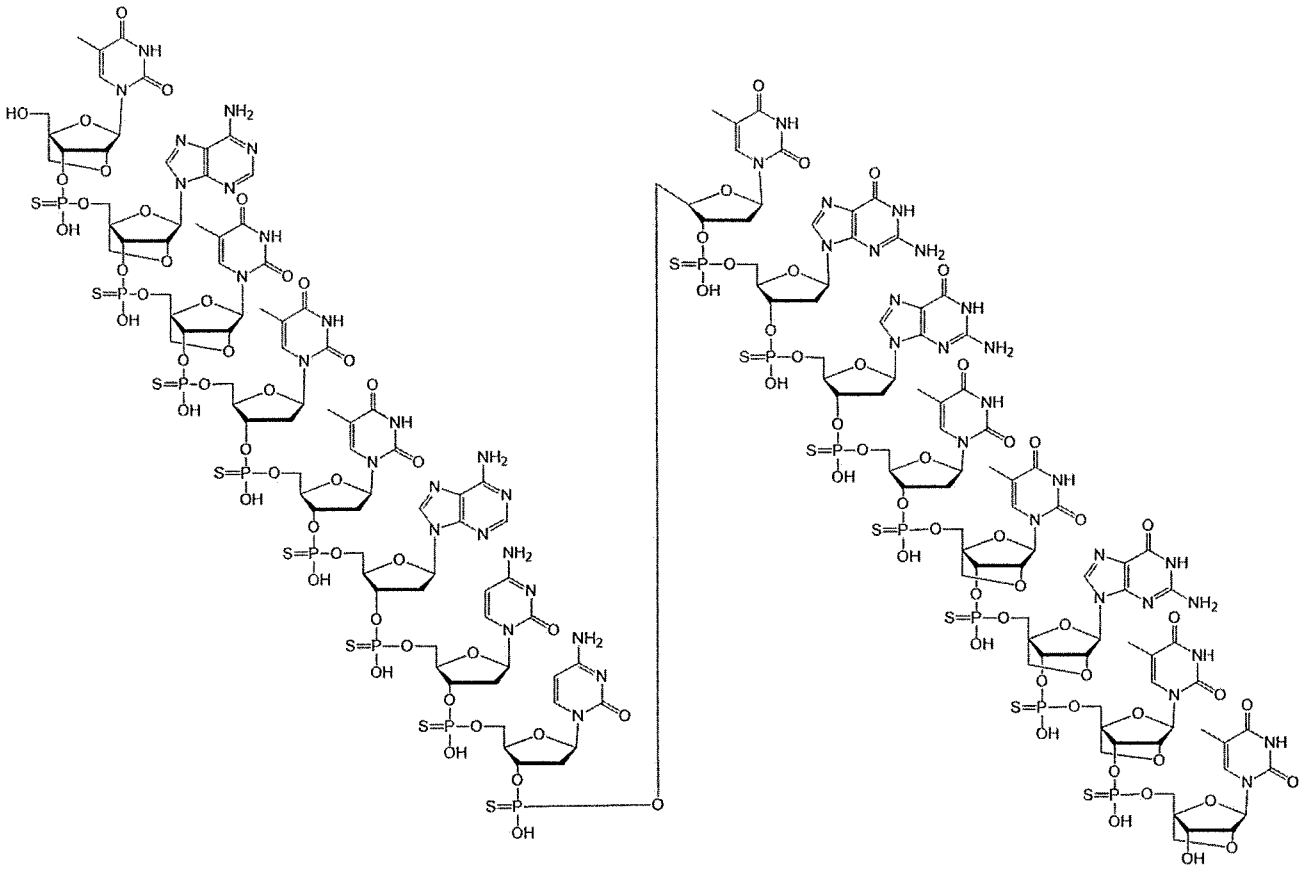
1. An antisense oligonucleotide of formula

$T_sA_sT_st_st_sa_sc_sc_st_sg_sg_st_sT_sG_sT_sT$ (SEQ ID NO 143),

wherein a capital letter represents an LNA nucleoside unit, a lower case letter represents a DNA nucleoside unit, subscript s represents a phosphorothioate internucleoside linkage.

2. The antisense oligonucleotide according to claim 1, wherein the LNA nucleosides are all beta-D-oxy LNA nucleosides.

3. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is of formula



4. The pharmaceutically acceptable salt of the antisense oligonucleotide according to any one of claims 1 - 3.

5. The pharmaceutically acceptable salt according to claim 4, wherein the salt is a sodium salt.

6. The pharmaceutically acceptable salt according to claim 4, wherein the salt is a potassium salt.

7. A pharmaceutical composition comprising the antisense oligonucleotide according to any one of claims 1 – 3; and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

8. The pharmaceutical composition according to claim 7, wherein the pharmaceutical composition comprises a pharmaceutically acceptable diluent.

9. The pharmaceutical composition according to claim 8, wherein the pharmaceutically acceptable diluent is phosphate buffered saline.

10. The pharmaceutical composition according to any one of claims 7 – 9, wherein the antisense oligonucleotide is in the form of a pharmaceutically acceptable salt.

11. A pharmaceutical composition comprising the pharmaceutically acceptable salt according to any one of claims 4 – 6; and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

12. The pharmaceutical composition according to any one of claims 7 - 11, wherein the pharmaceutically acceptable salt is a sodium salt or a potassium salt.

13. The antisense oligonucleotide according to any one of claims 1 – 3, or the pharmaceutically acceptable salt of any one of claims 4 – 6, or the pharmaceutical composition according to any one of claims 7 – 12, for use in medicine.

14. The antisense oligonucleotide according to any one of claims 1 – 3, or the pharmaceutically acceptable salt of any one of claims 4 – 6, or the pharmaceutical composition according to any one of claims 7 – 12, for use in the treatment or prevention of macular degeneration.

15. The use of the antisense oligonucleotide according to any one of claims 1 – 3, or the pharmaceutically acceptable salt of any one of claims 4 – 6, or the pharmaceutical composition according to any one of claims 7 - 12, for the preparation of a medicament for treatment or prevention of macular degeneration.

16. The antisense oligonucleotide, pharmaceutically acceptable salt, pharmaceutical composition, or use according to any one of claims 13 – 15, wherein the disease is selected from wetAMD, dryAMD, geographic atrophy, and intermediate dAMD.

17. An in vitro method for modulating HTRA1 expression in a target cell which is expressing HTRA1, said method comprising administering the antisense oligonucleotide, pharmaceutically acceptable salt, or pharmaceutical composition according to any one of claims 1 – 12 in an effective amount to said cell.