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(54) **Title:** ANTISENSE OLIGONUCLEOTIDES FOR MODULATING HTRA1 EXPRESSION

(57) **Abstract:** The present invention relates to antisense oligonucleotides (oligomers) that are complementary to HTRA1, leading to modulation of the expression of HTRA1. Modulation of HTRA expression is beneficial for a range of medical disorders, such as macular degeneration, e.g. age-related macular degeneration.

ANTISENSE OLIGONUCLEOTIDES FOR MODULATING HTRA1 EXPRESSION

FIELD OF INVENTION

The present invention relates to antisense oligonucleotides (oligomers) that are complementary to HTRA1, leading to modulation of the expression of HTRA1. Modulation of HTRA1 expression is beneficial for a range of medical disorders, such as macular degeneration, e.g. age-related macular degeneration.

BACKGROUND

The human high temperature requirement A (HTRA) family of serine proteases are ubiquitously expressed PDZ-proteases that are involved in maintaining protein homeostasis in extracellular compartments by combining the dual functions of a protease and a chaperone. HTRA proteases are implicated in organization of the extracellular matrix, cell proliferation and ageing. Modulation of HTRA activity is connected with severe diseases, including Duchenne muscular dystrophy (Bakay et al. 2002, Neuromuscul. Disord. 12: 125-141), arthritis, such as osteoarthritis (Grau et al. 2006, JBC 281: 6124-6129), cancer, familial ischemic cerebral small-vessel disease and age-related macular degeneration, as well as Parkinson's disease and Alzheimer's disease. The human HTRA1 contains an insulin-like growth factor (IGF) binding domain. It has been proposed to regulate IGF availability and cell growth (Zumbrunn and Trueb, 1996, FEES Letters 398:189-192) and to exhibit tumor suppressor properties. HTRA1 expression is down-regulated in metastatic melanoma, and may thus indicate the degree of melanoma progression. Overexpression of HTRA1 in a metastatic melanoma cell line reduced proliferation and invasion in vitro, and reduced tumor growth in a xenograft mouse model (Baldi et al., 2002, Oncogene 21:6684-6688). HTRA1 expression is also down-regulated in ovarian cancer. In ovarian cancer cell lines, HTRA1 overexpression induces cell death, while antisense HTRA1 expression promoted anchorage-independent growth (Chien et al., 2004, Oncogene 23:1636-1644).

In addition to its effect on the IGF pathway, HTRA1 also inhibits signaling by the TGFβ family of growth factors (Oka et al., 2004, Development 131:1041-1053). HTRA1 can cleave amyloid precursor protein (APP), and HTRA1 inhibitors cause the accumulation of Aβ peptide in cultured cells. Thus, HTRA1 is also implicated in Alzheimer's disease (Grau et al.,2005, Proc. Nat. Acad. Sci. USA. 102:6021-6026).

Furthermore,HTRA1 upregulation has been observed and seems to be associated to Duchenne muscular dystrophy (Bakay *et al.* 2002, Neuromuscul. Disord. 12: 125-141) and osteoarthritis (Grau et al. 2006, JBC 281: 6124-6129) and AMD (Fritsche, et al. Nat Gen 2013 45(4):433-9.)

A single nucleotide polymorphism (SNP) in the HTRA1 promoter region (rs11200638) is associated with a 10 fold increased the risk of developing age-related macular degeneration

(AMD). Moreover the HTRA1 SNPs are in linkage disequilibrium with the ARMS2 SNP (rs10490924) associated with increased risk of developing age-related macular degeneration (AMD). The risk allele is associated with 2-3 fold increased HTRA1 mRNA and protein expression, and HTRA1 is present in drusen in patients with AMD (Dewan et al., 2006, Science 314:989-992; Yang et al., 2006, Science 314:992-993). Over-expression of HtrA1 Induces AMD-like phenotype in mice. The hHTRA transgenic mouse (Veierkottn, PlosOne 2011) reveals degradation of the elastic lamina of Bruch's membrane, determines choroidal vascular abnormalities (Jones, PNAS 2011) and increases the Polypoidal choroidal vasculopathy (PCV) lesions (Kumar, IOVS 2014). Additionally it has been reported that Bruch's membrane damage in hHTRA1 Tg mice, which determines upon exposure to cigarette smoke 3 fold increases CNV (Nakayama, IOVS 2014)

Age-related macular degeneration (AMD) is the leading cause of irreversible loss of vision in people over the age of 65. With onset of AMD there is gradual loss of the light sensitive photoreceptor cells in the back of the eye, the underlying pigment epithelial cells that support them metabolically, and the sharp central vision they provide. Age is the major risk factor for the onset of AMD: the likelihood of developing AMD triples after age 55. Smoking, light iris color, sex (women are at greater risk), obesity, and repeated exposure to UV radiation also increase the risk of AMD. AMD progression can be defined in three stages: 1) early, 2) intermediate, and 3) advanced AMD. There are two forms of advanced AMD: dry AMD (also called geographic atrophy, GA) and wet AMD (also known as exudative AMD). Dry AMD is characterized by loss of photoreceptors and retinal pigment epithelium cells, leading to visual loss. Wet AMD, is associated with pathologic choroidal (also referred to as subretinal) neovascularization. Leakage from abnormal blood vessels forming in this process damages the macula and impairs vision, eventually leading to blindness. In some cases, patients can present pathologies associated with both types of advanced AMD. Treatment strategies for wet AMD require frequent injections into the eye and are focused mainly on delaying the disease progression. Currently no treatment is available for dry AMD. There is therefore an unmet medical need in the provision of effective drugs to treat macular degenerative conditions such as wet and dry AMD. WO 2008/013893 claims a composition for treating a subject suffering from age related macular degeneration comprising a nucleic acid molecules comprising an antisense sequence that hybridizes to HTRA1 gene or mRNA: No antisense molecules are disclosed. WO2009/006460 provides siRNAs targeting HTRA1 and their use in treating AMD.

OBJECTIVE OF THE INVENTION

The present invention provides antisense oligonucleotides which modulate HTRA1 *in vivo* or *in vitro*. The invention identified cryptic target sequence motifs present in the human HTRA1 mRNA (including pre-mRNA) which may be targeted by antisense oligonucleotides to give 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 OF INVENTION

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

Accordingly, the invention 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.

In a further aspect, the invention provides pharmaceutical compositions comprising the oligonucleotides of the invention and pharmaceutically acceptable diluents, carriers, salts and/or adjuvants.

The invention 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.

The invention provides for an antisense oligonucleotide comprising a contiguous nucleotide region of at 10 – 30, such as 12 – 22, nucleotides, wherein the contiguous nucleotide region is at least 90% such as 100% complementary to SEQ ID NO 113.

The invention provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 30, such as 12 – 22, nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 113:

5’
GACAGTCAGCATTTGTCTCCTCCTTTAACTGAGTCATCATCTTAGTCCAACTAATGCAGTCG
ATACAATGCGTAGATAGAAGAAGCCCCACGGGAGCCAGGATGGGACTGGTCGTGTTTGTG
CTTTTCTCCAAGTCAGCACCCAAAGGTCAATGCACAGAGACCCCGGGTGGGTGAGCGCTG
GCTTCTCAAACGGCCGAAGTTGCCTCTTTTAGGAATCTCTTTGGAATTGGGAGCACGATGA
CTCTGAGTTTGAGCTATTAAAGTACTTCTTAC 3’.

The reverse complement of SEQ ID NO 113 is SEQ ID NO 119: GTAAGAAGTACTTTAATAGCTCAAACTCAGAGTCATCGTGCTCCCAATTCCAAAGAGATTCC TAAAAGAGGCAACTTCGGCCGTTTGAGAAGCCAGCGCTCACCCACCCGGGGTCTCTGTGC ATTGACCTTTGGGTGCTGACTTGGAGAAAAGCACAAACACGACCAGTCCCATCCTGGCTCC CGTGGGGCTTCTTCTATCTACGCATTGTATCGACTGCATTAGTTGGACTAAGATGATGACT CAGTTAAAGGAGGAGACAAATGCTGACTGTC.

The invention provides for an antisense oligonucleotide comprising a contiguous nucleotide region of at 10 – 30, such as 12 – 22, nucleotides, wherein the contiguous nucleotide region is at least 90% such as 100% complementary to SEQ ID NO 114.

The invention provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 30, such as 12 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 114: 5' GACAGTCAGCATTTGTCTCCTCCTTTAACTGAGTCATCATCTTAGTCCAACTAATGCAGTCG ATACAATGCGTAGATAGAAGAAGCCCCACGGGAGCCAGGATGGGACTGGTCGTGTTTGTG CTTTTCTCCAAGTCAGCACCCAAAGGTCAATGCACAGAGACCCCGGGTGGGTGAGCGCTG GCTTCTCAAACGGCCGAAGTTGCCTCTTTTAGGAATCTCTTTGGAATTGGGAGCACGATGA CTCTGAGTTTGAGCTATTAAAGTACTTCTTACACATTGC 3'.

The reverse complement of SEQ ID NO 114 is SEQ ID NO 120: GCAATGTGTAAGAAGTACTTTAATAGCTCAAACTCAGAGTCATCGTGCTCCCAATTCCAAAG AGATTCCTAAAAGAGGCAACTTCGGCCGTTTGAGAAGCCAGCGCTCACCCACCCGGGGTC TCTGTGCATTGACCTTTGGGTGCTGACTTGGAGAAAAGCACAAACACGACCAGTCCCATCC TGGCTCCCGTGGGGCTTCTTCTATCTACGCATTGTATCGACTGCATTAGTTGGACTAAGAT GATGACTCAGTTAAAGGAGGAGACAAATGCTGACTGTC.

The invention provides for an antisense oligonucleotide comprising a contiguous nucleotide region of at 10 – 30, such as 12 – 22, nucleotides, wherein the contiguous nucleotide region is at least 90% such as 100% complementary to SEQ ID NO 115.

The invention provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 30,such as 12 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 115: 5' GACAGTCAGCATTTGTCTCCTCCTTTAACTGAGTCATCATCTTAGTCCAACTAATGCAGTCG

ATACAATGCGTAGATAGAAGAAGCCCCACGGGAGCCAGGATGGGACTGGTCGTGTTTGTG CTTTTCTCCAAGTCAGCACCCAAAGGTCAATGCACAGAGACCCCGGGTGGGTGAGCGCTG GCTTCTCAAACGGCCGAAGTTGCCTCTTTTAGGAATCTCTTTGGAATTGGGAGCACGATGA CTCTGAGTTTGAGCTATTAAAGT 3’.

The reverse complement of SEQ ID NO 115 is SEQ ID NO 121: ACTTTAATAGCTCAAACTCAGAGTCATCGTGCTCCCAATTCCAAAGAGATTCCTAAAAGAGG CAACTTCGGCCGTTTGAGAAGCCAGCGCTCACCCACCCGGGGTCTCTGTGCATTGACCTT TGGGTGCTGACTTGGAGAAAAGCACAAACACGACCAGTCCCATCCTGGCTCCCGTGGGGC TTCTTCTATCTACGCATTGTATCGACTGCATTAGTTGGACTAAGATGATGACTCAGTTAAAG GAGGAGACAAATGCTGACTGTC.

The invention provides for an antisense oligonucleotide comprising a contiguous nucleotide region of at 10 – 30, such as 12 – 22, nucleotides, wherein the contiguous nucleotide region is at least 90% such as 100% complementary to SEQ ID NO 116.

The invention provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 30, such as 12 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 116: 5’ CAACTAATGCAGTCGATACAATGCGTAGATAGAAGAAGCCCCACGGGAGCCAGGATGGGA CTGGTCGTGTTTGTGCTTTTCTCCAAGTCAGCACCCAAAGGTCAATGCACAGAGACCCCGG GTGGGTGAGCGCTGGCTTCTCAAACGGCCGAAGTTGCCTCTTTTAGGAATCTCTTTGGAAT TGGGAGCACGATGACTCTGAGTTTGAGCTATTAAAGTACTTCTTACACATTGC 3’.

The reverse complement of SEQ ID NO 116 is SEQ ID NO 122: GCAATGTGTAAGAAGTACTTTAATAGCTCAAACTCAGAGTCATCGTGCTCCCAATTCCAAAG AGATTCCTAAAAGAGGCAACTTCGGCCGTTTGAGAAGCCAGCGCTCACCCACCCGGGGTC TCTGTGCATTGACCTTTGGGTGCTGACTTGGAGAAAAGCACAAACACGACCAGTCCCATCC TGGCTCCCGTGGGGCTTCTTCTATCTACGCATTGTATCGACTGCATTAGTTG.

The invention provides for an antisense oligonucleotide comprising a contiguous nucleotide region of at 10 – 30, such as 12 – 22, nucleotides, wherein the contiguous nucleotide region is at least 90% such as 100% complementary to SEQ ID NO 117.

The invention provides for an antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide region of 10 – 30, such as 12 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 117: 5’ CAACTAATGCAGTCGATACAATGCGTAGATAGAAGAAGCCCCACGGGAGCCAGGATGGGA CTGGTCGTGTTTGTGCTTTTCTCCAAGTCAGCACCCAAAGGTCAATGCACAGAGACCCCGG

GTGGGTGAGCGCTGGCTTCTCAAACGGCCGAAGTTGCCTCTTTTAGGAATCTCTTTGGAAT TGGGAGCACGATGACTCTGAGTTTGAGCTATTAAAGTTACTTCTTAC 3’.

The reverse complement of SEQ ID NO 117 is SEQ ID NO 123: GTAAGAAGTAACTTTAATAGCTCAAACTCAGAGTCATCGTGCTCCCAATTCCAAAGAGATTC CTAAAAGAGGCAACTTCGGCCGTTTGAGAAGCCAGCGCTCACCCACCCGGGTCTCTGTG CATTGACCTTTGGGTGCTGACTTGGAGAAAAGCACAAACACGACCAGTCCCATCCTGGCTC CCGTGGGGCTTCTTCTATCTACGCATTGTATCGACTGCATTAGTTG.

In some embodiments the antisense oligonucleotide of the invention is not of sequence 5’ gcaatgtgtaagaagt 3’ (SEQ ID NO 112). In some embodiments the antisense oligonucleotide of the invention does not comprise or consist of sequence 5’ gcaatgtgtaagaagt 3’. In some embodiments the antisense oligonucleotide of the invention does not comprise or consist of 10 or more contiguous nucleotides present in sequence 5’ gcaatgtgtaagaagt 3’. In some embodiments the oligonucleotide of the invention is other than 5’ GCAatgtgtaagaAGT 3’, wherein Capital letters represent LNA nucleosides (beta-D-oxy LNA nucleosides were used), all LNA cytosines are 5-methyl cytosine, lower case letters represent DNA nucleosides, DNA cytosines preceded with a superscript m represents a 5-methyl C-DNA nucleoside. All internucleoside linkages are phosphorothioate internucleoside linkages.

The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10 contiguous nucleotides present in any one of SEQ ID NOs 5 – 111. The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 12 contiguous nucleotides present in any one of SEQ ID NOs 5 – 111. The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 14 contiguous nucleotides present in any one of SEQ ID NOs 5 – 111. The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 15 or 16 contiguous nucleotides present in any one of SEQ ID NOs 5 – 111. The invention provides an antisense oligonucleotide, wherein the contiguous nucleotide sequence of the oligonucleotide comprises or consists of a nucleobase sequence selected from the group consisting of any one of SEQ ID NOs 5 – 111.

The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, at least 13, or at least 14 or at least 15 or at least 16 contiguous nucleotides present SEQ ID NO 118: 5’ CTTCTTCTATCTACGCATTG 3’. The reverse complement of SEQ ID NO 118 is SEQ ID NO 231: CAATGCGTAGATAGAAGAAG.

The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, at least 13, or at least 14 or at least 15 or at least 16 contiguous nucleotides complementary to SEQ ID NO 231.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or 16 contiguous nucleotides present SEQ ID NO 67.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or 16 contiguous nucleotides present SEQ ID NO 86.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or at least 16 or at least 17 or 18 contiguous nucleotides present SEQ ID NO 73.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or 16 contiguous nucleotides complementary to SEQ ID NO 186.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or 16 contiguous nucleotides complementary to SEQ ID NO 205.
The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or at least 16 or at least 17 or 18 contiguous nucleotides complementary to SEQ ID NO 192.

The invention provides for an oligonucleotide comprising or consisting of an oligonucleotide selected from the group consisting of :

$T_sT_s{}^mC_st_sa_st_sc_st_sa_s{}^mc_sg_sc_sa_sT_sT_sG$ (SEQ ID NO 67,1),
${}^mC_sT_sT_s{}^mC_st_st_sc_st_sa_st_sc_st_sa_s{}^mc_sg_sc_sA_sT$ (SEQ ID NO 73,1), and
$T_sA_s{}^mC_sT_st_st_sa_sa_st_sa_sg_sc_sT_s{}^mC_sA_sA$ (SEQ ID NO 86,1);

wherein capital letters represent beta-D-oxy LNA nucleosides, lower case letters are DNA nucleosides, subscript s represents a phosphorothioate internucleoside linkage, and ${}^mC$ represent 5 methyl cytosine beta-D-oxy LNA nucleosides, and ${}^mc$ represents 5 methyl cytosine DNA nucleosides.

The invention provides for an oligonucleotide of formula:

$T_sT_s{}^mC_st_sa_st_sc_st_sa_s{}^mc_sg_sc_sa_sT_sT_sG$ (SEQ ID NO 67,1),

wherein capital letters represent beta-D-oxy LNA nucleosides, lower case letters are DNA nucleosides, subscript s represents a phosphorothioate internucleoside linkage, and ^{m}C represent 5 methyl cytosine beta-D-oxy LNA nucleosides, and ^{m}c represents 5 methyl cytosine DNA nucleosides.

The invention provides for an oligonucleotide of formula:

$^{m}C_sT_sT_s{}^{m}C_st_st_sc_st_sa_st_sc_st_sa_s{}^{m}c_sg_sc_sA_sT$ (SEQ ID NO 73,1)

wherein capital letters represent beta-D-oxy LNA nucleosides, lower case letters are DNA nucleosides, subscript s represents a phosphorothioate internucleoside linkage, and ^{m}C represent 5 methyl cytosine beta-D-oxy LNA nucleosides, and ^{m}c represents 5 methyl cytosine DNA nucleosides.

The invention provides for an oligonucleotide of formula:

$T_sA_s{}^{m}C_sT_st_st_sa_sa_st_sa_sg_sc_sT_s{}^{m}C_sA_sA$ (SEQ ID NO 86,1)

wherein capital letters represent beta-D-oxy LNA nucleosides, lower case letters are DNA nucleosides, subscript s represents a phosphorothioate internucleoside linkage, and ^{m}C represent 5 methyl cytosine beta-D-oxy LNA nucleosides, and ^{m}c represents 5 methyl cytosine DNA nucleosides.

The invention provides for the oligonucleotides provided in the examples.

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

The invention provides for a pharmaceutically acceptable salt of the oligonucleotide or conjugate of the invention.

In a further aspect, the invention 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 invention in an effective amount to said cell.
In a further aspect the invention 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 invention, or conjugate thereof, to a subject suffering from or susceptible to the disease, disorder or dysfunction.

In a further aspect the oligonucleotide or composition of the invention is used for the treatment or prevention of macular degeneration, and other disorders where HTRA1 is implicated.

The invention provides for the oligonucleotide or conjugate of the invention, 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.

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

The invention provides for the use of the oligonucleotide, conjugate or composition of the invention, 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.

The invention provides for the use of the oligonucleotide, conjugate or composition of the invention, 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 invention 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 invention to the subject.

The invention 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 invention to the subject.

The invention 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 AMD) or diabetic retinopathy, said method comprising administering at least two dosages of the oligonucleotide of the invention, 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 (*i.e.* a dosage interval is ≥ 4 weeks), or at least monthly (*i.e.* a dosage interval is ≥ 1 month).

BRIEF DESCRIPTION OF FIGURES

Figure 1. A library of n=231 HTRA1 LNA oligonucleotides were screened in U251 cell lines at 5 µM. The residual HTRA1 mRNA expression level was measured by qPCR and is shown as % of

control (PBS-treated cells). n=10 oligos located between position 53113 – 53384 were relatively active.

Figure 2. A library of n=210 HTRA1 LNA oligonucleotides were screened in U251 cell lines at 5 μM. The residual HTRA1 mRNA expression level was measured by qPCR and is shown as % of control (PBS-treated cells). n=33 oligos located between position 53113 – 53384 were relatively active.

Figure 3. A library of n=305 HTRA1 LNA oligonucleotides were screened in U251 and ARPE19 cell lines at 5 and 25 μM, respectively. The residual HTRA1 mRNA expression level was measured by qPCR and is shown as % of control (PBS-treated cells). n=95 oligos located between position 53113 – 53384 were relatively active in comparison to the rest.

Figure 4. Dose response of HTRA1 mRNA level upon treatment of human primary RPE cells with LNA oligonucleotides, , 10 days of treatment. Scrambled is a control oligo with a scrambled sequence not related to the Htra1 target sequence.

Figure 5. NHP PK/PD study, IVT administration, 25μg/eye. A) HTRA1 mRNA level measured in the retina by qPCR. B) oligo content in the retina measured by oligo ELISA. C) HTRA1 mRNA level illustrated by ISH. D-E) Quantification of HTRA1 protein level in retina and vitreous, respectively, by IP-MS. Dots show data for individual animals. Error bars show standard errors for technical replicates (n=3). F-G) Reduction in HTRA1 protein level in retina and vitreous, respectively illustrated by western blot.

Figure 6. A Compound of the invention (Compound ID NO 67,1). The compound may be in the form of a pharmaceutical salt, such as a sodium salt or a potassium salt.

Figure 7. A Compound of the invention (Compound ID NO 86,1). The compound may be in the form of a pharmaceutical salt, such as a sodium salt or a potassium salt.

Figure 8. A Compound of the invention (Compound ID NO73,1). The compound may be in the form of a pharmaceutical salt, such as a sodium salt or a potassium salt.

Figure 9. An example of a pharmaceutical salt of compound 67,1: M+ is a suitable cation, typically a positive metal ion, such as a sodium or potassium ion. The stoichiometric ratio of the cation to the oligonucleotide anion will depend on the charge of the cation used. Suitably, cations with one, two or three positive charge (M^+, M^{++}, or M^{+++}, may be used). For illustrative purpose, twice as many single + charged cations (monovalent), such as Na^+ or K^+ are needed as compared to a divalent cation such as Ca^{2+}.

Figure 10. An example of a pharmaceutical salt of compound 86,1: See the figure legend for figure 9 for the description of the cation M^+.

Figure 11. An example of a pharmaceutical salt of compound73,1: See the figure legend for figure 9 for the description of the cation M^+.

Figure 12A. Compounds #15,3 and #17 were administered intravitreally in cynomolgus monkeys, and aqueous humor samples were collected at days 3, 8, 15, and 22 post-injection. Proteins from undiluted samples were analyzed by capillary electrophoresis using a Peggy Sue device (Protein Simple). HTRA1 was detected using a custom-made polycolonal rabbit antiserum. Data from animals #J60154 (Vehicle), J60158 (C. Id#15,3), J60162 (C. Id#17) are presented.

Figure 12B. Signal intensities were quantified by comparison to purified recombinant (S328A mutant) HTRA1 protein (Origene, #TP700208). The calibration curve is shown here.

Figure 12C. Top panel: Calculated HTRA1 aqueous humor concentration from individual animal was plotted against time post injection. Bottom panel: average HTRA1 concentration for the vehicle group at each time point was determined and corresponding relative concentration in treated animals calculated. Open circle: individual value, closed circle: group average. % HTRA1 reduction for day 22 is indicated.

Figure 13. HTRA1 mRNA plotted against HTRA1 protein levels in aqueous humor (blue diamonds) or in retina (red squares) in cynomolgus monkeys treated with various LNA molecules targeting the HTRA1 transcript. Values are expressed as percentage normalized to PBS controls.

Figure 14. Correlation of HTRA1 protein in aqueous humor with (A) HTRA1 protein in retina and (B) HTRA1 mRNA in retina in cynomolgus monkeys treated with various LNA molecules targeting the HTRA1 transcript. Values are expressed as percentage normalized to PBS controls.

DEFINITIONS

Oligonucleotide

The term “oligonucleotide” as used herein is defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such covalently bound nucleosides may also be referred to as nucleic acid molecules or oligomers. Oligonucleotides are commonly made in the laboratory by solid-phase chemical synthesis followed by purification. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide of the invention is man-made, and is chemically synthesized, and is typically purified or isolated. The oligonucleotide of the invention may comprise one or more modified nucleosides or nucleotides.

Antisense oligonucleotides

The term “Antisense oligonucleotide” as used herein is defined as oligonucleotides capable of modulating expression of a target gene by hybridizing to a target nucleic acid, in particular to a contiguous sequence on a target nucleic acid. The antisense oligonucleotides are not essentially double stranded and are therefore not siRNAs. Preferably, the antisense oligonucleotides of the present invention are single stranded.

Contiguous Nucleotide Region

The term “contiguous nucleotide region” refers to the region of the oligonucleotide which is complementary to the target nucleic acid. The term may be used interchangeably herein with the term “contiguous nucleotide sequence” or “contiguous nucleobase sequence” and the term “oligonucleotide motif sequence”. In some embodiments all the nucleotides of the oligonucleotide are present in the contiguous nucleotide region. In some embodiments the oligonucleotide comprises the contiguous nucleotide region and may, optionally comprise further nucleotide(s), for example a nucleotide linker region which may be used to attach a functional group to the contiguous nucleotide sequence. The nucleotide linker region may or may not be complementary to the target nucleic acid. In some embodiments the internucleoside linkages present between the nucleotides of the contiguous nucleotide region are all phosphorothioate internucleoside linkages. In some embodiments, the contiguous nucleotide region comprises one or more sugar modified nucleosides.

Nucleotides

Nucleotides are the building blocks of oligonucleotides and polynucleotides, and for the purposes of the present invention include both naturally occurring and non-naturally occurring nucleotides. In nature, nucleotides, such as DNA and RNA nucleotides comprise a ribose sugar moiety, a nucleobase moiety and one or more phosphate groups (which is absent in nucleosides). Nucleosides and nucleotides may also interchangeably be referred to as “units” or “monomers”.

Modified nucleoside

The term “modified nucleoside” or “nucleoside modification” as used herein refers to nucleosides modified as compared to the equivalent DNA or RNA nucleoside by the introduction of one or more modifications of the sugar moiety or the (nucleo)base moiety. In a preferred embodiment the modified nucleoside comprise a modified sugar moiety. The term modified nucleoside may also be used herein interchangeably with the term “nucleoside analogue” or modified “units” or modified “monomers”.

Modified internucleoside linkage

The term “modified internucleoside linkage” is defined as generally understood by the skilled person as linkages other than phosphodiester (PO) linkages, that covalently couples two nucleosides together. Nucleotides with modified internucleoside linkage are also termed “modified nucleotides”. In some embodiments, the modified internucleoside linkage increases the nuclease resistance of the oligonucleotide compared to a phosphodiester linkage. For naturally occurring oligonucleotides, the internucleoside linkage includes phosphate groups creating a phosphodiester bond between adjacent nucleosides. Modified internucleoside linkages are particularly useful in stabilizing oligonucleotides for in vivo use, and may serve to protect against nuclease cleavage at regions of DNA or RNA nucleosides in the oligonucleotide of the invention, for example within the gap region of a gapmer oligonucleotide, as well as in regions of modified nucleosides.

In an embodiment, the oligonucleotide comprises one or more internucleoside linkages modified from the natural phosphodiester to a linkage that is for example more resistant to nuclease attack. Nuclease resistance may be determined by incubating the oligonucleotide in blood serum or by using a nuclease resistance assay (e.g. snake venom phosphodiesterase (SVPD)), both are well known in the art. Internucleoside linkages which are capable of enhancing the nuclease resistance of an oligonucleotide are referred to as nuclease resistant internucleoside linkages. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are modified. It will be recognized that, in some embodiments the nucleosides which link the oligonucleotide of the invention to a non-nucleotide functional group, such as a conjugate, may be phosphodiester. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages.

In some embodiments the modified internucleoside linkages may be phosphorothioate internucleoside linkages. In some embodiments, the modified internucleoside linkages are compatible with the RNaseH recruitment of the oligonucleotide of the invention, for example phosphorothioate.

In some embodiments the internucleoside linkage comprises sulphur (S), such as a phosphorothioate internucleoside linkage.

A phosphorothioate internucleoside linkage is particularly useful due to nuclease resistance, beneficial pharmakokinetics and ease of manufacture. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate.

Nucleobase

The term nucleobase includes the purine (e.g. adenine and guanine) and pyrimidine (e.g. uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present invention the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In this context “nucleobase” refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymidine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1.

In a some embodiments the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobased selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiozolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil 5-thiazolo-uracil, 2-thio-uracil, 2'thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine and 2-chloro-6-aminopurine.

The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, e.g. A, T, G, C or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the nucleobase moieties are selected from A, T, G, C, and 5-methyl cytosine. Optionally, for LNA gapmers, 5-methyl cytosine LNA nucleosides may be used. In some embodiments, the cytosine nucleobases in a 5'cg3' motif is 5-methyl cytosine.

Modified oligonucleotide

The term modified oligonucleotide describes an oligonucleotide comprising one or more sugar-modified nucleosides and/or modified internucleoside linkages. The term chimeric" oligonucleotide is a term that has been used in the literature to describe oligonucleotides with modified nucleosides.

Complementarity

The term complementarity describes the capacity for Watson-Crick base-pairing of nucleosides/nucleotides. Watson-Crick base pairs are guanine (G)-cytosine (C) and adenine (A) - thymine (T)/uracil (U). It will be understood that oligonucleotides may comprise nucleosides with modified nucleobases, for example 5-methyl cytosine is often used in place of cytosine, and as such the term complementarity encompasses Watson Crick base-paring between non-modified and modified nucleobases (see for example Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1).

The term "% complementary" as used herein, refers to the number of nucleotides in percent of a contiguous nucleotide region or sequence in a nucleic acid molecule (e.g. oligonucleotide) which, at a given position, are complementary to (*i.e.* form Watson Crick base pairs with) a contiguous nucleotide sequence, at a given position of a separate nucleic acid molecule (e.g. the target nucleic acid). The percentage is calculated by counting the number of aligned bases that form pairs between the two sequences, dividing by the total number of nucleotides in the oligonucleotide and multiplying by 100. In such a comparison a nucleobase/nucleotide which does not align (form a base pair) is termed a mismatch.

It will be understood that when referring to complementarity between two sequences, the determination of complementarity is measured across the length of the shorter of the two sequences, such as the length of the contiguous nucleotide region or sequence.

The term "fully complementary", refers to 100% complementarity. In the absence of a % term value or indication of a mismatch, complementary means fully complementary.

Identity

The term "Identity" as used herein, refers to the number of nucleotides in percent of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which, at a given position, are identical to (*i.e.* in their ability to form Watson Crick base pairs with the complementary nucleoside) a contiguous nucleotide sequence, at a given position of a separate nucleic acid molecule (e.g. the target nucleic acid). The percentage is calculated by counting the number of aligned bases that are identical between the two sequences, including gaps, dividing by the total number of nucleotides in the oligonucleotide and multiplying by 100. Percent Identity = (Matches x 100)/Length of aligned region (with gaps).

When determining the identity of the contiguous nucleotide region of an oligonucleotide, the identity is calculated across the length of the contiguous nucleotide region. In embodiments where the entire contiguous nucleotide sequence of the oligonucleotide is the contiguous nucleotide region, identity is therefore calculated across the length of the nucleotide sequence of the oligonucleotide. In this respect the contiguous nucleotide region may be identical to a region of the reference nucleic acid sequence, or in some embodiments may be identical to the entire reference nucleic acid. Unless otherwise indicated a sequence which has 100% identity to a reference sequence is referred to as being identical.

For example, the reference sequence may be selected from the group consisting of any one of SEQ ID NOs 5 – 111.

However, if the oligonucleotide comprises additional nucleotide(s) flanking the contiguous nucleotide region, for example region D' or D'', these additional flanking nucleotides may be disregarded when determining identity. In some embodiments, identity may be calculated across the entire oligonucleotide sequence.

In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 10 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.

In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 12 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.
In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 13 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.
In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 14 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.
In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 15 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.
In some embodiments, the antisense oligonucleotide oligonucleotide of the invention comprises a contiguous nucleotide region of at least 16 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.

In some embodiments, the contiguous nucleotide region consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of a sequence selected form the group consisting of SEQ ID NO 113 – 118, or SEQ ID NO 5 – 111.. . In some embodiments, the entire contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO
In some embodiments, the contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO 119.
In some embodiments, the contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO 120.
In some embodiments, the contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO 121.

In some embodiments, the contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO 122.

In some embodiments, the contiguous sequence of the oligonucleotide consists or comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides of SEQ ID NO 123.

The invention provides an antisense oligonucleotide which comprises a contiguous nucleotide region of at least 10, or at least 12, or at least 13, or at least 14 or at least 15 or at least 16 or at least 17 or at least 18 contiguous nucleotides present SEQ ID NO 118: 5' CTTCTTCTATCTACGCATTG 3'.

In some embodiments, the contiguous nucleotide region comprises 10, 11, 12, 13, 14, 15 or 16 contiguous nucleotides which are identical to SEQ ID NO 67.

In some embodiments, the contiguous nucleotide region comprises 10, 11, 12, 13, 14, 15, 16, 17 or 18 contiguous nucleotides which are identical to SEQ ID NO 73.

In some embodiments, the contiguous nucleotide region comprises 10, 11, 12, 13, 14, 15 or 16 contiguous nucleotides which are identical to SEQ ID NO 86.

The invention provides for an antisense oligonucleotide 11 – 30 nucleotides in length, such as 12 – 20 nucleotides in length, wherein the oligonucleotide comprises a contiguous nucleotide sequence identical to a sequence selected from the group consisting of SEQ ID NO 5 – 111.

The invention provides for an antisense oligonucleotide comprising or consisting of a contiguous nucleotide sequence, wherein the contiguous nucleotide sequence is identical to a reference sequence selected from the group consisting of SEQ ID NO 5 – 111 across at least 10 contiguous nucleotide of the reference sequence.

The invention provides for an antisense oligonucleotide comprising or consisting of a contiguous nucleotide sequence, wherein the contiguous nucleotide sequence is identical to a reference sequence selected from the group consisting of SEQ ID NO 5 – 111 across at least 12 contiguous nucleotide of the reference sequence.

The invention provides for an antisense oligonucleotide comprising or consisting of a contiguous nucleotide sequence, wherein the contiguous nucleotide sequence is identical to a reference sequence selected from the group consisting of SEQ ID NO 5 – 111 across at least 14 contiguous nucleotide of the reference sequence.

The invention provides for an antisense oligonucleotide comprising or consisting of a contiguous nucleotide sequence, wherein the contiguous nucleotide sequence is identical to a reference sequence selected from the group consisting of SEQ ID NO 5 – 111 across the length of the reference sequence.

Hybridization

The term “hybridizing” or “hybridizes” as used herein is to be understood as two nucleic acid strands (e.g. an oligonucleotide and a target nucleic acid) forming hydrogen bonds between base pairs on opposite strands thereby forming a duplex. The affinity of the binding between two nucleic acid strands is the strength of the hybridization. It is often described in terms of the melting temperature (T_m) defined as the temperature at which half of the oligonucleotides are duplexed with the target nucleic acid. At physiological conditions T_m is not strictly proportional to the affinity (Mergny and Lacroix, 2003,*Oligonucleotides* 13:515–537). The standard state Gibbs free energy ΔG° is a more accurate representation of binding affinity and is related to the dissociation constant (K_d) of the reaction by $\Delta G° = -RT\ln(K_d)$, where R is the gas constant and T is the absolute temperature. Therefore, a very low ΔG° of the reaction between an oligonucleotide and the target nucleic acid reflects a strong hybridization between the oligonucleotide and target nucleic acid. ΔG° is the energy associated with a reaction where aqueous concentrations are 1M, the pH is 7, and the temperature is 37°C. The hybridization of oligonucleotides to a target nucleic acid is a spontaneous reaction and for spontaneous reactions ΔG° is less than zero. ΔG° can be measured experimentally, for example, by use of the isothermal titration calorimetry (ITC) method as described in Hansen et al., 1965,*Chem. Comm.* 36–38 and Holdgate et al., 2005, *Drug Discov Today*. The skilled person will know that commercial equipment is available for ΔG° measurements. ΔG° can also be estimated numerically by using the nearest neighbor model as described by SantaLucia, 1998, *Proc Natl Acad Sci USA.* 95: 1460–1465 using appropriately derived thermodynamic parameters described by Sugimoto et al., 1995, *Biochemistry* 34:11211–11216 and McTigue et al., 2004, *Biochemistry* 43:5388–5405. In order to have the possibility of modulating its intended nucleic acid target by hybridization, oligonucleotides of the present invention hybridize to a target nucleic acid with estimated ΔG° values below -10 kcal for oligonucleotides that are 10-30 nucleotides in length. In some embodiments the degree or strength of hybridization is measured by the standard state Gibbs free energy ΔG°. The oligonucleotides may hybridize to a target nucleic acid with estimated ΔG° values below the range of -10 kcal, such as below -15 kcal, such as below -20 kcal and such as below -25 kcal for oligonucleotides that are 8-30 nucleotides in length. In some embodiments the oligonucleotides hybridize to a target nucleic acid with an estimated ΔG° value of -10 to -60 kcal, such as -12 to -40, such as from -15 to -30 kcal or-16 to -27 kcal such as -18 to -25 kcal.

Target Sequence

The oligonucleotide comprises a contiguous nucleotide region which is complementary to or hybridizes to a sub-sequence of the target nucleic acid molecule. The term “target sequence” as used herein refers to a sequence of nucleotides present in the target nucleic acid which comprises the nucleobase sequence which is complementary to the contiguous nucleotide region or sequence of the oligonucleotide of the invention. In some embodiments, the target sequence consists of a region on the target nucleic acid which is complementary to the contiguous nucleotide region or sequence of the oligonucleotide of the invention. In some embodiments the target sequence is longer than the complementary sequence of a single oligonucleotide, and may, for example represent a preferred region of the target nucleic acid which may be targeted by several oligonucleotides of the invention.

The oligonucleotide of the invention comprises a contiguous nucleotide region which is complementary to the target nucleic acid, such as a target sequence.

The oligonucleotide comprises a contiguous nucleotide region of at least 10 nucleotides which is complementary to or hybridizes to a target sequence present in the target nucleic acid molecule. The contiguous nucleotide region (and therefore the target sequence) comprises of at least 10 contiguous nucleotides, such as 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, contiguous nucleotides, such as from 12-22, such as from 14-18 contiguous nucleotides.

In some embodiments the target sequence is present within a sequence selected from the group consisting of SEQ ID NO 113, 114, 115, 116, 117 and 118.

Target Cell

The term a target cell as used herein refers to a cell which is expressing the target nucleic acid. In some embodiments the target cell may be *in vivo* or *in vitro*. In some embodiments the target cell is a mammalian cell such as a primate cell such as a monkey cell or a human cell. In some embodiments the target cell may be a retinal cell, such as a retinal pigment epithelium (PRE) cell. In some embodiments the cell is selected from the group consisting of RPE cells, Bipolar Cell, Amacrine cells, Endothelial cells, Ganglion cells and Microglia cells. For *in vitro* assessment, the target cell may be a primary cell or an established cell line, such as U251, ARPE19...

Target nucleic acid

According to the present invention, the target nucleic acid is a nucleic acid which encodes mammalian HTRA1 and may for example be a gene, a RNA, a mRNA, and pre-mRNA, a mature mRNA or a cDNA sequence. The target may therefore be referred to as an HTRA1 target nucleic acid.

Suitably, the target nucleic acid encodes an HTRA1 protein, in particular mammalian HTRA1, such as human HTRA1 (See for example tables 1 & 2 which provides the mRNA and pre-mRNA sequences for human and rat HTRA1).

In some embodiments, the target nucleic acid is selected from the group consisting of SEQ ID NO: 1, 2, 3, and 4, or naturally occurring variants thereof (e.g. sequences encoding a mammalian HTRA1 protein.

A target cell is a cell which is expressing the HTRA1 target nucleic acid. In preferred embodiments the target nucleic acid is the HTRA1 mRNA, such as the HTRA1 pre-mRNA or HTRA1 mature mRNA. The poly A tail of HTRA1 mRNA is typically disregarded for antisense oligonucleotide targeting.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

The target sequence may be a sub-sequence of the target nucleic acid. In some embodiments the oligonucleotide or contiguous nucleotide region is fully complementary to, or only comprises one or two mismatches to an HTRA1 sub-sequence, such as a sequence selected from the group consisting of SEQ ID NO 113, 114, 115, 116, 117 or 231.

The target sequence may be a sub-sequence of the target nucleic acid. In some embodiments the oligonucleotide or contiguous nucleotide region is fully complementary to, or only comprises one or two mismatches to an HTRA1 sub-sequence, such as a sequence selected from the group consisting of SEQ ID NO 124 – 230. In some embodiments the oligonucleotide or contiguous nucleotide region is fully complementary to, or only comprises one or two mismatches to an HTRA1 sub-sequence SEQ ID NO 231.

Complementarity to the target or sub-sequence thereof is measured over the length of the oligonucleotide, or contiguous nucleotide region thereof.

For *in vivo* or *in vitro* application, the oligonucleotide of the invention is typically capable of inhibiting the expression of the HTRA1 target nucleic acid in a cell which is expressing the HTRA1 target nucleic acid. The contiguous sequence of nucleobases of the oligonucleotide of the invention is typically complementary to the HTRA1 target nucleic acid, as measured across the length of the oligonucleotide, optionally with the exception of one or two mismatches, and optionally excluding nucleotide based linker regions which may link the oligonucleotide to an optional functional group such as a conjugate, or other non-complementary terminal nucleotides (e.g. region D). The target nucleic acid may, in some embodiments, be a RNA or DNA, such as a messenger RNA, such as a mature mRNA or a pre-mRNA. In some embodiments the target nucleic acid is a RNA or DNA which encodes mammalian HTRA1 protein, such as human HTRA1, e.g. the human HTRA1 mRNA sequence, such as that disclosed as SEQ ID NO 1 (NM_002775.4, GI:190014575). Further information on exemplary target nucleic acids is provided in tables 1 & 2.

Table 1. Genome and assembly information for human and Cyno HTRA1.

Species	**Chr.**	**Strand**	**Genomic coordinates** **Start**	**End**	**Assembly**	**NCBI reference sequence* accession number for mRNA**
Human	10	fwd	122461525	122514908	GRCh38.p2 release 107	NM_002775.4

Cyno	9	fwd	121764994	121817518	Macaca_fascicularis_5.0	NC_022280.1**

Fwd = forward strand. The genome coordinates provide the pre-mRNA sequence (genomic sequence). The NCBI reference provides the mRNA sequence (cDNA sequence).

*The National Center for Biotechnology Information reference sequence database is a comprehensive, integrated, non-redundant, well-annotated set of reference sequences including genomic, transcript, and protein. It is hosted at www.ncbi.nlm.nih.gov/refseq.

**In the NCBI reference sequence there is a stretch of 100 nucleotides from position 126 to position 227 whose identity is not known. In SEQ ID NO 3 & 4, this stretch has been replaced by the nucleotides appearing in both human and *Macaca mulatta* HTRA1 premRNA sequences in this region.

Table 2. Sequence details for human and Cyno HTRA1.

Species	RNA type	Length (nt)	SEQ ID NO
Human	mRNA	2138	1
Human	premRNA	53384	2
Cyno	mRNA	2123	3
Cyno	premRNA	52575	4

Naturally occurring variant

The term “naturally occurring variant” refers to variants of HTRA1 gene or transcripts which originate from the same genetic loci as the target nucleic acid, but may differ for example, by virtue of degeneracy of the genetic code causing a multiplicity of codons encoding the same amino acid, or due to alternative splicing of pre-mRNA, or the presence of polymorphisms, such as single nucleotide polymorphisms, and allelic variants. Based on the presence of the sufficient complementary sequence to the oligonucleotide, the oligonucleotide of the invention may therefore target the target nucleic acid and naturally occurring variants thereof. In some embodiments, the naturally occurring variants have at least 95% such as at least 98% or at least 99% homology to a mammalian HTRA1 target nucleic acid, such as a target nucleic acid selected form the group consisting of SEQ ID NO 1, 2, 3, or 4.

Modulation of expression

The term “modulation of expression” as used herein is to be understood as an overall term for an oligonucleotide’s ability to alter the amount of HTRA1 when compared to the amount of HTRA1 before administration of the oligonucleotide. Alternatively modulation of expression may be determined by reference to a control experiment where the oligonucleotide of the invention is not administered. One type of modulation is an oligonucleotide’s ability to inhibit, down-regulate, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of HTRA1, e.g. by degradation of mRNA or blockage of transcription. The antisense oligonucleotide of the invention are capable of inhibiting, down-regulating, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of HTRA1.

High affinity modified nucleosides

A high affinity modified nucleoside is a modified nucleotide which, when incorporated into the oligonucleotide enhances the affinity of the oligonucleotide for its complementary target, for example as measured by the melting temperature (T^m). A high affinity modified nucleoside of the present invention preferably result in an increase in melting temperature between +0.5 to +12°C, more preferably between +1.5 to +10°C and most preferably between+3 to +8°C per modified nucleoside. Numerous high affinity modified nucleosides are known in the art and include for example, many 2' substituted nucleosides as well as locked nucleic acids (LNA) (see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213).

Sugar modifications

The oligomer of the invention may comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA.

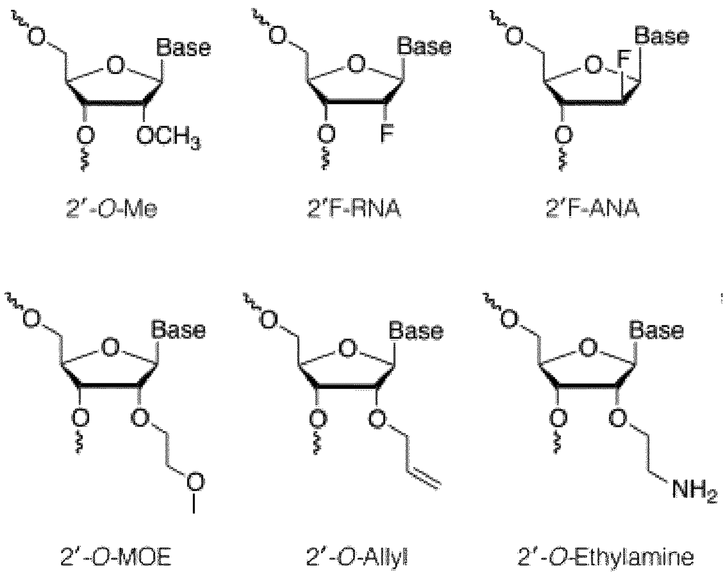
Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (e.g. UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions. Nucleosides with modified sugar moieties also include 2' modified nucleosides, such as 2' substituted nucleosides. Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides, such as enhanced nucleoside resistance and enhanced affinity.

2' modified nucleosides.

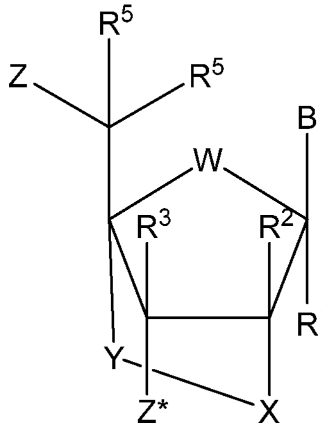
A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or –OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradicle, and includes 2' substituted nucleosides and LNA (2' – 4' biradicle bridged) nucleosides. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide. Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213, and Deleavey and Damha, Chemistry and Biology 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.



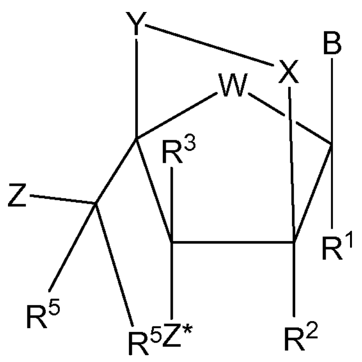
Locked Nucleic Acid Nucleosides (LNA).

LNA nucleosides are modified nucleosides which comprise a linker group (referred to as a biradicle or a bridge) between C2' and C4' of the ribose sugar ring of a nucleotide. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature.

In some embodiments, the modified nucleoside or the LNA nucleosides of the oligomer of the invention has a general structure of the formula I or II:



or



beta-D alpha-L

Formula I Formula II

wherein W is selected from -O-, -S-, -N(R^a)-, -C(R^{a}R^b)-, such as, in some embodiments –O-;
B designates a nucleobase moiety;
Z designates an internucleoside linkage to an adjacent nucleoside, or a 5'-terminal group;
Z* designates an internucleoside linkage to an adjacent nucleoside, or a 3'-terminal group;
X designates a group selected from the list consisting of -C(R^{a}R^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO$_2$-, -N(R^a)-, and >C=Z

In some embodiments, X is selected from the group consisting of: –O-, -S-, NH-, NR^{a}R^b, -CH$_2$-, CR^{a}R^b, -C(=CH$_2$)-, and -C(=CR^{a}R^b)-

In some embodiments, X is -O-

Y designates a group selected from the group consisting of -C(R^{a}R^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO$_2$-, -N(R^a)-, and >C=Z

In some embodiments, Y is selected from the group consisting of: –CH$_2$-, -C(R^{a}R^b)-, –CH$_2$CH$_2$-, -C(R^{a}R^b)-C(R^{a}R^b)-, –CH$_2$CH$_2$CH$_2$-, -C(R^{a}R^b)C(R^{a}R^b)C(R^{a}R^b)-, -C(R^a)=C(R^b)-, and -C(R^a)=N-

In some embodiments, Y is selected from the group consisting of: -CH$_2$-, -CHR^a-, -CHCH$_3$-, CR^{a}R^b-

or -X-Y- together designate a bivalent linker group (also referred to as a radicle) together designate a bivalent linker group consisting of 1, 2, or 3 groups/atoms selected from the group consisting of -C(R^{a}R^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO$_2$-, -N(R^a)-, and >C=Z,

In some embodiments, -X-Y- designates a biradicle selected from the groups consisting of: -X-CH$_2$-, -X-CR^{a}R^b-, -X-CHR^{a-}, -X-C(HCH$_3$)$^-$, -O-Y-, -O-CH$_2$-, -S-CH$_2$-, -NH-CH$_2$-, -O-CHCH$_3$-, -CH$_2$-

O-CH_2, -O-CH(CH_3CH_3)-, -O-CH_2-CH_2-, OCH_2-CH_2-CH_2-,-O-CH_2OCH_2-, -O-NCH_2-, -C(=CH_2)-CH_2-, -NR^a-CH_2-, N-O-CH_2, -S-C$R^a$$R^b$- and -S-CH$R^a$-.

In some embodiments –X-Y- designates –O-CH_2- or –O-CH(CH_3)-.

wherein Z is selected from -O-, -S-, and -N(R^a)-,

and R^a and, when present R^b, each is independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{2-6}-alkynyl, hydroxy, optionally substituted C_{1-6}-alkoxy, C_{2-6}-alkoxyalkyl, C_{2-6}-alkenyloxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy-carbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy-carbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)-amino-carbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkyl-carbonylamino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, azido, sulphanyl, C_{1-6}-alkylthio, halogen, where aryl and heteroaryl may be optionally substituted and where two geminal substituents R^a and R^b together may designate optionally substituted methylene (=CH_2), wherein for all chiral centers, asymmetric groups may be found in either *R* or *S* orientation.

wherein R^1, R^2, R^3, R^5 and R^{5*} are independently selected from the group consisting of: hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted C_{2-6}-alkynyl, hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkoxyalkyl, C_{2-6}-alkenyloxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy-carbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxy-carbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)-amino-carbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkyl-carbonylamino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, azido, sulphanyl, C_{1-6}-alkylthio, halogen, where aryl and heteroaryl may be optionally substituted, and where two geminal substituents together may designate oxo, thioxo, imino, or optionally substituted methylene.

In some embodiments R^1, R^2, R^3, R^5 and R^{5*} are independently selected from C_{1-6} alkyl, such as methyl, and hydrogen.

In some embodiments R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen.

In some embodiments R^1, R^2, R^3, are all hydrogen, and either R^5 and R^{5*} is also hydrogen and the other of R^5 and $R^{5*}$is other than hydrogen, such as C_{1-6} alkyl such as methyl.

In some embodiments, R^a is either hydrogen or methyl. In some embodiments, when present, R^b is either hydrogen or methyl.

In some embodiments, one or both of R^a and R^b is hydrogen

In some embodiments, one of R^a and R^b is hydrogen and the other is other than hydrogen

In some embodiments, one of R^a and R^b is methyl and the other is hydrogen

In some embodiments, both of R^a and R^b are methyl.

In some embodiments, the biradicle –X-Y- is $–O-CH_2-$, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such LNA nucleosides are disclosed in WO99/014226, WO00/66604, WO98/039352 and WO2004/046160 which are all hereby incorporated by reference, and include what are commonly known as beta-D-oxy LNA and alpha-L-oxy LNA nucleosides.

In some embodiments, the biradicle –X-Y- is $–S-CH_2-$, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such thio LNA nucleosides are disclosed in WO99/014226 and WO2004/046160 which are hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- is $–NH-CH_2-$, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such amino LNA nucleosides are disclosed in WO99/014226 and WO2004/046160 which are hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- is $–O-CH_2-CH_2-$ or $–O-CH_2-CH_2-CH_2-$, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such LNA nucleosides are disclosed in WO00/047599 and Morita et al, Bioorganic & Med.Chem. Lett. 12 73-76, which are hereby incorporated by reference, and include what are commonly known as 2'-O-4'C-ethylene bridged nucleic acids (ENA).

In some embodiments, the biradicle –X-Y- is $–O-CH_2-$, W is O, and all of R^1, R^2, R^3, and one of R^5 and R^{5*} are hydrogen, and the other of R^5 and R^{5*} is other than hydrogen such as C_{1-6} alkyl, such as methyl. Such 5' substituted LNA nucleosides are disclosed in WO2007/134181 which is hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- is $–O-CR^aR^b-$, wherein one or both of R^a and R^b are other than hydrogen, such as methyl, W is O, and all of R^1, R^2, R^3, and one of R^5 and R^{5*} are hydrogen, and the other of R^5 and R^{5*} is other than hydrogen such as C_{1-6} alkyl, such as methyl. Such bis modified LNA nucleosides are disclosed in WO2010/077578 which is hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- designate the bivalent linker group $–O-CH(CH_2OCH_3)-$ (2' O-methoxyethyl bicyclic nucleic acid - Seth at al., 2010, J. Org. Chem. Vol 75(5) pp. 1569-81). In some embodiments, the biradicle –X-Y- designate the bivalent linker group $–O-CH(CH_2CH_3)-$ (2'O-ethyl bicyclic nucleic acid - Seth at al., 2010, J. Org. Chem. Vol 75(5) pp. 1569-81). In some embodiments, the biradicle –X-Y- is $–O-CHR^a-$, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such 6' substituted LNA nucleosides are disclosed in WO10036698 and WO07090071 which are both hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- is –O-CH(CH_2OCH_3)-, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such LNA nucleosides are also known as cyclic MOEs in the art (cMOE) and are disclosed in WO07090071.

In some embodiments, the biradicle –X-Y- designate the bivalent linker group –O-CH(CH_3)-. – in either the R- or S- configuration. In some embodiments, the biradicle –X-Y- together designate the bivalent linker group –O-CH_2-O-CH_2- (Seth at al., 2010, J. Org. Chem). In some embodiments, the biradicle –X-Y- is –O-CH(CH_3)-, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such 6' methyl LNA nucleosides are also known as cET nucleosides in the art, and may be either (S)cET or (R)cET stereoisomers, as disclosed in WO07090071 (beta-D) and WO2010/036698 (alpha-L) which are both hereby incorporated by reference).

In some embodiments, the biradicle –X-Y- is –O-CR^aR^b-, wherein in neither R^a or R^b is hydrogen, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments, R^a and R^b are both methyl. Such 6' di-substituted LNA nucleosides are disclosed in WO 2009006478 which is hereby incorporated by reference.

In some embodiments, the biradicle –X-Y- is –S-CHR^a-, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such 6' substituted thio LNA nucleosides are disclosed in WO11156202 which is hereby incorporated by reference. In some 6' substituted thio LNA embodiments R^a is methyl.

In some embodiments, the biradicle –X-Y- is –C(=CH2)-C(R^aR^b)-, such as –C(=CH_2)-CH_2- , or –C(=CH_2)-CH(CH_3)-W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. Such vinyl carbo LNA nucleosides are disclosed in WO08154401 and WO09067647 which are both hereby incorporated by reference.

In some embodiments the biradicle –X-Y- is –N(-OR^a)-, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments R^a is C_{1-6} alkyl such as methyl. Such LNA nucleosides are also known as N substituted LNAs and are disclosed in WO2008/150729 which is hereby incorporated by reference. In some embodiments, the biradicle –X-Y- together designate the bivalent linker group –O-NR^a-CH_3- (Seth at al., 2010, J. Org. Chem). In some embodiments the biradicle –X-Y- is –N(R^a)-, W is O, and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments R^a is C_{1-6} alkyl such as methyl.

In some embodiments, one or both of R^5 and R^{5*} is hydrogen and, when substituted the other of R^5 and R^{5*} is C_{1-6} alkyl such as methyl. In such an embodiment, R^1, R^2, R^3, may all be hydrogen, and the biradicle –X-Y- may be selected from –O-CH2- or –O-C(HCR^a)-, such as –O-C(HCH3)-.

In some embodiments, the biradicle is –CR^aR^b-O-CR^aR^b-, such as CH_2-O-CH_2-, W is O and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments R^a is C_{1-6} alkyl such as methyl.

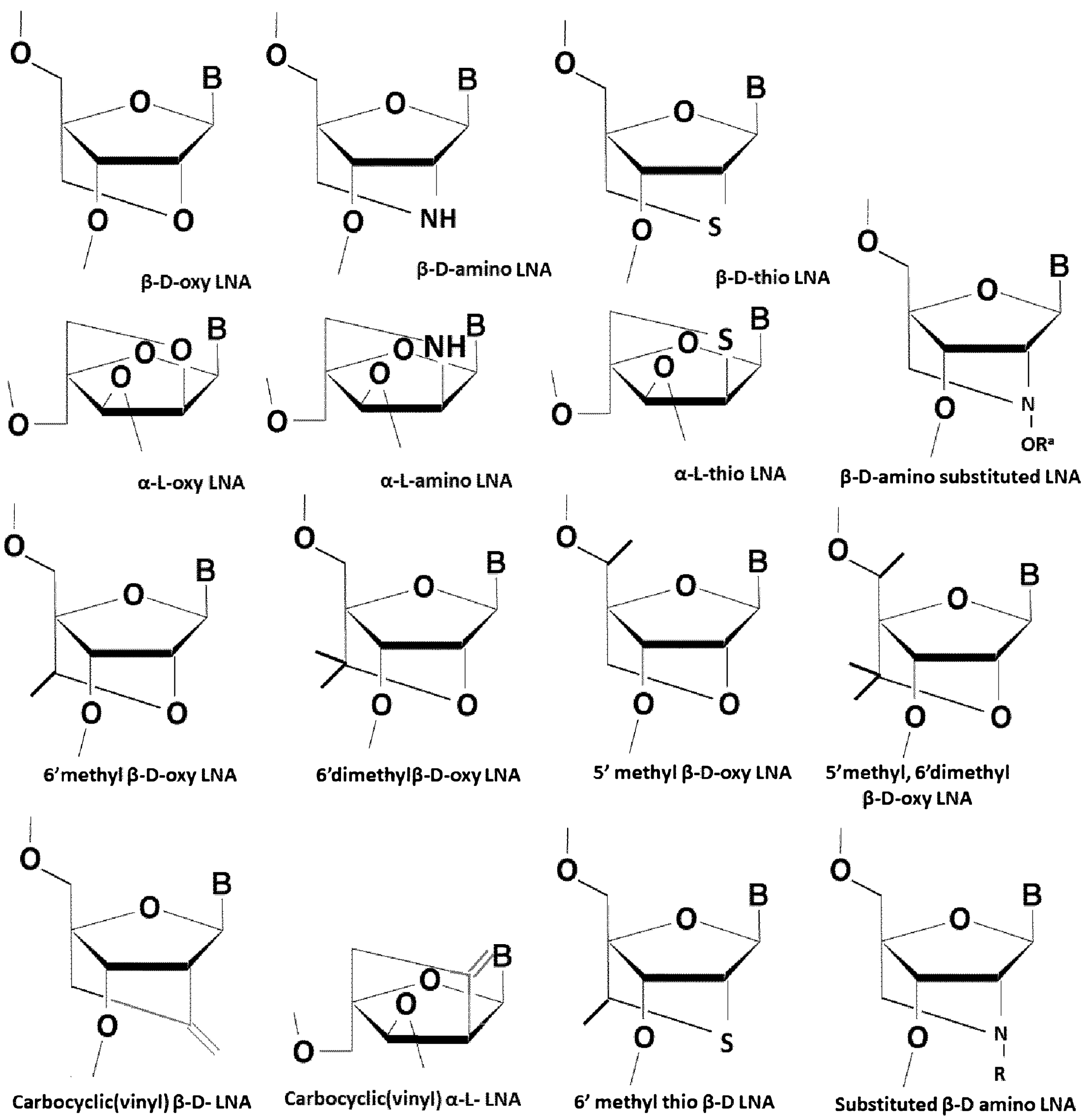
Such LNA nucleosides are also known as conformationally restricted nucleotides (CRNs) and are disclosed in WO2013036868 which is hereby incorporated by reference.

In some embodiments, the biradicle is –O-CR^aR^b-O-CR^aR^b-, such as O-CH_2-O-CH_2-, W is O and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments R^a is C_{1-6} alkyl such as methyl. Such LNA nucleosides are also known as COC nucleotides and are disclosed in Mitsuoka et al., Nucleic Acids Research 2009 37(4), 1225-1238, which is hereby incorporated by reference.

It will be recognized than, unless specified, the LNA nucleosides may be in the beta-D or alpha-L stereoisoform.

Examples of LNA nucleosides are presented in Scheme 1.

Scheme 1



As illustrated in the examples, in some embodiments of the invention the LNA nucleosides in the oligonucleotides are beta-D-oxy-LNA nucleosides.

Nuclease mediated degradation

Nuclease mediated degradation refers to an oligonucleotide capable of mediating degradation of a complementary nucleotide sequence when forming a duplex with such a sequence.

In some embodiments, the oligonucleotide may function via nuclease mediated degradation of the target nucleic acid, where the oligonucleotides of the invention are capable of recruiting a nuclease, particularly and endonuclease, preferably endoribonuclease (RNase), such as RNase H. Examples of oligonucleotide designs which operate via nuclease mediated mechanisms are oligonucleotides which typically comprise a region of at least 5 or 6 DNA nucleosides and are flanked on one side or both sides by affinity enhancing nucleosides, for example gapmers, headmers and tailmers.

RNase H Activity and Recruitment

The RNase H activity of an antisense oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH. Typically an oligonucleotide is deemed capable of recruiting RNase H if it, when provided with a complementary target nucleic acid sequence, has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613 (hereby incorporated by reference).

Gapmer

The term gapmer as used herein refers to an antisense oligonucleotide which comprises a region of RNase H recruiting oligonucleotides (gap) which is flanked 5' and 3' by regions which comprise one or more affinity enhancing modified nucleosides (flanks or wings). Various gapmer designs are described herein. Headmers and tailmers are oligonucleotides capable of recruiting RNase H where one of the flanks is missing, *i.e.* only one of the ends of the oligonucleotide comprises affinity enhancing modified nucleosides. For headmers the 3' flank is missing (i.e. the 5' flank comprises affinity enhancing modified nucleosides) and for tailmers the 5' flank is missing (i.e. the 3' flank comprises affinity enhancing modified nucleosides).

LNA Gapmer

The term LNA gapmer is a gapmer oligonucleotide wherein at least one of the affinity enhancing modified nucleosides is an LNA nucleoside. In some embodiments the LNA nucleoside(s) in an LNA gapmer are beta-D-oxy LNA nucleosides and/or 6'methyl beta-D-oxy LNA nucleosides (such as (S)cET nucleosides.

Mixed Wing Gapmer

The term mixed wing gapmer refers to a LNA gapmer wherein the flank regions comprise at least one LNA nucleoside and at least one non-LNA modified nucleoside, such as at least one DNA nucleoside or at least one 2' substituted modified nucleoside, such as, for example, 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA and 2'-F-ANA nucleoside(s). In some embodiments the mixed wing gapmer has one flank which comprises LNA nucleosides (e.g. 5' or 3') and the other flank (3' or 5' respectfully) comprises 2' substituted modified nucleoside(s). In some embodiments the LNA nucleoside(s) in an mixed wing gapmer are beta-D-oxy LNA nucleosides and/or 6'methyl beta-D-oxy LNA nucleosides (such as (S)cET nucleosides.

Conjugate

The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

In some embodiments, the non-nucleotide moiety selected from the group consisting of a protein, such as an enzyme, an antibody or an antibody fragment or a peptide; a lipophilic moiety such as a lipid, a phospholipid, a sterol; a polymer, such as polyethyleneglycol or polypropylene glycol; a receptor ligand; a small molecule; a reporter molecule; and a non-nucleosidic carbohydrate.

Linkers

A linkage or linker is a connection between two atoms that links one chemical group or segment of interest to another chemical group or segment of interest via one or more covalent bonds. Conjugate moieties can be attached to the oligonucleotide directly or through a linking moiety (e.g. linker or tether). Linkers serve to covalently connect a third region, e.g. a conjugate moiety to an oligonucleotide (e.g. the termini of region A or C).

In some embodiments of the invention the conjugate or oligonucleotide conjugate of the invention may optionally, comprise a linker region which is positioned between the oligonucleotide and the conjugate moiety. In some embodiments, the linker between the conjugate and oligonucleotide is biocleavable.

Biocleavable linkers comprising or consisting of a physiologically labile bond that is cleavable under conditions normally encountered or analogous to those encountered within a mammalian body. Conditions under which physiologically labile linkers undergo chemical transformation (e.g., cleavage) include chemical conditions such as pH, temperature, oxidative or reductive conditions or agents, and salt concentration found in or analogous to those encountered in mammalian cells. Mammalian intracellular conditions also include the presence of enzymatic activity normally present in a mammalian cell such as from proteolytic enzymes or hydrolytic enzymes or nucleases. In one embodiment the biocleavable linker is susceptible to S1 nuclease cleavage. In a preferred embodiment the nuclease susceptible linker comprises between 1 and 10 nucleosides, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 nucleosides, more preferably between 2 and 6 nucleosides and most preferably between 2 and 4 linked nucleosides comprising at least two consecutive phosphodiester linkages, such as at least 3 or 4 or 5 consecutive phosphodiester linkages. Preferably the nucleosides are DNA or RNA. Phosphodiester containing biocleavable linkers are described in more detail in WO 2014/076195 (hereby incorporated by reference), and may be referred to as region D herein.

Conjugates may also be linked to the oligonucleotide via non biocleavable linkers, or in some embodiments the conjugate may comprise a non-cleavable linker which is covalently attached to the biocleavable linker. Linkers that are not necessarily biocleavable but primarily serve to covalently connect a conjugate moiety to an oligonucleotide or biocleavable linker. Such linkers may comprise a chain structure or an oligomer of repeating units such as ethylene glycol, amino acid units or amino alkyl groups. In some embodiments the linker (region Y) is an amino alkyl, such as a $C_2 – C_{36}$ amino alkyl group, including, for example C_6 to C_{12} amino alkyl groups. In some embodiments the linker (region Y) is a C_6 amino alkyl group. Conjugate linker groups may be routinely attached to an oligonucleotide via use of an amino modified oligonucleotide, and an activated ester group on the conjugate group.

Treatment

The term 'treatment' as used herein refers to both treatment of an existing disease (*e.g.* a disease or disorder as herein referred to), or prevention of a disease, *i.e.* prophylaxis. It will therefore be recognized that treatment as referred to herein may, in some embodiments, be prophylactic.

DETAILED DESCRIPTION OF THE INVENTION

The Oligonucleotides of the Invention

The invention relates to oligonucleotides capable of inhibiting the expression of HTRA1. The modulation is may achieved by hybridizing to a target nucleic acid encoding HTRA1 or which is involved in the regulation of HTRA1. The target nucleic acid may be a mammalian HTRA 1 sequence, such as a sequence selected from the group consisting of SEQ ID 1, 2, 3 or 4.

The oligonucleotide of the invention is an antisense oligonucleotide which targets HTRA1, such as a mammalian HTRA1.

In some embodiments the antisense oligonucleotide of the invention is capable of modulating the expression of the target by inhibiting or down-regulating it. Preferably, such modulation produces an inhibition of expression of at least 20% compared to the normal expression level of the target, such as at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% inhibition compared to the normal expression level of the target. In some embodiments compounds of the invention may be capable of inhibiting expression levels of HTRA1 mRNA by at least 60% or 70% in vitro using ARPE-19 cells. In some embodiments compounds of the invention may be capable of inhibiting expression levels of *HTRA1* mRNA by at least 60% or 70% *in vitro* using ARPE-19 cells. In some embodiments compounds of the invention may be capable of inhibiting expression levels of HTRA1 protein by at least 50% in vitro using ARPE-19 cells. Suitably, the examples provide assays which may be used to measure HTRA1 RNA or protein inhibition. The target modulation is triggered by the hybridization between a contiguous nucleotide sequence of the oligonucleotide and the target nucleic acid. In some embodiments the oligonucleotide of the invention comprises mismatches between the oligonucleotide and the target nucleic acid. Despite mismatches hybridization to the target nucleic acid may still be sufficient to show a desired modulation of HTRA1 expression. Reduced binding affinity resulting from mismatches may advantageously be compensated by increased number of nucleotides in the oligonucleotide and/or an increased number of modified nucleosides capable of increasing the binding affinity to the target, such as 2' modified nucleosides, including LNA, present within the oligonucleotide sequence.

An aspect of the present invention relates to an antisense oligonucleotide which comprises a contiguous nucleotide region of 10 to 30 nucleotides in length with at least 90% complementarity to HTRA1 target sequence, such as fully complementary to an HTRA1 target sequence, e.g. a nucleic acid selected from the group consisting SEQ ID NO 1, 2, 3 & 4.

In some embodiments, the oligonucleotide comprises a contiguous sequence which is at least 90% complementary, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, or 100% complementary with a region of the target nucleic acid.

In some embodiments, the oligonucleotide of the invention, or a contiguous nucleotide sequence thereof is fully complementary (100% complementary) to a region of the target nucleic acid, or in some embodiments may comprise one or two mismatches between the oligonucleotide and the target nucleic acid.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of a sequence selected from the group consisting of SEQ ID NO 119, 120, 121, 122 or 123.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of a sequence selected from the group consisting of SEQ ID NOs 124- 230.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 186.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 192.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 205.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 13 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 186.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 13 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 192.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 13 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 205.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 14 nucleotides thereof, is fully (or 100%) complementary to a sequence selected from the group consisting of SEQ ID NO 113, 114, 115, 116, 117 and 231.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 14 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 186.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 14 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 192.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 14 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 205.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 15 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 186.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 15 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 192.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 15 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 205.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 16 nucleotides thereof, is fully (or 100%) complementary to a sequence selected from the group consisting of SEQ ID NO SEQ ID NO 113, 114, 115, 116, 117 and 231. .

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 16 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 186.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 16, such as 16, 17 or 18 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 192.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 16 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to a region of SEQ ID NO 205.

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof is fully (or 100%) complementary to a sequence selected from the group consisting of a sequence selected from the group consisting of SEQ ID NO SEQ ID NO 113, 114, 115, 116, 117 and 231.

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof is fully (or 100%) complementary to a sequence selected from the group consisting of a sequence selected from the group consisting of SEQ ID NO 124 – 230.

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof is fully (or 100%) complementary to SEQ ID NO 186.

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof is fully (or 100%) complementary to SEQ ID NO 192.

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof is fully (or 100%) complementary to SEQ ID NO 205.

It is understood that the oligonucleotide motif sequences can be modified to for example increase nuclease resistance and/or binding affinity to the target nucleic acid. Modifications are described in the definitions and in the “Oligonucleotide design” section.

In some embodiments, the oligonucleotide of the invention, or contiguous nucleotide region thereof is fully complementary (100% complementary) to a region of the target nucleic acid, or in some embodiments may comprise one or two mismatches between the oligonucleotide and the target nucleic acid. In some embodiments the oligonucleotide, or contiguous nucleotide sequence of at least 12 nucleotides thereof, is at least 90% complementary, such as fully (or 100%) complementary to the target nucleic acid sequence.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 12 nucleotides thereof, has 100% identity to a sequence selected from the group consisting of SEQ ID NOs 5 – 111.

In some embodiments the oligonucleotide, or a contiguous nucleotide sequence of at least 14 nucleotides thereof, has 100% identity to a sequence selected from the group consisting of SEQ ID NOs 5 – 111

In some embodiments the oligonucleotide, or contiguous nucleotide sequence of at least 16 nucleotides thereof, has 100% identity to a sequence selected from the group consisting of SEQ ID NOs 5 – 111

In some embodiments the oligonucleotide, or contiguous nucleotide region thereof, comprises or consists of a sequence selected from SEQ ID NOs 5 – 111.

In some embodiments the oligonucleotide of the invention is selected from the following group (Note the target subsequence is the reverse complement of the oligonucleotide motif):

SEQ ID NO	Motif	Compound Design	Target subsequence SEQ ID	Target subsequence
5	agttaaaggaggagacaaat	AGTTaaaggaggagacAAAT	124	atttgtctcctcctttaact
6	tcagttaaaggaggagacaa	TCAgttaaaggaggagaCAA	125	ttgtctcctcctttaactga
7	ctcagttaaaggaggagaca	CTCagttaaaggaggagaCA	126	tgtctcctcctttaactgag
8	ctcagttaaaggaggagac	CTCagttaaaggaggaGAC	127	gtctcctcctttaactgag
9	actcagttaaaggaggagac	ACTCagttaaaggaggagAC	128	gtctcctcctttaactgagt
10	actcagttaaaggaggaga	ACTCagttaaaggaggaGA	129	tctcctcctttaactgagt
11	actcagttaaaggaggag	ACtcagttaaaggaGGAG	130	ctcctcctttaactgagt
12	gatgactcagttaaaggagg	GAtgactcagttaaaggAGG	131	cctcctttaactgagtcatc

13	atgatgactcagttaaagga	ATGAtgactcagttaaagGA	132	tcctttaactgagtcatcat
14	tgatgactcagttaaagg	TGAtgactcagttaAAGG	133	cctttaactgagtcatca
15	gatgatgactcagttaaagg	GAtgatgactcagttaAAGG	134	cctttaactgagtcatcatc
16	gatgatgactcagttaaag	GATGatgactcagttaAAG	135	ctttaactgagtcatcatc
17	tatcgactgcattagttgg	TATcgactgcattagttGG	136	ccaactaatgcagtcgata
18	gtatcgactgcattagttgg	GtatcgactgcattagttGG	137	ccaactaatgcagtcgatac
19	tcgactgcattagttg	TCGactgcattagTTG	138	caactaatgcagtcga
19	tcgactgcattagttg	TCGactgcattagtTG	138	caactaatgcagtcga
19	tcgactgcattagttg	TCGActgcattaGTTG	138	caactaatgcagtcga
20	tatcgactgcattagttg	TAtcgactgcattaGTTG	139	caactaatgcagtcgata
21	gtatcgactgcattagttg	GTAtcgactgcattagtTG	140	caactaatgcagtcgatac
22	tgtatcgactgcattagttg	TGtatcgactgcattagtTG	141	caactaatgcagtcgataca
23	atcgactgcattagtt	ATCgactgcattaGTT	142	aactaatgcagtcgat
23	atcgactgcattagtt	ATCGactgcattAGTT	142	aactaatgcagtcgat
23	atcgactgcattagtt	ATCGactgcattaGTT	142	aactaatgcagtcgat
24	tatcgactgcattagtt	TATCgactgcattaGTT	143	aactaatgcagtcgata
25	gtatcgactgcattagtt	GTATcgactgcattagTT	144	aactaatgcagtcgatac
26	tgtatcgactgcattagtt	TGTatcgactgcattagTT	145	aactaatgcagtcgataca
27	ttgtatcgactgcattagtt	TTGtatcgactgcattagTT	146	aactaatgcagtcgatacaa
28	tatcgactgcattagt	TATcgactgcattaGT	147	actaatgcagtcgata
28	tatcgactgcattagt	TATCgactgcatTAGT	147	actaatgcagtcgata
29	gtatcgactgcattagt	GTATcgactgcattaGT	148	actaatgcagtcgatac
30	tgtatcgactgcattagt	TGTatcgactgcattaGT	149	actaatgcagtcgataca
31	gtatcgactgcattag	GTAtcgactgcatTAG	150	ctaatgcagtcgatac
31	gtatcgactgcattag	GTAtcgactgcattAG	150	ctaatgcagtcgatac
31	gtatcgactgcattag	GTATcgactgcaTTAG	150	ctaatgcagtcgatac
32	tgtatcgactgcattag	TGtatcgactgcaTTAG	151	ctaatgcagtcgataca
33	ttgtatcgactgcattag	TTGtatcgactgcatTAG	152	ctaatgcagtcgatacaa
34	attgtatcgactgcattag	ATtgtatcgactgcaTTAG	153	ctaatgcagtcgatacaat
35	tgtatcgactgcatta	TGTatcgactgcaTTA	154	taatgcagtcgataca
35	tgtatcgactgcatta	TGTAtcgactgcATTA	154	taatgcagtcgataca
36	attgtatcgactgcatta	ATTGtatcgactgcaTTA	155	taatgcagtcgatacaat
37	ttgtatcgactgcatt	TTGtatcgactgcaTT	156	aatgcagtcgatacaa
37	ttgtatcgactgcatt	TTGtatcgactgCATT	156	aatgcagtcgatacaa
38	attgtatcgactgcat	ATTgtatcgactgCAT	157	atgcagtcgatacaat
38	attgtatcgactgcat	ATTgtatcgactgcAT	157	atgcagtcgatacaat
38	attgtatcgactgcat	ATTGtatcgactGCAT	157	atgcagtcgatacaat
39	acgcattgtatcgact	ACGcattgtatcgACT	158	agtcgatacaatgcgt
39	acgcattgtatcgact	ACGCattgtatcGACT	158	agtcgatacaatgcgt
40	tacgcattgtatcgac	TACgcattgtatcGAC	159	gtcgatacaatgcgta
40	tacgcattgtatcgac	TACGcattgtatCGAC	159	gtcgatacaatgcgta
41	ctacgcattgtatcgac	CTacgcattgtatCGAC	160	gtcgatacaatgcgtag
42	tctacgcattgtatcgac	TCTAcgcattgtatcgAC	161	gtcgatacaatgcgtaga

43	atctacgcattgtatcgac	ATCtacgcattgtatcgAC	162	gtcgatacaatgcgtagat
44	tatctacgcattgtatcgac	TAtctacgcattgtatcGAC	163	gtcgatacaatgcgtagata
45	ctacgcattgtatcga	CTAcgcattgtatCGA	164	tcgatacaatgcgtag
45	ctacgcattgtatcga	CTACgcattgtaTCGA	164	tcgatacaatgcgtag
46	tatctacgcattgtatcga	TAtctacgcattgtatCGA	165	tcgatacaatgcgtagata
47	tctacgcattgtatcg	TCTacgcattgtaTCG	166	cgatacaatgcgtaga
47	tctacgcattgtatcg	TCTacgcattgtatCG	166	cgatacaatgcgtaga
47	tctacgcattgtatcg	TCTAcgcattgtATCG	166	cgatacaatgcgtaga
48	atctacgcattgtatcg	ATCTacgcattgtaTCG	167	cgatacaatgcgtagat
49	tatctacgcattgtatcg	TATCtacgcattgtatCG	168	cgatacaatgcgtagata
50	tctatctacgcattgtatcg	TCtatctacgcattgtatCG	169	cgatacaatgcgtagataga
51	atctacgcattgtatc	ATCtacgcattgtATC	170	gatacaatgcgtagat
51	atctacgcattgtatc	ATCTacgcattgTATC	170	gatacaatgcgtagat
52	tatctacgcattgtatc	TATctacgcattgTATC	171	gatacaatgcgtagata
53	ctatctacgcattgtatc	CTatctacgcattgTATC	172	gatacaatgcgtagatag
54	tctatctacgcattgtatc	TCTatctacgcattgtaTC	173	gatacaatgcgtagataga
55	ttctatctacgcattgtatc	TTCtatctacgcattgtaTC	174	gatacaatgcgtagatagaa
56	tatctacgcattgtat	TATctacgcattgTAT	175	atacaatgcgtagata
56	tatctacgcattgtat	TATCtacgcattGTAT	175	atacaatgcgtagata
57	ctatctacgcattgtat	CTAtctacgcattGTAT	176	atacaatgcgtagatag
58	tctatctacgcattgtat	TCtatctacgcattGTAT	177	atacaatgcgtagataga
59	ttctatctacgcattgtat	TTCtatctacgcattgTAT	178	atacaatgcgtagatagaa
60	ctatctacgcattgta	CTAtctacgcattGTA	179	tacaatgcgtagatag
60	ctatctacgcattgta	CTATctacgcatTGTA	179	tacaatgcgtagatag
61	tctatctacgcattgta	TCTatctacgcattGTA	180	tacaatgcgtagataga
62	ttctatctacgcattgta	TTCtatctacgcattGTA	181	tacaatgcgtagatagaa
63	ttctatctacgcattgt	TTCtatctacgcatTGT	182	acaatgcgtagatagaa
64	tcttctatctacgcattgt	TCttctatctacgcattGT	183	acaatgcgtagatagaaga
65	ttcttctatctacgcattgt	TtcttctatctacgcattGT	184	acaatgcgtagatagaagaa
66	ttcttctatctacgcattg	TTCttctatctacgcatTG	185	caatgcgtagatagaagaa
67	ttctatctacgcattg	TTCtatctacgcaTTG	186	caatgcgtagatagaa
68	cttctatctacgcatt	CTTCtatctacgCATT	187	aatgcgtagatagaag
69	tcttctatctacgcatt	TCTtctatctacgCATT	188	aatgcgtagatagaaga
70	ttcttctatctacgcatt	TTCTtctatctacgcATT	189	aatgcgtagatagaagaa
71	tcttctatctacgcat	TCTTctatctacgCAT	190	atgcgtagatagaaga
72	ttcttctatctacgcat	TTCTtctatctacgCAT	191	atgcgtagatagaagaa
73	cttcttctatctacgcat	CTTCttctatctacgcAT	192	atgcgtagatagaagaag
74	ttcttctatctacgca	TTCttctatctacGCA	193	tgcgtagatagaagaa
75	cttcttctatctacgca	CTTCttctatctacgCA	194	tgcgtagatagaagaag
76	gcttcttctatctacgca	GcttcttctatctacgCA	195	tgcgtagatagaagaagc
77	cttcttctatctacgc	CTtcttctatctACGC	196	gcgtagatagaagaag
78	gcttcttctatctacg	GCTtcttctatctACG	197	cgtagatagaagaagc
79	cgtggggcttcttcta	CGTggggcttcttCTA	198	tagaagaagccccacg

80	tgacttggagaaaagcacaa	TGacttggagaaaagcacAA	199	ttgtgcttttctccaagtca
81	ctgacttggagaaaagcac	CtgacttggagaaaagcAC	200	gtgcttttctccaagtcag
82	agagtcatcgtgctcc	AGAgtcatcgtgcTCC	201	ggagcacgatgactct
83	aagtactttaatagctcaaa	AAGTactttaatagctCAAA	202	tttgagctattaaagtactt
84	aagtactttaatagctcaa	AAGTactttaatagcTCAA	203	ttgagctattaaagtactt
85	gaagtactttaatagctcaa	GAAGtactttaatagctCAA	204	ttgagctattaaagtacttc
86	tactttaatagctcaa	TACTttaatagcTCAA	205	ttgagctattaaagta
87	aagtactttaatagctca	AAGTactttaatagcTCA	206	tgagctattaaagtactt
88	gaagtactttaatagctca	GAAGtactttaatagcTCA	207	tgagctattaaagtacttc
89	agaagtactttaatagctc	AGAAgtactttaatagCTC	208	gagctattaaagtacttct
90	aagaagtactttaatagctc	AAGAagtactttaatagCTC	209	gagctattaaagtacttctt
91	gaagtactttaatagct	GAAGtactttaatAGCT	210	agctattaaagtacttc
92	taagaagtactttaatagct	TAAgaagtactttaatAGCT	211	agctattaaagtacttctta
93	agaagtactttaatagc	AGAAgtactttaaTAGC	212	gctattaaagtacttct
94	taagaagtactttaatagc	TAAGaagtactttaaTAGC	213	gctattaaagtacttctta
95	gtaagaagtactttaatagc	GTaagaagtactttaaTAGC	214	gctattaaagtacttcttac
96	taagaagtactttaatag	TAAGaagtactttaATAG	215	ctattaaagtacttctta
97	gtaagaagtactttaatag	GTAAgaagtactttaATAG	216	ctattaaagtacttcttac
98	tgtaagaagtactttaatag	TGTAagaagtactttaATAG	217	ctattaaagtacttcttaca
99	aatgtgtaagaagtacttt	AATGtgtaagaagtaCTTT	218	aaagtacttcttacacatt
100	caatgtgtaagaagtacttt	CAATgtgtaagaagtaCTTT	219	aaagtacttcttacacattg
101	atgtgtaagaagtactt	ATGTgtaagaagtACTT	220	aagtacttcttacacat
102	aatgtgtaagaagtactt	AATGtgtaagaagtACTT	221	aagtacttcttacacatt
103	caatgtgtaagaagtactt	CAATgtgtaagaagtACTT	222	aagtacttcttacacattg
104	gcaatgtgtaagaagtactt	GCaatgtgtaagaagtACTT	223	aagtacttcttacacattgc
105	atgtgtaagaagtact	ATGtgtaagaagtACT	224	agtacttcttacacat
105	atgtgtaagaagtact	ATGTgtaagaagTACT	224	agtacttcttacacat
106	gcaatgtgtaagaagtact	GCAAtgtgtaagaagtACT	225	agtacttcttacacattgc
107	aatgtgtaagaagtac	AATGtgtaagaaGTAC	226	gtacttcttacacatt
107	aatgtgtaagaagtac	AATgtgtaagaaGTAC	226	gtacttcttacacatt
108	caatgtgtaagaagtac	CAATgtgtaagaaGTAC	227	gtacttcttacacattg
109	gcaatgtgtaagaagtac	GCAatgtgtaagaaGTAC	228	gtacttcttacacattgc
110	caatgtgtaagaagta	CAAtgtgtaagaaGTA	229	tacttcttacacattg
110	caatgtgtaagaagta	CAAtgtgtaagaAGTA	229	tacttcttacacattg
110	caatgtgtaagaagta	CAATgtgtaagaAGTA	229	tacttcttacacattg
111	gcaatgtgtaagaagta	GCAatgtgtaagaAGTA	230	tacttcttacacattgc

or conjugate thereof; wherein for the column entitled compound design, capital letters are LNA nucleosides, lower case letters are DNA nucleosides, cytosine nucleosides are optionally 5 methyl cytosine, and internucleoside linkages are at least 80%, such as at least 90% or 100% modified internucleoside linkages, such as phosphorothioate internucleoside linkages. In some embodiments all internucleoside linkages of the compounds in the compound design column in the above table are phosphorothioate internucleoside linkages. The motif and target subsequence sequences are nucleobase sequences.

The invention provides the following oligonucleotides:

CMP ID NO	Compound
5,1	AGTTaaaggaggagacAAAT
6,1	TCAgttaaaggaggagaCAA
7,1	CTCagttaaaggaggagaCA
8,1	CTCagttaaaggaggaGAC
9,1	ACTCagttaaaggaggagAC
10,1	ACTCagttaaaggaggaGA
11,1	ACtcagttaaaggaGGAG
12,1	GAtgactcagttaaaggAGG
13,1	ATGAtgactcagttaaagGA
14,1	TGAtgactcagttaAAGG
15,1	GAtgatgactcagttaAAGG
16,1	GATGatgactcagttaAAG
17,1	TAT^{m}cgactgcattagttGG
18,1	Gtat^{m}cgactgcattagttGG
19,1	TCGactgcattagTTG
19,2	TCGactgcattagtTG
19,3	TCGActgcattaGTTG
20,1	TAt^{m}cgactgcattaGTTG
21,1	GTAt^{m}cgactgcattagtTG
22,1	TGtat^{m}cgactgcattagtTG
23,1	ATCgactgcattaGTT
23,2	ATCGactgcattAGTT
23,3	ATCGactgcattaGTT
24,1	TATCgactgcattaGTT
25,1	GTAT^{m}cgactgcattagTT
26,1	TGTat^{m}cgactgcattagTT
27,1	TTGtat^{m}cgactgcattagTT
28,1	TAT^{m}cgactgcattaGT
28,2	TATCgactgcatTAGT
29,1	GTAT^{m}cgactgcattaGT
30,1	TGTat^{m}cgactgcattaGT
31,1	GTAt^{m}cgactgcatTAG
31,2	GTAt^{m}cgactgcattAG
31,3	GTAT^{m}cgactgcaTTAG
32,1	TGtat^{m}cgactgcaTTAG

33,1	TTGtat^{m}cgactgcatTAG
34,1	ATtgtat^{m}cgactgcaTTAG
35,1	TGTat^{m}cgactgcaTTA
35,2	TGTAt^{m}cgactgcATTA
36,1	ATTGtat^{m}cgactgcaTTA
37,1	TTGtat^{m}cgactgcaTT
37,2	TTGtat^{m}cgactgCATT
38,1	ATTgtat^{m}cgactgCAT
38,2	ATTgtat^{m}cgactgcAT
38,3	ATTGtat^{m}cgactGCAT
39,1	ACGcattgtat^{m}cgACT
39,2	ACGCattgtat^{m}cGACT
40,1	TACgcattgtat^{m}cGAC
40,2	TACGcattgtatCGAC
41,1	CTa^{m}cgcattgtatCGAC
42,1	TCTA^{m}cgcattgtat^{m}cgAC
43,1	ATCta^{m}cgcattgtat^{m}cgAC
44,1	TAtcta^{m}cgcattgtatcGAC
45,1	CTA^{m}cgcattgtatCGA
45,2	CTACgcattgtaTCGA
46,1	TAtcta^{m}cgcattgtatCGA
47,1	TCTa^{m}cgcattgtaTCG
47,2	TCTa^{m}cgcattgtatCG
47,3	TCTA^{m}cgcattgtATCG
48,1	ATCTa^{m}cgcattgtaTCG
49,1	TATCta^{m}cgcattgtatCG
50,1	TCtatcta^{m}cgcattgtatCG
51,1	ATCta^{m}cgcattgtATC
51,2	ATCTa^{m}cgcattgTATC
52,1	TATcta^{m}cgcattgTATC
53,1	CTatcta^{m}cgcattgTATC
54,1	TCTatcta^{m}cgcattgtaTC
55,1	TTCtatcta^{m}cgcattgtaTC
56,1	TATcta^{m}cgcattgTAT
56,2	TATCta^{m}cgcattGTAT
57,1	CTAtcta^{m}cgcattGTAT
58,1	TCtatcta^{m}cgcattGTAT
59,1	TTCtatcta^{m}cgcattgTAT
60,1	CTAtcta^{m}cgcattGTA
60,2	CTATcta^{m}cgcatTGTA
61,1	TCTatcta^{m}cgcattGTA
62,1	TTCtatcta^{m}cgcattGTA
63,1	TTCtatcta^{m}cgcatTGT

64,1	TCttctatcta^{m}cgcattGT
65,1	Ttcttctatcta^{m}cgcattGT
66,1	TTCttctatcta^{m}cgcatTG
67,1	TTCtatcta^{m}cgcaTTG
68,1	CTTCtatcta^{m}cgCATT
69,1	TCTtctatcta^{m}cgCATT
70,1	TTCTtctatcta^{m}cgcATT
71,1	TCTTctatcta^{m}cgCAT
72,1	TTCTtctatcta^{m}cgCAT
73,1	CTTCttctatcta^{m}cgcAT
74,1	TTCttctatctacGCA
75,1	CTTCttctatcta^{m}cgCA
76,1	Gcttcttctatcta^{m}cgCA
77,1	CTtcttctatctACGC
78,1	GCTtcttctatctACG
79,1	CGTggggcttcttCTA
80,1	TGacttggagaaaagcacAA
81,1	CtgacttggagaaaagcAC
82,1	AGAgtcat^{m}cgtgcTCC
83,1	AAGTactttaatagctCAAA
84,1	AAGTactttaatagcTCAA
85,1	GAAGtactttaatagctCAA
86,1	TACTttaatagcTCAA
87,1	AAGTactttaatagcTCA
88,1	GAAGtactttaatagcTCA
89,1	AGAAgtactttaatagCTC
90,1	AAGAagtactttaatagCTC
91,1	GAAGtactttaatAGCT
92,1	TAAgaagtactttaatAGCT
93,1	AGAAgtactttaaTAGC
94,1	TAAGaagtactttaaTAGC
95,1	GTaagaagtactttaaTAGC
96,1	TAAGaagtactttaATAG
97,1	GTAAgaagtactttaATAG
98,1	TGTAagaagtactttaATAG
99,1	AATGtgtaagaagtaCTTT
100,1	CAATgtgtaagaagtaCTTT
101,1	ATGTgtaagaagtACTT
102,1	AATGtgtaagaagtACTT
103,1	CAATgtgtaagaagtACTT
104,1	GCaatgtgtaagaagtACTT
105,1	ATGtgtaagaagtACT
105,2	ATGTgtaagaagTACT

106,1	GCAAtgtgtaagaagtACT
107,1	AATGtgtaagaaGTAC
107,2	AATgtgtaagaaGTAC
108,1	CAATgtgtaagaaGTAC
109,1	GCAatgtgtaagaaGTAC
110,1	CAAtgtgtaagaaGTA
110,2	CAAtgtgtaagaAGTA
110,3	CAATgtgtaagaAGTA
111,1	GCAatgtgtaagaAGTA

or a conjugate thereof; wherein in the compounds of the above table, capital letters represent beta-D-oxy LNA nucleosides, all LNA cytosines are 5-methyl cytosine (as indicated by the superscript ^{m}), lower case letters represent DNA nucleosides, superscript m before a lower case c represents a 5 methyl cytosine DNA nucleoside. All internucleoside linkages are phosphorothioate internucleoside linkages.

Oligonucleotide design

Oligonucleotide design refers to the pattern of nucleoside sugar modifications in the oligonucleotide sequence. The oligonucleotides of the invention comprise sugar-modified nucleosides and may also comprise DNA or RNA nucleosides. In some embodiments, the oligonucleotide comprises sugar-modified nucleosides and DNA nucleosides. Incorporation of modified nucleosides into the oligonucleotide of the invention may enhance the affinity of the oligonucleotide for the target nucleic acid. In that case, the modified nucleosides can be referred to as affinity enhancing modified nucleotides.

In an embodiment, the oligonucleotide comprises at least 1 modified nucleoside, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15 or at least 16 modified nucleosides. In an embodiment the oligonucleotide comprises from 1 to 10 modified nucleosides, such as from 2 to 9 modified nucleosides, such as from 3 to 8 modified nucleosides, such as from 4 to 7 modified nucleosides, such as 6 or 7 modified nucleosides. In an embodiment, the oligonucleotide of the invention may comprise modifications, which are independently selected from these three types of modifications (modified sugar, modified nucleobase and modified internucleoside linkage) or a combination thereof. Preferably the oligonucleotide comprises one or more sugar modified nucleosides, such as 2' sugar modified nucleosides. Preferably the oligonucleotide of the invention comprise the one or more 2' sugar modified nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides. Even more preferably the one or more modified nucleoside is LNA.

In some embodiments, at least 1 of the modified nucleosides is a locked nucleic acid (LNA), such as at least 2, such as at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 of the modified nucleosides are LNA. In a still further embodiment all the modified nucleosides are LNA.

In a further embodiment the oligonucleotide comprises at least one modified internucleoside linkage. In a preferred embodiment the the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate or boranophosphate internucleoside linkages. In some embodiments all the internucleotide linkages in the contiguous sequence of the oligonucleotide are phosphorothioate linkages.

In some embodiments, the oligonucleotide of the invention comprise at least one modified nucleoside which is a 2'-MOE-RNA, such as 2, 3, 4, 5, 6, 7, 8, 9 or 10 2'-MOE-RNA nucleoside units. In some embodiments, at least one of said modified nucleoside is 2'-fluoro DNA, such as 2, 3, 4, 5, 6, 7, 8, 9 or 10 2'-fluoro-DNA nucleoside units.

In some embodiments, the oligonucleotide of the invention comprises at least one LNA unit, such as 1, 2, 3, 4, 5, 6, 7, or 8 LNA units, such as from 2 to 6 LNA units, such as from 3 to 7 LNA units, 4 to 8 LNA units or 3, 4, 5, 6 or 7 LNA units. In some embodiments, all the modified nucleosides are LNA nucleosides. In some embodiments, all LNA cytosine units are 5-methyl-cytosine. In some embodiments the oligonucleotide or contiguous nucleotide region thereof has at least 1 LNA unit at the 5' end and at least 2 LNA units at the 3' end of the nucleotide sequence. In some embodiments all cytosine nucleobases present in the oligonucleotide of the invention are 5-methyl-cytosine.

In some embodiments, the oligonucleotide of the invention comprises at least one LNA unit and at least one 2' substituted modified nucleoside.

In some embodiments of the invention, the oligonucleotide comprise both 2' sugar modified nucleosides and DNA units.

In an embodiment of the invention the oligonucleotide of the invention is capable of recruiting RNase H.

In some embodiments, the oligonucleotide of the invention or contiguous nucleotide region thereof is a gapmers oligonucleotide.

Gapmer design

In some embodiments the oligonucleotide of the invention, or contiguous nucleotide region thereof, has a gapmer design or structure also referred herein merely as “Gapmer”. In a gapmer structure the oligonucleotide comprises at least three distinct structural regions a 5'-flank, a gap and a 3'-flank, F-G-F' in '5 -> 3' orientation. In this design, flanking regions F and F' (also termed wing regions) comprise at least one sugar modified nucleoside which is adjacent to region G, and may in some embodiments comprise a contiguous stretch of 2 – 7 sugar modified nucleoside, or a contiguous stretch of sugar modified and DNA nucleosides (mixed wings comprising both sugar modified and DNA nucleosides). Consequently, the nucleosides of the 5' flanking region and the 3' flanking region which are adjacent to the gap region are sugar modified nucleosides, such as 2' modified nucleosides. The gap region, G, comprises a contiguous stretch of nucleotides which are capable of recruiting RNase H, when the oligonucleotide is in duplex with the HTRA1target nucleic acid. In some embodiments, region G comprises a contiguous stretch of 5 – 16 DNA nucleosides. The gapmer region F-G-F' is complementary to the HTRA1 target nucleic acid, and may therefore be the contiguous nucleotide region of the oligonucleotide.

Regions F and F', flanking the 5' and 3' ends of region G, may comprise one or more affinity enhancing modified nucleosides. In some embodiments, the 3' flank comprises at least one LNA nucleoside, preferably at least 2 LNA nucleosides. In some embodiments, the 5' flank comprises at least one LNA nucleoside. In some embodiments both the 5' and 3' flanking regions comprise a LNA nucleoside. In some embodiments all the nucleosides in the flanking regions are LNA nucleosides. In other embodiments, the flanking regions may comprise both LNA nucleosides and other nucleosides (mixed flanks), such as DNA nucleosides and/or non-LNA modified nucleosides, such as 2' substituted nucleosides. In this case the gap is defined as a contiguous sequence of at least 5 RNase H recruiting nucleosides (such as 5 – 16 DNA nucleosides) flanked at the 5' and 3' end by an affinity enhancing modified nucleoside, such as an LNA, such as beta-D-oxy-LNA.

Region F

Region F (5' flank or 5' wing) attached to the '5 end of region G comprises, contains or consists of at least one sugar modified nucleoside such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 modified nucleosides. In some embodiments region F comprises or consists of from 1 to 7 modified nucleosides, such as from 2 to 6 modified nucleosides, such as from 2 to 5 modified nucleosides, such as from 2 to 4 modified nucleosides, such as from 1 to 3 modified nucleosides, such as 1, 2, 3 or 4 modified nucleosides.

In an embodiment, one or more or all of the modified nucleosides in region F are 2' modified nucleosides.

In a further embodiment one or more of the 2' modified nucleosides in region F are selected from 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, LNA units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units.

In one embodiment of the invention all the modified nucleosides in region F are LNA nucleosides. In a further embodiment the LNA nucleosides in region F are independently selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA, cET, and/or ENA, in either the beta-D or alpha-L configurations or combinations thereof. In a preferred embodiment region F has at least 1 beta-D-oxy LNA unit, at the 5' end of the contiguous sequence.

Region G

Region G (gap region) may comprise, contain or consist of at 5 - 16 consecutive DNA nucleosides capable of recruiting RNaseH. In a further embodiment region G comprise, contain or consist of from 5 to 12, or from 6 to 10 or from 7 to 9, such as 8 consecutive nucleotide units capable of recruiting RNaseH.

In a still further embodiment at least one nucleoside unit in region G is a DNA nucleoside unit, such as from 4 to 20 or or 6 to 18 DNA units, such as 5 to 16, In some embodiments, all of the nucleosides of region G are DNA units.

In further embodiments the region G may consist of a mixture of DNA and other nucleosides capable of mediating RNase H cleavage. In some embodiments, at least 50% of the nucleosides of region G are DNA, such as at least 60 %, at least 70% or at least 80 %, or at least 90% DNA.

Region F'

Region F' (3' flank or 3' wing) attached to the '3 end of region G comprises, contains or consists of at least one sugar modified nucleoside such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 modified nucleosides. In some embodiments region F' comprises or consists of from 1 to 7 modified nucleosides, such as from 2 to 6 modified nucleosides, such as from 2 to 5 modified nucleosides, such as from 2 to 4 modified nucleosides, such as from 1 to 3 modified nucleosides, such as 1, 2, 3 or 4 modified nucleosides.

In an embodiment, one or more or all of the modified nucleosides in region F' are 2' modified nucleosides.

In a further embodiment one or more of the 2' modified nucleosides in region F' are selected from 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, LNA units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units.

In one embodiment of the invention all the modified nucleosides in region F' are LNA nucleosides. In a further embodiment the LNA nucleosides in region F' are independently selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA, cET, and/or ENA, in either the beta-D or alpha-L configurations or combinations thereof. In a preferred embodiment region F' has at least 1 beta-D-oxy LNA unit, at the 5' end of the contiguous sequence.

Region D, D' and D"

The oligonucleotide of the invention ncomprises a contiguous nucleotide region which is complementary to the target nucleic acid. In some embodiments, the oligonucleotide may further comprise additional nucleotides positioned 5' and/or 3' to the contiguous nucleotide region, which are referred to as region D herein. Region D' and D'' can be attached to the 5' end of region F or the 3' end of region F', respectively. The D regions (region D' or D'') may in some embodiments form part of the contiguous nucleotide sequence which is complementary to the target nucleic acid, or in other embodiments the D region(s) may be non-complementary to the target nucleic acid.

In some embodiments the oligonucleotide of the invention consists or comprises of the contiguous nucleotide region and optionally 1 – 5 additional 5' nucleotides (region D').

In some embodiments the oligonucleotide of the invention consists or comprises of the contiguous nucleotide region and optionally 1 – 5 additional 3' nucleotides (region D'').

Region D' or D'' may independently comprise 1, 2, 3, 4 or 5 additional nucleotides, which may be complementary or non-complementary to the target nucleic acid. In this respect the oligonucleotide of the invention, may in some embodiments comprise a contiguous nucleotide sequence capable of modulating the target which is flanked at the 5' and/or 3' end by additional nucleotides. Such additional nucleotides may serve as a nuclease susceptible biocleavable linker, and may therefore be used to attach a functional group such as a conjugate moiety to the oligonucleotide of the invention. In some embodiments the additional 5' and/or 3' end nucleotides are linked with phosphodiester linkages, and may be DNA or RNA. In another embodiment, the additional 5' and/or 3' end nucleotides are modified nucleotides which may for example be included to enhance nuclease stability or for ease of synthesis. In some embodiments the oligonucleotide of the invention comprises a region D' and/or D'' in addition to the contiguous nucleotide region.

In some embodiments, the gapmer oligonucleotide of the present invention can be represented by the following formulae:

F-G-F'; in particular F_{1-7}-G_{4-12}-F'_{1-7}
D'-F-G-F', in particular D'_{1-3}-F_{1-7}-G_{4-12}-F'_{1-7}
F-G-F'-D'', in particular F_{1-7}-G_{4-12}-F'_{1-7}-D''_{1-3}
D'-F-G-F'-D'', in particular D'_{1-3}-F_{1-7}-G_{4-12}-F'_{1-7}-D''_{1-3}

Method of manufacture

In a further aspect, the invention provides methods for manufacturing the oligonucleotides of the invention comprising reacting nucleotide units and thereby forming covalently linked contiguous nucleotide units comprised in the oligonucleotide. Preferably, the method uses phophoramidite chemistry (see for example Caruthers et al, 1987, Methods in Enzymology vol. 154, pages 287-313). In a further embodiment the method further comprises reacting the contiguous nucleotide sequence with a conjugating moiety (ligand). In a further aspect a method is provided for manufacturing the composition of the invention, comprising mixing the oligonucleotide or conjugated oligonucleotide of the invention with a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

Pharmaceutical Salts

For use as a therapeutic, the oligonucleotide of the invention may be provided as a suitable pharmaceutical salt, such as a sodium or potassium salt. In some embodiments the oligonucleotide of the invention is a sodium salt.

Pharmaceutical Composition

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS) and pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In some embodiments the pharmaceutically acceptable diluent is sterile phosphate buffered saline. In some embodiments the oligonucleotide is used in the pharmaceutically acceptable diluent at a concentration of 50 - 300μM solution. In some embodiments, the oligonucleotide of the invention is administered at a dose of 10 - 1000μg.

WO 2007/031091 provides suitable and preferred examples of pharmaceutically acceptable diluents, carriers and adjuvants (hereby incorporated by reference). Suitable dosages, formulations, administration routes, compositions, dosage forms, combinations with other therapeutic agents, pro-drug formulations are also provided in WO2007/031091.

Oligonucleotides or oligonucleotide conjugates of the invention may be mixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

In some embodiments, the oligonucleotide or oligonucleotide conjugate of the invention is a prodrug. In particular with respect to oligonucleotide conjugates the conjugate moiety is cleaved of the oligonucleotide once the prodrug is delivered to the site of action, e.g. the target cell.

Applications

The oligonucleotides of the invention may be utilized as research reagents for, for example, diagnostics, therapeutics and prophylaxis.

In research, such oligonucleotides may be used to specifically modulate the synthesis of HTRA1 protein in cells (e.g. *in vitro* cell cultures) and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Typically the target modulation is achieved by degrading or inhibiting the mRNA producing the protein, thereby prevent protein formation or by degrading or inhibiting a modulator of the gene or mRNA producing the protein.

In diagnostics the oligonucleotides may be used to detect and quantitate HTRA1 expression in cell and tissues by northern blotting, *in-situ* hybridisation or similar techniques.

For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of HTRA1.

The invention provides methods for treating or preventing a disease, comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide, an oligonucleotide conjugate or a pharmaceutical composition of the invention to a subject suffering from or susceptible to the disease.

The invention also relates to an oligonucleotide, a composition or a conjugate as defined herein for use as a medicament.

The oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition according to the invention is typically administered in an effective amount.

The invention also provides for the use of the oligonucleotide or oligonucleotide conjugate of the invention as described for the manufacture of a medicament for the treatment of a disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein.

The disease or disorder, as referred to herein, is associated with expression of HTRA1. In some embodiments disease or disorder may be associated with a mutation in the HTRA1 gene or a gene whose protein product is associated with or interacts with HTRA1. Therefore, in some embodiments, the target nucleic acid is a mutated form of the HTRA1 sequence and in other embodiments, the target nucleic acid is a regulator of the HTRA1 sequence.

The methods of the invention are preferably employed for treatment or prophylaxis against diseases caused by abnormal levels and/or activity of HTRA1.

The invention further relates to use of an oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of abnormal levels and/or activity of HTRA1.

In one embodiment, the invention relates to oligonucleotides, oligonucleotide conjugates or pharmaceutical compositions for use in the treatment of diseases or disorders selected from eye disorders, such as macular degeneration, including age related macular degeneration (AMD), such as dry AMD or wet AMD, and diabetic retinopathy. In some embodiments the oligonucleotide conjugates or pharmaceutical compositions of the invention may be for use in the treatment of geographic atrophy or intermediate dAMD. HTRA1 has also been indicated in Alzheimer’s and Parkinson’s disease, and therefore in some embodiments, the oligonucleotide conjugates or pharmaceutical compositions of the invention may be for use in the treatment of Alzheimer's or Parkinson's. HTRA1 has also been indicated in Duchenne muscular dystrophy, arthritis, such as osteoarthritis, familial ischemic cerebral small-vessel disease, and therefore in some embodiments, the oligonucleotide conjugates or pharmaceutical compositions of the invention may be for use in the treatment of Duchenne muscular dystrophy, arthritis, such as osteoarthritis, or familial ischemic cerebral small-vessel disease.

Administration

The oligonucleotides or pharmaceutical compositions of the present invention may be administered topical (such as, to the skin, inhalation, ophthalmic or otic) or enteral (such as, orally or through the gastrointestinal tract) or parenteral (such as, intravenous, subcutaneous, intra-muscular, intracerebral, intracerebroventricular or intrathecal).

In some embodiments the oligonucleotide, conjugate or pharmaceutical compositions of the present invention are administered by a parenteral route including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion, intrathecal or intracranial, e.g. intracerebral or intraventricular, administration. In some embodiments the active oligonucleotide or oligonucleotide conjugate is administered intravenously. In another embodiment the active oligonucleotide or oligonucleotide conjugate is administered subcutaneously.

For use in treating eye disorders, such as macular degeneration, e.g. AMD (wet or dry), intraocular injection may be used.

In some embodiments, the compound of the invention, or pharmaceutically acceptable salt thereof, is administered via an intraocular injection in a dose from about 10µg to about 200µg per eye, such as about 50µg to about 150 µg per eye, such as about 100µg per eye. In some embodiments, the dosage interval, *i.e.* the period of time between consecutive dosings is at least monthy, such as at least bi monthly or at least once every three months.

Combination therapies

In some embodiments the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is for use in a combination treatment with another therapeutic agent. The therapeutic agent can for example be the standard of care for the diseases or disorders described above

EXAMPLES

Materials and methods

Oligonucleotide synthesis

Oligonucleotide synthesis is generally known in the art. Below is a protocol which may be applied. The oligonucleotides of the present invention may have been produced by slightly varying methods in terms of apparatus, support and concentrations used.

Oligonucleotides are synthesized on uridine universal supports using the phosphoramidite approach on an Oligomaker 48 at 1 μmol scale. At the end of the synthesis, the oligonucleotides are cleaved from the solid support using aqueous ammonia for 5-16hours at 60˚C. The oligonucleotides are purified by reverse phase HPLC (RP-HPLC) or by solid phase extractions and characterized by UPLC, and the molecular mass is further confirmed by ESI-MS.

Elongation of the oligonucleotide:

The coupling of β-cyanoethyl- phosphoramidites (DNA-A(Bz), DNA- G(ibu), DNA- C(Bz), DNA-T, LNA-5-methyl-C(Bz), LNA-A(Bz), LNA- G(dmf), LNA-T) is performed by using a solution of 0.1 M of the 5'-O-DMT-protected amidite in acetonitrile and DCI (4,5–dicyanoimidazole) in acetonitrile (0.25 M) as activator. For the final cycle a phosphoramidite with desired modifications can be used, e.g. a C6 linker for attaching a conjugate group or a conjugate group as such. Thiolation for introduction of phosphorthioate linkages is carried out by using xanthane hydride (0.01 M in acetonitrile/pyridine 9:1). Phosphordiester linkages can be introduced using 0.02 M iodine in THF/Pyridine/water 7:2:1. The rest of the reagents are the ones typically used for oligonucleotide synthesis.

For post solid phase synthesis conjugation a commercially available C6 aminolinker phorphoramidite can be used in the last cycle of the solid phase synthesis and after deprotection and cleavage from the solid support the aminolinked deprotected oligonucleotide is isolated. The conjugates are introduced via activation of the functional group using standard synthesis methods.

Purification by RP-HPLC:

The crude compounds are purified by preparative RP-HPLC on a Phenomenex Jupiter C18 10μ 150x10 mm column. 0.1 M ammonium acetate pH 8 and acetonitrile is used as buffers at a flow rate of 5 mL/min. The collected fractions are lyophilized to give the purified compound typically as a white solid.

Abbreviations:

DCI: 4,5-Dicyanoimidazole

DCM: Dichloromethane

DMF: Dimethylformamide

DMT: 4,4'-Dimethoxytrityl

THF: Tetrahydrofurane

Bz: Benzoyl

Ibu: Isobutyryl

RP-HPLC: Reverse phase high performance liquid chromatography

T_m Assay:

Oligonucleotide and RNA target (phosphate linked, PO) duplexes are diluted to 3 mM in 500 ml RNase-free water and mixed with 500 ml 2x T_m-buffer (200mM NaCl, 0.2mM EDTA, 20mM Naphosphate, pH 7.0). The solution is heated to 95ºC for 3 min and then allowed to anneal in room temperature for 30 min. The duplex melting temperatures (T_m) is measured on a Lambda 40 UV/VIS Spectrophotometer equipped with a Peltier temperature programmer PTP6 using PE Templab software (Perkin Elmer). The temperature is ramped up from 20ºC to 95ºC and then down to 25ºC, recording absorption at 260 nm. First derivative and the local maximums of both the melting and annealing are used to assess the duplex T_m.

Oligonucleotides used:

SEQ ID NO	Motif	CMP ID NO	Compound
5	agttaaaggaggagacaaat	5,1	AGTTaaaggaggagacAAAT
6	tcagttaaaggaggagacaa	6,1	TCAgttaaaggaggagaCAA
7	ctcagttaaaggaggagaca	7,1	CTCagttaaaggaggagaCA
8	ctcagttaaaggaggagac	8,1	CTCagttaaaggaggaGAC
9	actcagttaaaggaggagac	9,1	ACTCagttaaaggaggagAC
10	actcagttaaaggaggaga	10,1	ACTCagttaaaggaggaGA
11	actcagttaaaggaggag	11,1	ACtcagttaaaggaGGAG
12	gatgactcagttaaaggagg	12,1	GAtgactcagttaaaggAGG
13	atgatgactcagttaaagga	13,1	ATGAtgactcagttaaagGA
14	tgatgactcagttaaagg	14,1	TGAtgactcagttaAAGG
15	gatgatgactcagttaaagg	15,1	GAtgatgactcagttaAAGG
16	gatgatgactcagttaaag	16,1	GATGatgactcagttaAAG
17	tatcgactgcattagttgg	17,1	TAT^{m}cgactgcattagttGG
18	gtatcgactgcattagttgg	18,1	Gtat^{m}cgactgcattagttGG
19	tcgactgcattagttg	19,1	TCGactgcattagTTG
19	tcgactgcattagttg	19,2	TCGactgcattagtTG
19	tcgactgcattagttg	19,3	TCGActgcattaGTTG
20	tatcgactgcattagttg	20,1	TAt^{m}cgactgcattaGTTG
21	gtatcgactgcattagttg	21,1	GTAt^{m}cgactgcattagtTG
22	tgtatcgactgcattagttg	22,1	TGtat^{m}cgactgcattagtTG

23	atcgactgcattagtt	23,1	ATCgactgcattaGTT
23	atcgactgcattagtt	23,2	ATCGactgcattAGTT
23	atcgactgcattagtt	23,3	ATCGactgcattaGTT
24	tatcgactgcattagtt	24,1	TATCgactgcattaGTT
25	gtatcgactgcattagtt	25,1	GTAT^{m}cgactgcattagTT
26	tgtatcgactgcattagtt	26,1	TGTat^{m}cgactgcattagTT
27	ttgtatcgactgcattagtt	27,1	TTGtat^{m}cgactgcattagTT
28	tatcgactgcattagt	28,1	TAT^{m}cgactgcattaGT
28	tatcgactgcattagt	28,2	TATCgactgcatTAGT
29	gtatcgactgcattagt	29,1	GTAT^{m}cgactgcattaGT
30	tgtatcgactgcattagt	30,1	TGTat^{m}cgactgcattaGT
31	gtatcgactgcattag	31,1	GTAt^{m}cgactgcatTAG
31	gtatcgactgcattag	31,2	GTAt^{m}cgactgcattAG
31	gtatcgactgcattag	31,3	GTAT^{m}cgactgcaTTAG
32	tgtatcgactgcattag	32,1	TGtat^{m}cgactgcaTTAG
33	ttgtatcgactgcattag	33,1	TTGtat^{m}cgactgcatTAG
34	attgtatcgactgcattag	34,1	ATtgtat^{m}cgactgcaTTAG
35	tgtatcgactgcatta	35,1	TGTat^{m}cgactgcaTTA
35	tgtatcgactgcatta	35,2	TGTAt^{m}cgactgcATTA
36	attgtatcgactgcatta	36,1	ATTGtat^{m}cgactgcaTTA
37	ttgtatcgactgcatt	37,1	TTGtat^{m}cgactgcaTT
37	ttgtatcgactgcatt	37,2	TTGtat^{m}cgactgCATT
38	attgtatcgactgcat	38,1	ATTgtat^{m}cgactgCAT
38	attgtatcgactgcat	38,2	ATTgtat^{m}cgactgcAT
38	attgtatcgactgcat	38,3	ATTGtat^{m}cgactGCAT
39	acgcattgtatcgact	39,1	ACGcattgtat^{m}cgACT
39	acgcattgtatcgact	39,2	ACGCattgtat^{m}cGACT
40	tacgcattgtatcgac	40,1	TACgcattgtat^{m}cGAC
40	tacgcattgtatcgac	40,2	TACGcattgtatCGAC
41	ctacgcattgtatcgac	41,1	CTa^{m}cgcattgtatCGAC
42	tctacgcattgtatcgac	42,1	TCTA^{m}cgcattgtat^{m}cgAC
43	atctacgcattgtatcgac	43,1	ATCta^{m}cgcattgtat^{m}cgAC
44	tatctacgcattgtatcgac	44,1	TAtcta^{m}cgcattgtatcGAC
45	ctacgcattgtatcga	45,1	CTA^{m}cgcattgtatCGA
45	ctacgcattgtatcga	45,2	CTACgcattgtaTCGA
46	tatctacgcattgtatcga	46,1	TAtcta^{m}cgcattgtatCGA
47	tctacgcattgtatcg	47,1	TCTa^{m}cgcattgtaTCG
47	tctacgcattgtatcg	47,2	TCTa^{m}cgcattgtatCG
47	tctacgcattgtatcg	47,3	TCTA^{m}cgcattgtATCG
48	atctacgcattgtatcg	48,1	ATCTa^{m}cgcattgtaTCG
49	tatctacgcattgtatcg	49,1	TATCta^{m}cgcattgtatCG
50	tctatctacgcattgtatcg	50,1	TCtatcta^{m}cgcattgtatCG
51	atctacgcattgtatc	51,1	ATCta^{m}cgcattgtATC
51	atctacgcattgtatc	51,2	ATCTa^{m}cgcattgTATC
52	tatctacgcattgtatc	52,1	TATcta^{m}cgcattgTATC
53	ctatctacgcattgtatc	53,1	CTatcta^{m}cgcattgTATC

54	tctatctacgcattgtatc	54,1	TCTatcta^{m}cgcattgtaTC
55	ttctatctacgcattgtatc	55,1	TTCtatcta^{m}cgcattgtaTC
56	tatctacgcattgtat	56,1	TATcta^{m}cgcattgTAT
56	tatctacgcattgtat	56,2	TATCta^{m}cgcattGTAT
57	ctatctacgcattgtat	57,1	CTAtcta^{m}cgcattGTAT
58	tctatctacgcattgtat	58,1	TCtatcta^{m}cgcattGTAT
59	ttctatctacgcattgtat	59,1	TTCtatcta^{m}cgcattgTAT
60	ctatctacgcattgta	60,1	CTAtcta^{m}cgcattGTA
60	ctatctacgcattgta	60,2	CTATcta^{m}cgcatTGTA
61	tctatctacgcattgta	61,1	TCTatcta^{m}cgcattGTA
62	ttctatctacgcattgta	62,1	TTCtatcta^{m}cgcattGTA
63	ttctatctacgcattgt	63,1	TTCtatcta^{m}cgcatTGT
64	tcttctatctacgcattgt	64,1	TCttctatcta^{m}cgcattGT
65	ttcttctatctacgcattgt	65,1	Ttcttctatcta^{m}cgcattGT
66	ttcttctatctacgcattg	66,1	TTCttctatcta^{m}cgcatTG
67	ttctatctacgcattg	67,1	TTCtatcta^{m}cgcaTTG
68	cttctatctacgcatt	68,1	CTTCtatcta^{m}cgCATT
69	tcttctatctacgcatt	69,1	TCTtctatcta^{m}cgCATT
70	ttcttctatctacgcatt	70,1	TTCTtctatcta^{m}cgcATT
71	tcttctatctacgcat	71,1	TCTTctatcta^{m}cgCAT
72	ttcttctatctacgcat	72,1	TTCTtctatcta^{m}cgCAT
73	cttcttctatctacgcat	73,1	CTTCttctatcta^{m}cgcAT
74	ttcttctatctacgca	74,1	TTCttctatctacGCA
75	cttcttctatctacgca	75,1	CTTCttctatcta^{m}cgCA
76	gcttcttctatctacgca	76,1	Gcttcttctatcta^{m}cgCA
77	cttcttctatctacgc	77,1	CTtcttctatctACGC
78	gcttcttctatctacg	78,1	GCTtcttctatctACG
79	cgtggggcttcttcta	79,1	CGTggggcttcttCTA
80	tgacttggagaaaagcacaa	80,1	TGacttggagaaaagcacAA
81	ctgacttggagaaaagcac	81,1	CtgacttggagaaaagcAC
82	agagtcatcgtgctcc	82,1	AGAgtcat^{m}cgtgcTCC
83	aagtactttaatagctcaaa	83,1	AAGTactttaatagctCAAA
84	aagtactttaatagctcaa	84,1	AAGTactttaatagcTCAA
85	gaagtactttaatagctcaa	85,1	GAAGtactttaatagctCAA
86	tactttaatagctcaa	86,1	TACTttaatagcTCAA
87	aagtactttaatagctca	87,1	AAGTactttaatagcTCA
88	gaagtactttaatagctca	88,1	GAAGtactttaatagcTCA
89	agaagtactttaatagctc	89,1	AGAAgtactttaatagCTC
90	aagaagtactttaatagctc	90,1	AAGAagtactttaatagCTC
91	gaagtactttaatagct	91,1	GAAGtactttaatAGCT
92	taagaagtactttaatagct	92,1	TAAgaagtactttaatAGCT
93	agaagtactttaatagc	93,1	AGAAgtactttaaTAGC
94	taagaagtactttaatagc	94,1	TAAGaagtactttaaTAGC
95	gtaagaagtactttaatagc	95,1	GTaagaagtactttaaTAGC
96	taagaagtactttaatag	96,1	TAAGaagtactttaATAG
97	gtaagaagtactttaatag	97,1	GTAAgaagtactttaATAG

98	tgtaagaagtactttaatag	98,1	TGTAagaagtactttaATAG
99	aatgtgtaagaagtacttt	99,1	AATGtgtaagaagtaCTTT
100	caatgtgtaagaagtacttt	100,1	CAATgtgtaagaagtaCTTT
101	atgtgtaagaagtactt	101,1	ATGTgtaagaagtACTT
102	aatgtgtaagaagtactt	102,1	AATGtgtaagaagtACTT
103	caatgtgtaagaagtactt	103,1	CAATgtgtaagaagtACTT
104	gcaatgtgtaagaagtactt	104,1	GCaatgtgtaagaagtACTT
105	atgtgtaagaagtact	105,1	ATGtgtaagaagtACT
105	atgtgtaagaagtact	105,2	ATGTgtaagaagTACT
106	gcaatgtgtaagaagtact	106,1	GCAAtgtgtaagaagtACT
107	aatgtgtaagaagtac	107,1	AATGtgtaagaaGTAC
107	aatgtgtaagaagtac	107,2	AATgtgtaagaaGTAC
108	caatgtgtaagaagtac	108,1	CAATgtgtaagaaGTAC
109	gcaatgtgtaagaagtac	109,1	GCAatgtgtaagaaGTAC
110	caatgtgtaagaagta	110,1	CAAtgtgtaagaaGTA
110	caatgtgtaagaagta	110,2	CAAtgtgtaagaAGTA
110	caatgtgtaagaagta	110,3	CAATgtgtaagaAGTA
111	gcaatgtgtaagaagta	111,1	GCAatgtgtaagaAGTA
112	gcaatgtgtaagaagt	112,1	GCAatgtgtaagaAGT
		A	See below
		B	See below

For Compounds: Capital letters represent LNA nucleosides (beta-D-oxy LNA nucleosides were used), all LNA cytosines are 5-methyl cytosine, lower case letters represent DNA nucleosides, DNA cytosines preceded with a superscript ^{m} represent a 5-methyl C-DNA nucleoside. All internucleoside linkages are phosphorothioate internucleoside linkages. Compound A is disclosed as compound 143,1 and compound B is disclosed as compound 145,1 in EP16177508.5 and EP17170129.5, and are used as positive control compounds.

Example 1. Testing *in vitro* efficacy of LNA oligonucleotides in U251 cell line at a single concentration.

Identification of promising “hot spot” region for HTRA1. A library of n=231 HTRA1 LNA oligonucleotides were screened in U251 cell line at 5µM, 6 days of treatment. From this library, we identified a series of active oligonucleotides targeting human HTRA1 pre-mRNA between position 53113 - 53384 as shown in figure 1 (SEQ ID NO 116 or 117).

Human glioblastoma U251 cell line was purchased from ECACC and maintained as recommended by the supplier in a humidified incubator at 37°C with 5% CO_2. For assays, 15000 U251 cells/well were seeded in a 96 multi well plate in starvation media (media recommended by the supplier with the exception of 1% FBS instead of 10%). Cells were incubated for 24 hours before addition of oligonucleotides dissolved in PBS. Concentration of oligonucleotides: 5 µM. 3-4 days after addition of oligonucleotides, media was removed and new media (without oligonucleotide) was added. 6 days after addition of oligonucleotides, the cells were harvested. RNA was extracted using the PureLink Pro 96 RNA Purification kit (Ambion, according to the manufacturer’s instructions). cDNA was then synthesized using M-

MLT Reverse Transcriptase, random decamers RETROscript, RNase inhibitor (Ambion, according the manufacturer's instruction) with 100mM dNTP set PCR Grade (Invitrogen) and DNase/RNase free Water (Gibco). For gene expressions analysis, qPCR was performed using TagMan Fast Advanced Master Mix (2X) (Ambion) in a doublex set up. Following TaqMan primer assays were used for qPCR: HTRA1, Hs01016151_m1 (FAM-MGB) and house keeping gene, TBP, Hs4326322E (VIC-MGB) from Life Technologies. n= 2 independent biological replicates. The residual HTRA1 mRNA expression level in the table is shown as % of control (PBS-treated cells).

SEQ ID NO	CMP ID NO	mRNA level
19	19.1	16
31	31.1	2
38	38.1	9
47	47.1	3
78	78.1	4
79	79.1	21
82	82.1	35
107	107.1	17
110	110.1	24
112	112.1	15

Example 2.Testing *in vitro* efficacy of LNA oligonucleotides in U251 cell line at a single concentration.

The "hot spot" region 53113 – 53384 described in Example 1 was further validated in a new library of n=210 HTRA1 LNA oligonucleotides that were screened in U251 cell line at 5μM. n=33 LNA oligonucleotides were targeting human HTRA1 pre-mRNA between position 53113 – 53384 and these oligos were relatively active in comparison to the rest as shown in figure 2. The assay was performed as described in example 1. n= 2 independent biological replicates. The residual HTRA1 mRNA expression level is shown in the table as % of control (PBS-treated cells).

SEQ ID NO	CMP ID NO	mRNA level
19	19.2	3
19	19.3	16
23	23.1	1
23	23.2	44
28	28.1	2
28	28.2	19
31	31.2	0.4
31	31.3	9
35	35.1	24
35	35.2	5
37	37.1	0.3
37	37.2	7
38	38.2	1
38	38.3	17
39	39.1	5
39	39.2	17
40	40.1	6
40	40.2	34
45	45.1	4
45	45.2	23
47	47.2	1
47	47.3	4
51	51.1	6
51	51.2	13
56	56.1	2
56	56.2	12
60	60.1	2
60	60.2	5
105	105.1	30
105	105.2	76
107	107.2	25
110	110.2	27

110	110.3	20

Example 3. Testing *in vitro* efficacy of LNA oligonucleotides in U251 and ARPE19 cell lines at a single concentration.

The “hot spot” region 53113 – 53384 described in Example 1 and 2 was further validated in a new library of n=305 HTRA1 LNA oligonucleotides that were screened in U251 and ARPE19 cell lines at 5µM and 25µM, respectively. n=95 LNA oligonucleotides were targeting human HTRA1 pre-mRNA between position 53113 – 53384 and these oligos were relatively active in comparison to the rest as shown in figure 3.

Human retinal pigmented epithelium ARPE19 cell line was purchased by from ATCC and maintained in DMEM-F12 (Sigma, D8437), 10% FBS, 1% pen/strep in a humidified incubator at 37°C with 5% CO_2. The U251 cell line was described in example 1. For assays, 2000 U251 or ARPE19 cells/well were seeded in a 96 multi well plate in culture media recommended by the supplier. Cells were incubated for 2 hours before addition of oligonucleotides dissolved in PBS. Concentration of oligo was 5 and 25µM in U251 and ARPE19 cells, respectively. 4 days after addition of oligonucleotides, the cells were harvested. RNA extraction was performed as described in example 1, cDNA synthesis and qPCR were performed using qScript XLT one-step RT-qPCR ToughMix Low ROX, 95134-100 (Quanta Biosciences). Following TaqMan primer assays were used for U251 and ARPE19 cells in a douplex set up: HTRA1, Hs01016151_m1 (FAM-MGB) and house keeping gene, GAPDH, Hs4310884E (VIC-MGB). All primer sets were purchased from Life Technologies. n=1 biological replicate. The relative HTRA1 mRNA expression level in the table is shown as % of control (PBS-treated cells).

SEQ ID NO	CMP ID NO	ARPE19 mRNA level	U251 mRNA level
5	5,1	90	56
6	6,1	107	60
7	7,1	92	74
8	8,1	83	57
9	9,1	98	64
10	10,1	77	67
11	11,1	71	56
12	12,1	81	43
13	13,1	84	65
14	14,1	36	20

15	15,1	37	29
16	16,1	55	28
17	17,1	53	43
18	18,1	69	59
20	20,1	41	42
21	21,1	24	22
22	22,1	38	51
23	23,3	53	37
24	24,1	52	27
25	25,1	27	18
26	26,1	16	26
27	27,1	28	42
29	29,1	24	16
30	30,1	18	22
31	31,2	23	3
32	32,1	14	23
33	33,1	11	23
34	34,1	14	34
35	35,1	8	3
36	36,1	12	18
37	37,1	24	5
41	41,1	51	26
42	42,1	39	26
43	43,1	53	42
44	44,1	67	49
46	46,1	59	43
47	47,2	16	8
48	48,1	23	15
49	49,1	39	29
50	50,1	45	42
51	51,1	14	28
52	52,1	15	22
53	53,1	32	23
54	54,1	12	31
55	55,1	46	36
56	56,1	9	11
57	57,1	62	38
58	58,1	77	30
59	59,1	29	31
60	60,1	47	22
61	61,1	25	18
62	62,1	32	26
63	63,1	32	17

64	64,1	67	43
65	65,1	51	78
66	66,1	24	18
67	67,1	11	0,7
68	68,1	37	17
69	69,1	36	17
70	70,1	23	12
71	71,1	34	15
72	72,1	16	15
73	73,1	16	14
74	74,1	17	8
75	75,1	29	13
76	76,1	74	43
77	77,1	58	13
80	80,1	127	98
81	81,1	119	104
83	83,1	49	49
84	84,1	52	31
85	85,1	29	10
86	86,1	13	5
87	87,1	32	28
88	88,1	29	15
89	89,1	28	16
90	90,1	21	14
91	91,1	74	53
92	92,1	76	51
93	93,1	40	22
94	94,1	33	20
95	95,1	10	31
96	96,1	49	35
97	97,1	34	20
98	98,1	16	21
99	99,1	66	43
100	100,1	51	21
101	101,1	87	66
102	102,1	52	32
103	103,1	49	24
104	104,1	79	51
106	106,1	71	49
108	108,1	47	32
109	109,1	59	48
111	111,1	66	41
A	A	21	28

Example 4. Testing *in vitro* potency and efficacy of selected compounds in U251 and ARPE19 cell lines in a dose response curve.

The U251 and ARPE19 cell lines were described in example 1 and 3, respectively. The U251 assay was performed as described in Example 1. The ARPE19 assay was performed as follows: 5000 ARPE19 cells/well were seeded in a 96 multi well plate in culture media recommended by the supplier (with the exception of 5% FBS instead of 10%). Cells were incubated for 2 hour before addition of oligonucleotides dissolved in PBS. Concentration of oligonucleotides: from 50µM, half-log dilution, 8 points. 4 days after addition of oligonucleotides, the cells were harvested. RNA extraction, cDNA synthesis and qPCR were performed as described in Example 1. n=2 independent biological replicates. The EC50 value and the residual HTRA1 mRNA level at 50µM are shown in the table as % of control (PBS).

SEQ ID NO	**CMP ID NO**	**ARPE19**		**U251**	
		EC50 (µM)	mRNA level at max KD	EC50 (µM)	mRNA level at max KD
19	19.2	2.3	54	0.6	3
31	31.2	2.3	12	0.40	0.2
37	37.1	4.0	11	0.46	0.2
38	38.2	7.4	19	0.70	0.2
47	47.2	4.6	8	0.62	0.2
23	23.1	6.8	25	0.80	1
35	35.1	3.5	4	0.38	0.1

Example 5, Testing *in vitro* potency and efficacy of selected compounds in U251 and ARPE19 cell lines in a dose response curve.

The assays were performed as described in Example 3. Concentration of oligonucleotides: from 50µM, half-log dilution, 8 points. n=2 and n=1 independent biological replicates for U251 and ARPE19, respectively. The EC50 value and the residual HTRA1 mRNA level at 50µM are shown in the table as % of control (PBS).

SEQ ID NO	**CMP ID NO**	**ARPE19**	**U251**

		EC50 (µM)	mRNA level at max KD	EC50 (µM)	mRNA level at max KD
31	31.2	3.2	15	0.90	0.38
37	37.1	11	22	1.3	0.75
47	47.2	2.8	13	0.89	0.83
35	35.1	2.6	8.3	0.79	0.40
85	85.1	8.2	24	0.48	3.6
90	90.1	3.3	16	0.50	2.2
95	95.1	0.55	28	1.0	4.1
98	98.1	1.7	24	0.86	4.5
30	30.1	1.2	20	1.00	2.2
32	32.1	1.7	22	1.6	1.4
26	26.1	1.1	14	1.4	0.45
33	33.1	0.75	28	0.66	0.63
34	34.1	0.44	21	0.80	0.35
36	36.1	5.2	28	1.1	0.80
52	52.1	2.1	28	1.1	1.1
54	54.1	0.79	25	0.62	1.4
72	72.1	2.9	33	0.71	1.7
70	70.1	1.9	36	0.52	1.5
74	74.1	0.78	24	0.35	1.1
73	73.1	0.78	11	0.59	0.33
75	75.1	1.7	22	0.60	0.80
86	86.1	1.7	6.5	0.47	0.65
67	67.1	0.59	4.3	0.38	0.23
A	A	6.5	24	1.2	3.6
B	B	8.1	30	0.79	4.2

Example 6. Testing *in vitro* potency and efficacy of selected compounds in U251 cell line in a dose response curve.

The assay was performed as described in Example 3. Concentration of oligonucleotides: from 50µM, half-log dilution, 8 points. n=2 independent biological replicates.The EC50 value and the residual HTRA1 mRNA level at 50µM are shown in the table as % of control (PBS).

SEQ ID NO	**CMP ID NO**	**U251**

		EC50 (µM)	mRNA level at max KD
38	38.1	3.3	3
78	78.1	0.58	2
31	31.2	1.2	0.4
37	37.1	1.6	0.6
47	47.2	0.91	0.6
35	35.1	0.52	0.3
39	39.1	0.82	3
40	40.1	1.3	4
45	45.1	0.89	3
51	51.1	2.7	2
56	56.1	2.7	1
60	60.1	2.1	1
37	37.2	8.0	24
31	31.3	2.8	10
35	35.2	1.3	4
47	47.3	0.86	4
60	60.2	1.3	3
26	26.1	0.52	1
73	73.1	0.24	0.7
86	86.1	0.27	0.9
67	67.1	0.46	0.2
A	A	1.1	3.1
B	B	1.2	3.3

Example 7. Testing *in vitro* potency and efficacy of selected compounds in U251 cell line in a dose response curve.

The ARPE19 cell line was described in example 3. For assays, ARPE19 cells, 24000 cells/well were seeded in 100µL in a 96 multi well plate in starvation media (culture media as recommended by the supplier with the exception of 1% FBS instead of 10%). Cells were incubated for 2 hour before addition of oligonucleotides dissolved in PBS. Concentration of oligonucleotides: from 50µM, half-log dilution, 8 points. At day 4 and 7 after addition of oligonucleotide compounds 75µL fresh starvation media without oligonucleotides was added to the cells (without removing the old media). RNA extraction, cDNA synthesis and qPCR were performed as described in Example 3. n=2 independent biological replicates. The EC50 value and the residual HTRA1 mRNA level at 50µM are shown in the table as % of control (PBS).

SEQ ID NO	CMP ID NO	ARPE19	
		EC50 (µM)	mRNA level at max KD
30	30,1	0,31	1
33	33,1	0,60	0,5
35	35,1	0,58	1
35	35,2	2,7	4
36	36,1	0,97	2
37	37,1	1,0	4
40	40,1	3,8	21
45	45,1	1,6	3
56	56,1	5,8	2
67	67,1	0,84	1
73	73,1	0,36	2
86	86,1	0,59	4
90	90,1	0,75	5
95	95,1	0,74	3
A	A	1,3	1,9
B	B	0,84	1,5

Example 8.

Testing in vitro efficacy in human primary RPE cells.

Human primary Retinal Pigmented Epithelium (hpRPE) cells were purchased from Sciencell (Cat# 6540). For assays, 5000 hpRPE cells/well were seeded in a Laminin (Laminin 521, BioLamina Cat# LN521-03) coated 96 multi well plate in culture media (EpiCM, Sciencell Cat# 4101). They were expanded with this media for one week and differentiated using the following media for 2 weeks : MEM Alpha media (Sigma Cat# M-4526) supplemented with N1 supplement (Sigma Cat# N-6530), Glutamine-Penicillin-Streptomycin (Sigma Cat# G-1146), Non Essential Amino Acid (NEAA, Sigma Cat# M-7145), Taurine (Sigma Cat# T-0625), Hydrocortisone (Sigma Cat# H-03966), Triiodo-thyronin (Sigma Cat# T-5516) and Bovine Serum Albumin (BSA, Sigma Cat# A-9647). Cells were cultured in a humidified incubator at 37°C with 5% CO_2.

On the day of the experiment, cells were incubated for 1 hour with fresh differentiation media before addition of oligonucleotides. These were dissolved in PBS and applied on cells at day 0 and day 4. On day 7, the media was changed, and on day 10 cells were harvested with 50µl of RLT buffer with β-mercapto-ethanol (Qiagen Cat# 79216). The extraction of the RNA was performed according to the user's manual of the Qiagen RNeasy Mini Kit (Cat# 74104; Lot 151048073) including DNase I treatment (Cat# 79254; Lot 151042674). RNA quality control was performed with the Agilent Bioanalyzer Nano Kit (Agilent; Cat# 5067-1511; Lot 1446). Reverse transcription of total RNA into cDNA (cDNA synthesis) was performed using the High Capacity cDNA Reverse Transcription Kit (based on random hexamer oligonucleotides), according to the manufacturer's instructions (Thermo Fisher Scientific, Cat# 4368814; Lot 00314158). The measurement of the cDNA samples was carried out in triplicates, in a 384-well plate format on the 7900HT real-time PCR instrument (Thermo Fisher Scientific). The following TaqMan primer assays were used for qPCR: HTRA1, Hs01016151_m1 and Hs00170197_m1, housekeeping genes, GAPDH, Hs99999905_m1 and PPIA, Hs99999904_m1, from Life Technologies. n=3 biological replicates. The residual HTRA1 mRNA expression level is shown in figure 4 and the following table as % of control (PBS).

SEQ ID NO	**CMP ID NO**	**mRNA level**		
		50µM	10µM	1µM
37	37.1	32	60	77
35	35.1	9	20	64
85	85.1	22	49	46
90	90.1	22	39	61
95	95.1	20	47	74
98	98.1	14	27	55
30	30.1	19	41	75
32	32.1	14	25	53
26	26.1	21	39	73
33	33.1	18	70	58
34	34.1	16	35	63
52	52.1	13	31	61
54	54.1	7	20	53
72	72.1	7	18	56
70	70.1	8	18	53
74	74.1	3	12	40
73	73.1	13	13	65
75	75.1	7	15	55
86	86.1	8	27	70

67	67.1	8	27	77
A	A	31	57	72

Example 9. Cynomolgus monkey *in vivo* pharmacokinetics and pharmacodynamics study, 21 days of treatment, intravitreal (IVT) injection, single dose.

Knock down was observed for 3 HTRA1 LNA oligonucleotides targeting the "hotspot" in human HTRA1 pre-mRNA between position 53113 - 53384 both at mRNA in the retina and at protein level in the retina and in the vitreous (see figure 5)

Animals

All experiments were performed on Cynomolgus monkeys (*Macaca fascicularis*).

Four animals were included in each group of the study, 20 in total.

Compounds and dosing procedures

Buprenorphine analgesia was administered prior to, and two days after test compound injection. The animals were anesthetized with an intramuscular injection of ketamine and xylazine. The test item and negative control (PBS) were administered intravitreally in both eyes of anesthetized animals (50 µL per administration) on study day 1 after local application of tetracaine anesthetic.

Euthanasia

At the end of the in-life phase (Day 22) all monkeys were euthanized by intraperitoneal an overdose injection of pentobarbital.

Oligo content measurement and quantification of Htra1 RNA expression by qPCR

Immediately after euthanasia, eye tissues were quickly and carefully dissected out on ice and stored at -80°C until shipment. Retina sample was lysed in 700 µL MagNa Pure 96 LC RNA Isolation Tissue buffer and homogenized by adding 1 stainless steel bead per 2 ml tube 2 x 1,5 min using a precellys evolution homogenizer followed by 30 min incubation at RT. The samples were centrifuged, 13000 rpm, 5 min. Half was set aside for bioanalysis and for the other half, RNA extraction was continued directly.

For bioanalysis, the samples were diluted 10-50 fold for oligo content measurements with a hybridization ELISA method. A biotinylated LNA-capture probe and a digoxigenin-conjugated LNA-detection probe (both 35nM in 5xSSCT, each complementary to one end of the LNA oligonucleotide to be detected) was mixed with the diluted homogenates or relevant standards, incubated for 30 minutes at RT and then added to a streptavidine-coated ELISA plates (Nunc cat. no. 436014).

The plates were incubated for 1 hour at RT, washed in 2xSSCT (300mM sodium chloride, 30mM sodium citrate and 0,05% v/v Tween-20, pH 7.0) The captured LNA duplexes were detected using an anti-DIG antibodies conjugated with alkaline phosphatase (Roche Applied Science cat. No. 11093274910) and an alkaline phosphatase substrate system (Blue Phos substrate, KPL product code 50-88-00). The amount of oligo complexes was measured as absorbance at 615 nm on a Biotek reader.

For RNA extraction, cellular RNA large volume kit (05467535001, Roche) was used in the MagNA Pure 96 system with the program: Tissue FF standard LV3.1 according to the instructions of the manufacturer, including DNAse treatment. RNA quality control and concentration were measured with an Eon reader (Biotek). The RNA concentration was normalized across samples, and subsequent cDNA synthesis and qPCR was performed in a one-step reaction using qScript XLT one-step RT-qPCR ToughMix Low ROX, 95134-100 (Quanta Biosciences). The following TaqMan primer assays were used in singplex reactions: Htra1, Mf01016150_, Mf01016152_m1 and Rh02799527_m1 and housekeeping genes, ARFGAP2, Mf01058488_g1 and Rh01058485_m1, and ARL1, Mf02795431_m1, from Life Technologies. The qPCR analyses were run on a ViiA7 machine (Life Technologies).

Eyes/group: n=3 eyes. Each eye was treated as an individual sample. The relative Htra1 mRNA expression level is shown as % of control (PBS).

Histology

Eyeballs were removed and fixed in 10% neutral buffered formalin for 24 hours, trimmed and embedded in paraffin.

For ISH analysis, sections of formalin-fixed, paraffin-embedded cyno retina tissue 4µm thick were processed using the fully automated Ventana Dicovery ULTRA Staining Module (Procedure: mRNA Discovery Ultra Red 4.0 – v0.00.0152) using the RNAscope 2.5 VS Probe-Mmu-HTRA1, REF 486979, Advanced Cell Diagnostics, Inc.. Chromogen used is Fastred, Hematoxylin II counterstain.

HTRA1 protein quantification using a plate-based immunoprecipitation mass spectrometry (IP-MS) approach

Sample preparation, Retina

Retinas were homogenized in 4 volumes (w/v) of RIPA buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 0.25% deoxycholic acid, 1% NP-40, 1mM EDTA, Millipore) with protease inhibitors (Complete EDTA-free, Roche) using a Precellys 24 (5500, 15 s, 2 cycles). Homogenates were centrifuged (13,000 rpm, 3 min) and the protein contents of the supernatants determined (Pierce BCA protein assay)

Sample preparation, Vitreous

Vitreous humors (300 µl) were diluted with 5x RIPA buffer (final concentration: 50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 0.25% deoxycholic acid, 1% NP-40, 1mM EDTA) with protease inhibitors (Complete EDTA-free, Roche) and homogenized using a Precellys 24 (5500, 15 s, 2 cycles). Homogenates were centrifuged (13,000 rpm, 3 min) and the protein contents of the supernatants determined (Pierce BCA protein assay)

Plate-based HTRA1 immunoprecipitation and tryptic digest

A 96 well plate (Nunc MaxiSorp) was coated with anti-HTRA1 mouse monoclonal antibody (R&D MAB2916, 500 ng/well in 50 µl PBS) and incubated overnight at 4ºC. The plate was washed twice with PBS (200 µl) and blocked with 3% (w/v) BSA in PBS for 30 min at 20 ºC followed by two PBS washes. Samples (75 µg retina, 100 µg vitreous in 50 µl PBS) were randomized and added to the plate followed by overnight incubation at 4 ºC on a shaker (150 rpm). The plate was then washed twice with PBS and once with water. 10 mM DTT in 50 mM TEAB (30 µl) were then added to each well followed by incubation for 1 h at 20 ºC to reduce cysteine sulfhydryls. 150 mM iodoacetamide in 50 mM TEAB (5 µl) were then added to each well followed by incubation for 30 min at 20 ºC in the dark in order to block cysteine sulfhydryls. 10 µl Digestion solution were added to each well (final concentrations: 1.24 ng/µl trypsin, 20 fmol/µl BSA peptides, 26 fmol/µl isotope-labeled HTRA1 peptides, 1 fmol/µl iRT peptides, Biognosys) followed by incubation overnight at 20 ºC.

HTRA1 peptide quantification by targeted mass spectrometry (selected reaction monitoring, SRM)

Mass spectrometry analysis was performed on an Ultimate RSLCnano LC coupled to a TSQ Quantiva triple quadrupole mass spectrometer (Thermo Scientific). Samples (20 µL) were injected directly from the 96 well plate used for IP and loaded at 5 µL/min for 6 min onto a Acclaim Pepmap 100 trap column (100 µm x 2 cm, C18, 5 µm, 100 Å, Thermo Scientific) in loading buffer (0.5% v/v formic acid, 2% v/v ACN). Peptides were then resolved on a PepMap Easy-SPRAY analytical column (75 µm x 15 cm, 3 µm, 100 Å, Thermo Scientific) with integrated electrospray emitter heated to 40ºC using the following gradient at a flow rate of 250 nL/min: 6 min, 98% buffer A (2% ACN, 0.1% formic acid), 2% buffer B (ACN + 0.1% formic acid); 36 min, 30% buffer B; 41 min, 60% buffer B; 43 min, 80% buffer B; 49 min, 80% buffer B; 50 min, 2% buffer B. The TSQ Quantiva was operated in SRM mode with the following parameters: cycle time, 1.5 s; spray voltage, 1800 V; collision gas pressure, 2 mTorr; Q1 and Q3 resolution, 0.7 FWHM; ion transfer tube temperature 300 ºC. SRM transitions were acquired for the HTRA1 peptide “LHRPPVIVLQR” and an isotope labelled (L-[U-13C, U-15N]R) synthetic version, which was used an internal standard.

Data analysis was performed using Skyline version 3.6.

Western blot

Dissected retina sample in 0.5 Precellyses tubes (CK14_0.5ml, Bertin Technologies) were lysed and homogenized in RIPA lysis buffer (20-188, Milipore) with protease inhibitors (Complete EDTA-free Proteases-Inhibitor Mini, 11 836 170 001, Roche).

Vitreous sample were added to a 0.5 Precellyses tubes (CK14_0.5ml, Bertin Technologies) were lysed and homogenized in 1/4x RIPA lysis buffer (20-188, Milipore) with protease inhibitors (Complete EDTA-free Proteases-Inhibitor Mini, 11 836 170 001, Roche).

Samples (retina 20 µg protein, vitreous 40 µg protein) were analyzed on 4-15% gradient gel (#567-8084 Bio-Rad) under reducing conditions and transferred on Nitrocellulose (#170-4159 Bio-Rad) using a Trans-Blot Turbo Device from Bio-Rad.
Primary antibodies: Rabbit anti human HTRA1 (SF1) was a kind gift of Sascha Fauser (University of Cologne), mouse anti human Gapdh (#98795 Sigma-Aldrich). Secondary antibody: goat anti rabbit 800CW and goat anti mouse 680RD were from Li-Cor
Blot was imaged and analyzed on an Odyssee CLX from Li-Cor.

Example 10 – Cynomolgus monkey in vivo Assessment: HTRA1 protein determination in aqueous humor and comparison to HTRA1 mRNA and protein inhibition in retina.
Experimental Methodology: See above example. Aqueous humor samples were taken and samples were prepared as according to example 9 vitreous humor samples. Cynomolgus Monkey Aqueous humor samples (AH) were analyzed with a size-based assay on a Analytical Methodology: Capillary Electrophoresis System (Peggy Sue™, Proteinsimple)
Samples were thawed on ice and used undiluted. For quantification, recombinant HTRA1-S328A mutant (Origene #TP700208). Preparation was as described by the provider.
Primary rabbit anti- human HTRA Antibody SF1 was provided by Prof. Dr. Sascha Fauser and used diluted 1:300. All other reagents were from Proteinsimple.
Samples were processed in technical triplicate, calibration curve in duplicate using a 12 -230 kDa Separation module. Area under the peak was computed and analyzed using Xlfit (IDBS software).

Results

Figure numbering	Compound ID	mRNA_retina	protein_retina	protein_AH
PBS	-	82	101	95
PBS	-	107	99	118
# 15,3	B	56	73	51
# 15,3	B	52	53	68
# 17	# 73,1	23	41	47
# 17	# 73,1	26	44	44
# 18	# 86,1	32	29	44
# 18	# 86,1	23	28	64
# 19	# 67,1	34	39	44
# 19	# 67,1	34	61	42

Note – the compound IDs shown in figures 12 – 14 utilize a different numbering system as the rest of the examples. The above table provides the key to the numbering used figures 12 -14 as compared to that used in the previous examples and elsewhere herein.

Figure 12A shows a visualization of the HTRA1 protein levels in the aqueous humor of monkeys administered with **c**ompounds B and #73,1, with samples taken at days 3, 8, 15, and 22 post-injection. Figure 12B provides the calibration curve used in calculating HTRA1 protein levels. Figure 12C provides the calculated HTRA1 levels from aqueous humor from individual animal was plotted against time post injection.

Figure 13 illustrates a direct correlation between the level of HTRA1 protein in the aqueous humor and the level of HTRA1 mRNA in the retina. Aqueous humor HTRA1 protein levels may therefore be used as a biomarker for HTRA1 retina mRNA levels or HTRA1 retinal mRNA inhibition.

Figure 14 illustrates that there is also a correlation between HTRA1 protein levels in retina and the HTRA1 protein levels in aqueous humor, although the correlation was not, in this experiment, as strong as the correlation between HTRA1 mRNA inhibition in the retina and HTRA1 protein levels in the aqueous humor, indicating that aqueous humor HTRA1 protein levels are particularly suited as biomarker for HTRA1 mRNA antagonists.

CLAIMS

1. An antisense oligonucleotide of 10 – 30 nucleotides in length, wherein said antisense oligonucleotide targets a HTRA1 nucleic acid, and comprises a contiguous nucleotide region of 10 – 22 nucleotides which are at least 90% such as 100% complementarity to SEQ ID NO 113.
2. The antisense oligonucleotide according to claim 1, wherein the contiguous nucleotide region is fully complementary to a sequence selected from the group consisting of SEQ ID No 231, 186, 192 and 205.
3. The antisense oligonucleotide according to claim 1 or 2, wherein the contiguous nucleotide region comprises at least 12 contiguous nucleotides fully complementary to a sequence selected from the group consisting of SEQ ID NO 124 – 230.
4. The antisense oligonucleotide according to any one of claims 1 – 3, wherein the contiguous nucleotide region comprises at least 12 contiguous nucleotides which are fully complementary to SEQ ID NO 113.
5. The antisense oligonucleotide according to any one of claims 1 – 4, wherein the contiguous nucleotide region comprises at least 14 contiguous nucleotides which are fully complementary to SEQ ID NO 113.
6. The antisense oligonucleotide according to any one of claims 1 – 5, wherein the contiguous nucleotide region of the oligonucleotide consists or comprises of a sequence selected from any one of SEQ ID NO 67, 73 and 86, or at least 12 contiguous nucleotides thereof.
7. The antisense oligonucleotide according to any one of claims 1 – 6 wherein the contiguous nucleotide region of the oligonucleotide comprises one or more 2' sugar modified nucleosides such as one or more 2' sugar modified nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.
8. The antisense oligonucleotide according to any one of claims 1 - 7, where the contiguous nucleotide region of the oligonucleotide comprises at least one modified internucleoside linkage, such as one or more phosphorothioate internucleoside linkages, or such as all the internucleoside linkages within the contiguous nucleotide region are phosphorothioate internucleoside linkages.
9. The antisense oligonucleotide according to any one of claims 1 - 8, wherein the oligonucleotide or contiguous nucleotide sequence thereof is or comprises a gapmersuch as a gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise 1 - 7 sugar modified nucleosides and G is a region 6 - 16 nucleosides which is

capable of recruiting RNaseH, wherein the nucleosides of regions F and F’ which are adjacent to region G are sugar modified nucleosides.

10. The antisense oligonucleotide according to claim 9, wherein at least one of or both of region F and F’ each comprise at least one LNA nucleoside.
11. The antisense oligonucleotide according to any one of claims 1 – 10, wherein the contiguous nucleotide region is selected from the group selected from:

    TTCtatctacgcaTTG (SEQ ID NO 67),

    CTTCttctatctacgcAT (SEQ ID NO 73), and

    TACTttaatagcTCAA (SEQ ID NO 86);

    wherein capital letters are LNA nucleotides, and lower case letters are DNA nucleosides, and cytosine residues are optionally 5-methyl cytosine.
12. The antisense oligonucleotide according to claim 10 or 11, wherein the LNA nucleosides are beta-D-oxy LNA nucleosides.
13. The antisense oligonucleotide according to any one of claims 1 – 12, wherein the internucleoside linkages between the nucleotides of the contiguous nucleotide region are all phosphorothioate internucleotides linkages.
14. An oligonucleotide comprising or consisting of an oligonucleotide selected from the group consisting of :

    $T_sT_s{}^mC_st_sa_st_sc_st_sa_s{}^mc_sg_sc_sa_sT_sT_sG$ (SEQ ID NO 67,1),

    ${}^mC_sT_sT_s{}^mC_st_st_sc_st_sa_st_sc_st_sa_s{}^mc_sg_sc_sA_sT$ (SEQ ID NO 73,1), and

    $T_sA_s{}^mC_sT_st_st_sa_sa_st_sa_sg_sc_sT_s{}^mC_sA_sA$ (SEQ ID NO 86,1);

    wherein capital letters represent beta-D-oxy LNA nucleosides, lower case letters are DNA nucleosides, subscript s represents a phosphorothioate internucleoside linkage, and ${}^mC$ represent 5 methyl cytosine beta-D-oxy LNA nucleosides, and ${}^mc$ represents 5 methyl cytosine DNA nucleosides.
15. A pharmaceutically acceptable salt of any one of the oligonucleotides of claims 1 – 14.
16. A conjugate comprising the oligonucleotide according to any one of claims 1 – 15, and at least one conjugate moiety covalently attached to said oligonucleotide.
17. A pharmaceutical composition comprising the oligonucleotide of claim 1 – 15 or the conjugate of claim 16 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
18. An *in vivo* or *in vitro* method for modulating HTRA1 expression in a target cell which is expressing HTRA1, said method comprising administering an oligonucleotide of any one of claims 1 – 15 or the conjugate according to claim 16 or the pharmaceutical composition of claim 17 in an effective amount to said cell.
19. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide of any one of claims 1 – 15 or

the conjugate according to claim 16 or the pharmaceutical composition of claim 17 to a subject suffering from or susceptible to the disease.

20. The oligonucleotide of any one of claims 1 – 15 or the conjugate according to claim 16 or the pharmaceutical composition of claim 17 for use in medicine.

21. The oligonucleotide of any one of claims 1 – 15 or the conjugate according to claim 16 or the pharmaceutical composition of claim 17 for use in the treatment or prevention of a disease is selected from the group consisting of macular degeneration (such as wetAMD, dryAMD, geographic atrophy, intermediate dAMD, diabetic retinopathy), Parkinson's disease, Alzhiemer's disease, Duchenne muscular dystrophy, arthritis, such as osteoarthritis, and familial ischemic cerebral small-vessel disease.

22. Use of the oligonucleotide of claim 1 – 15 or the conjugate according to claim 16 or the pharmaceutical composition of claim 17, for the preparation of a medicament for treatment or prevention of a disease is selected from the group consisting of macular degeneration (such as wetAMD, dryAMD, geographic atrophy, intermediate dAMD, diabetic retinopathy), Parkinson's disease, Alzhiemer's disease, Duchenne muscular dystrophy, arthritis, such as osteoarthritis, and familial ischemic cerebral small-vessel disease.

23. The use or method according to any one of claims 19 – 22 wherein the method or use is for the treatment of macular degeneration.

FIGURES

Figure 1

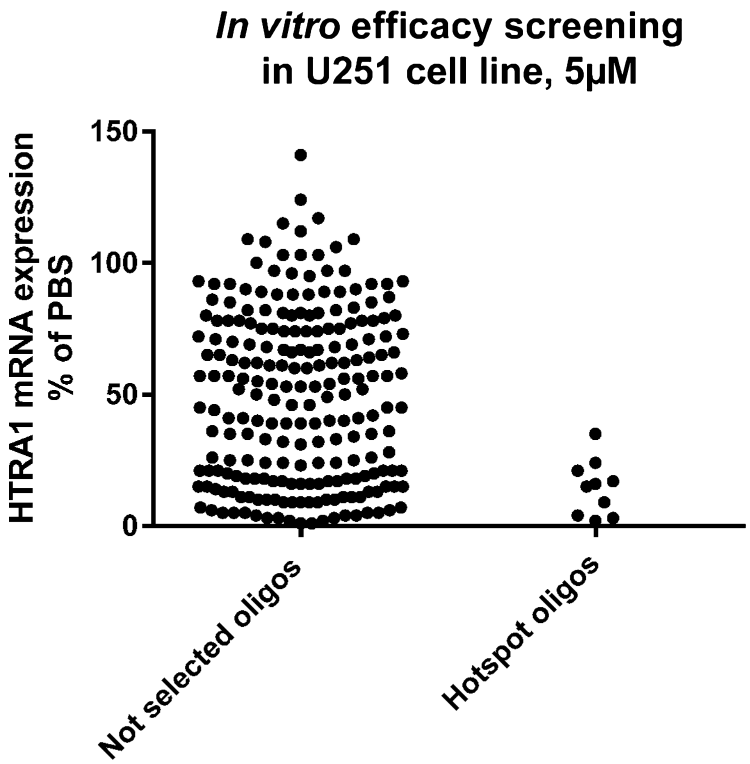


Figure 2

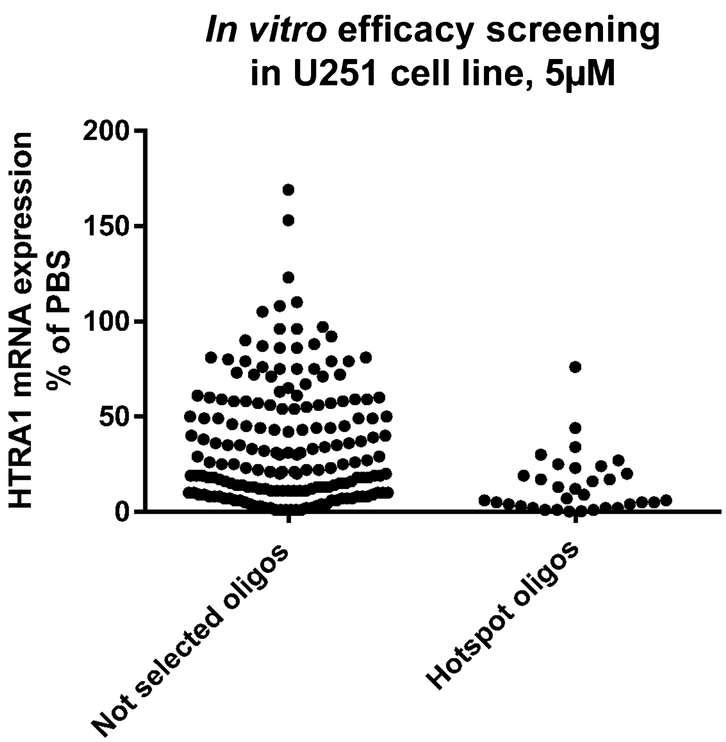
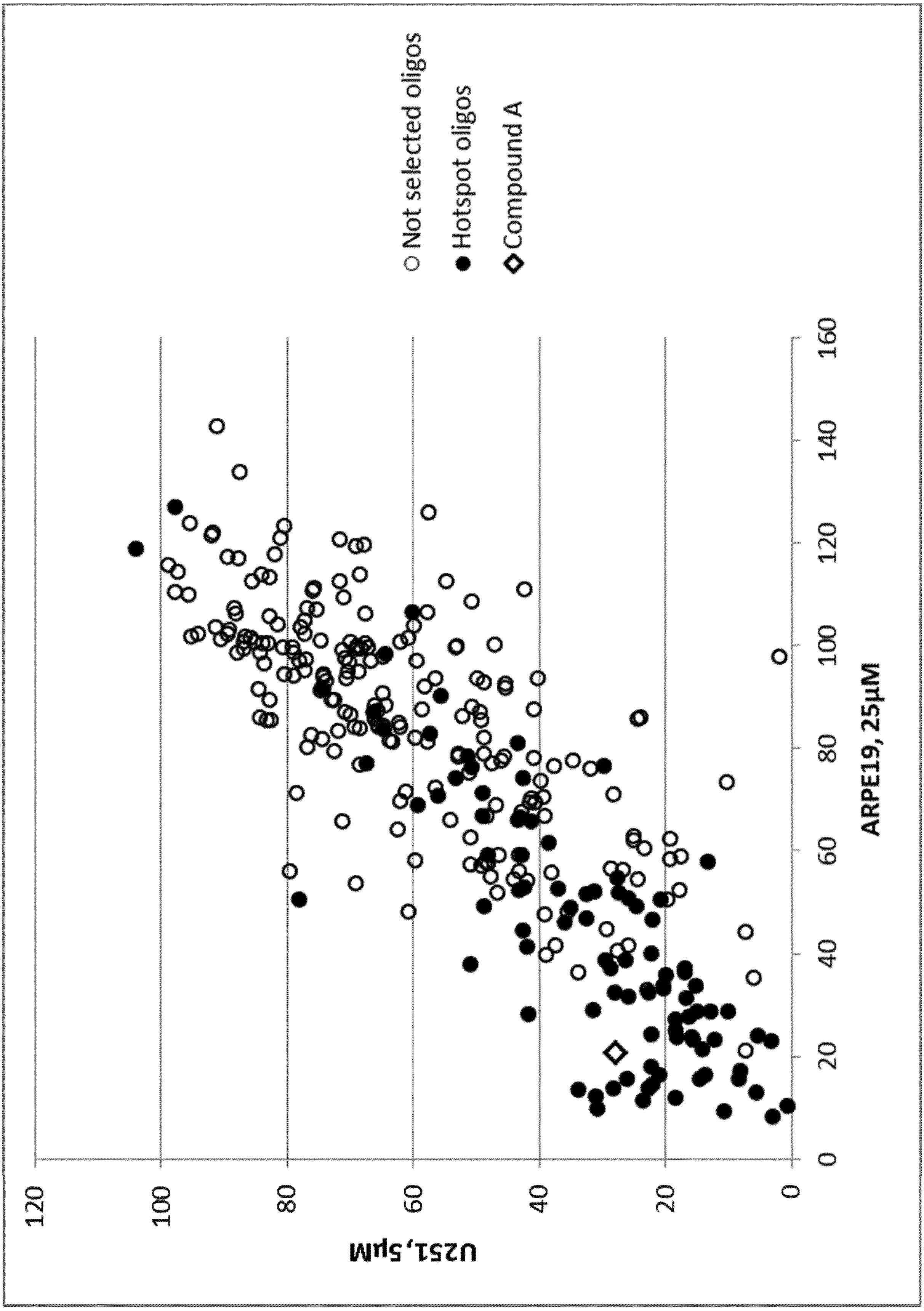


Figure 3


Not selected oligos
Hotspot oligos
Compound A
ARPE19, 25µM
U251, 5µM
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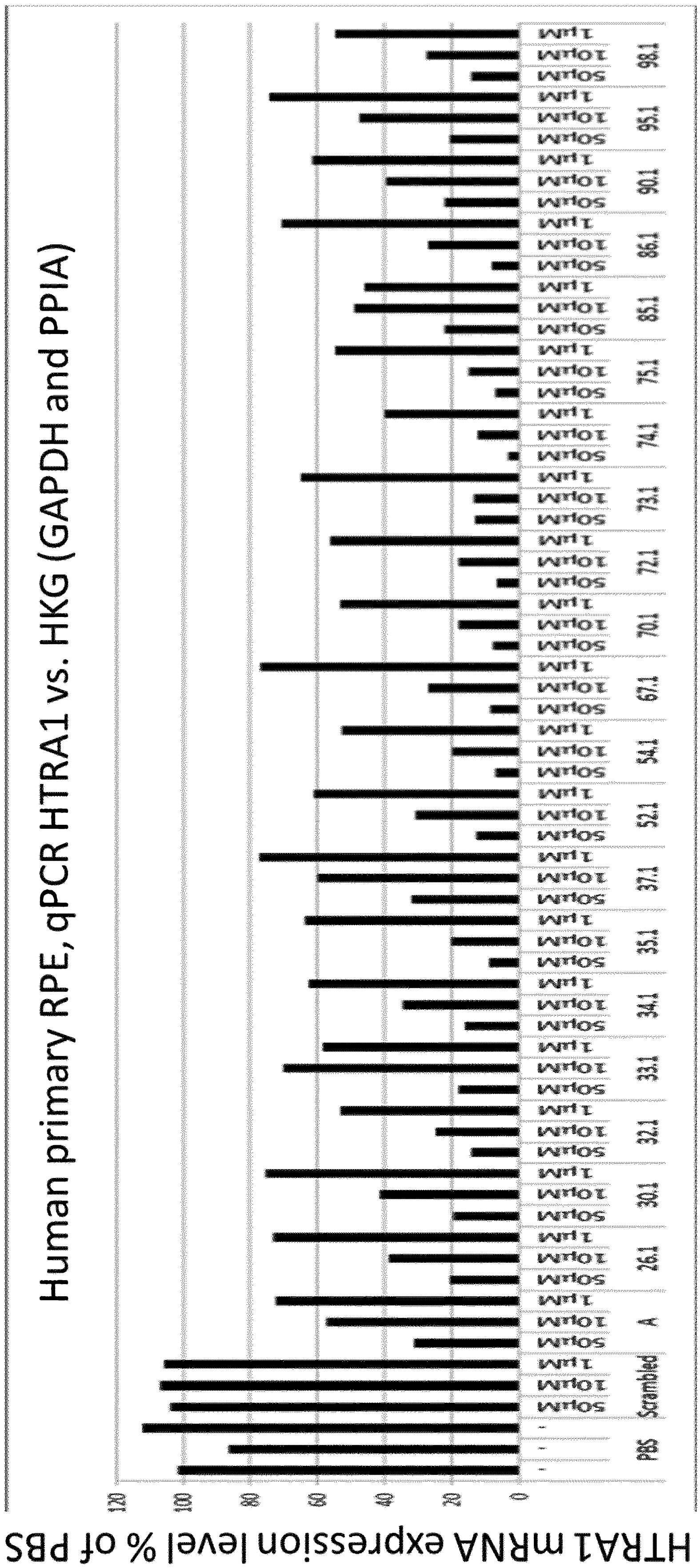
20
40
60
80
100
120
140
160
0
20
40
60
80
100
120

Figure 4


Human primary RPE, qPCR HTRA1 vs. HKG (GAPDH and PPIA)
HTRA1 mRNA expression level % of PBS
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20
40
60
80
100
120
PBS
Scrambled
A
26.1
30.1
32.1
33.1
34.1
35.1
37.1
52.1
54.1
67.1
70.1
72.1
73.1
74.1
75.1
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86.1
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50µM
10µM
1µM

Figure 5A

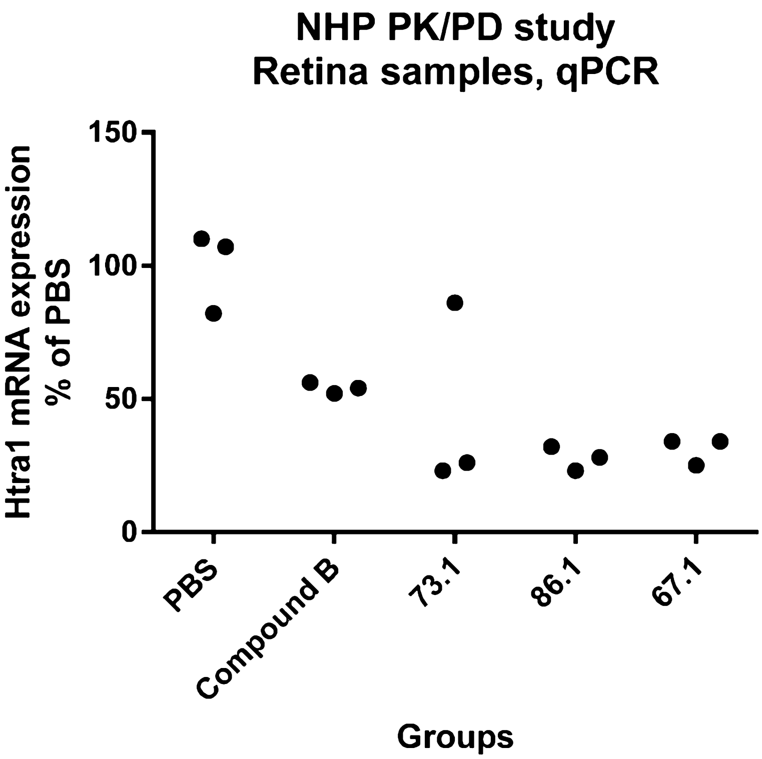
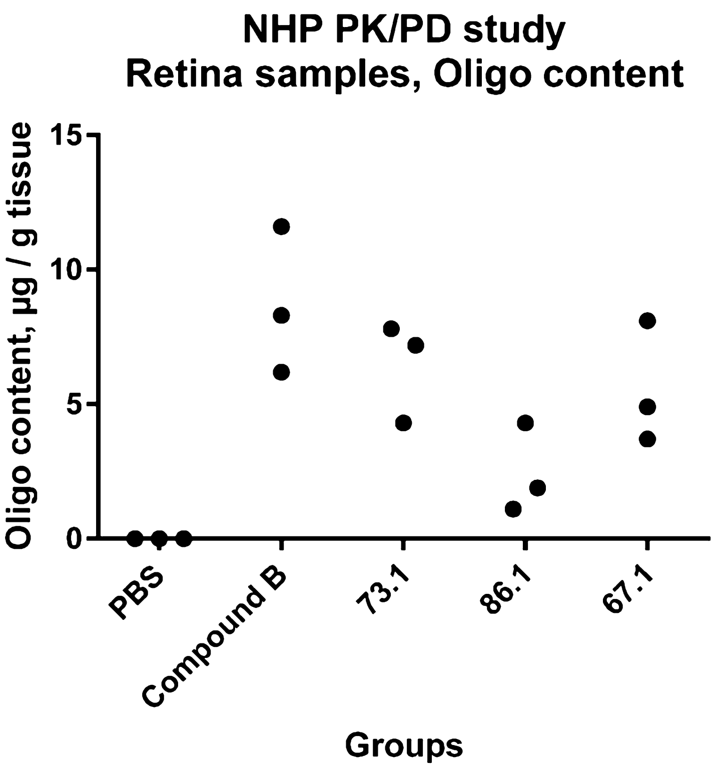


Figure 5B



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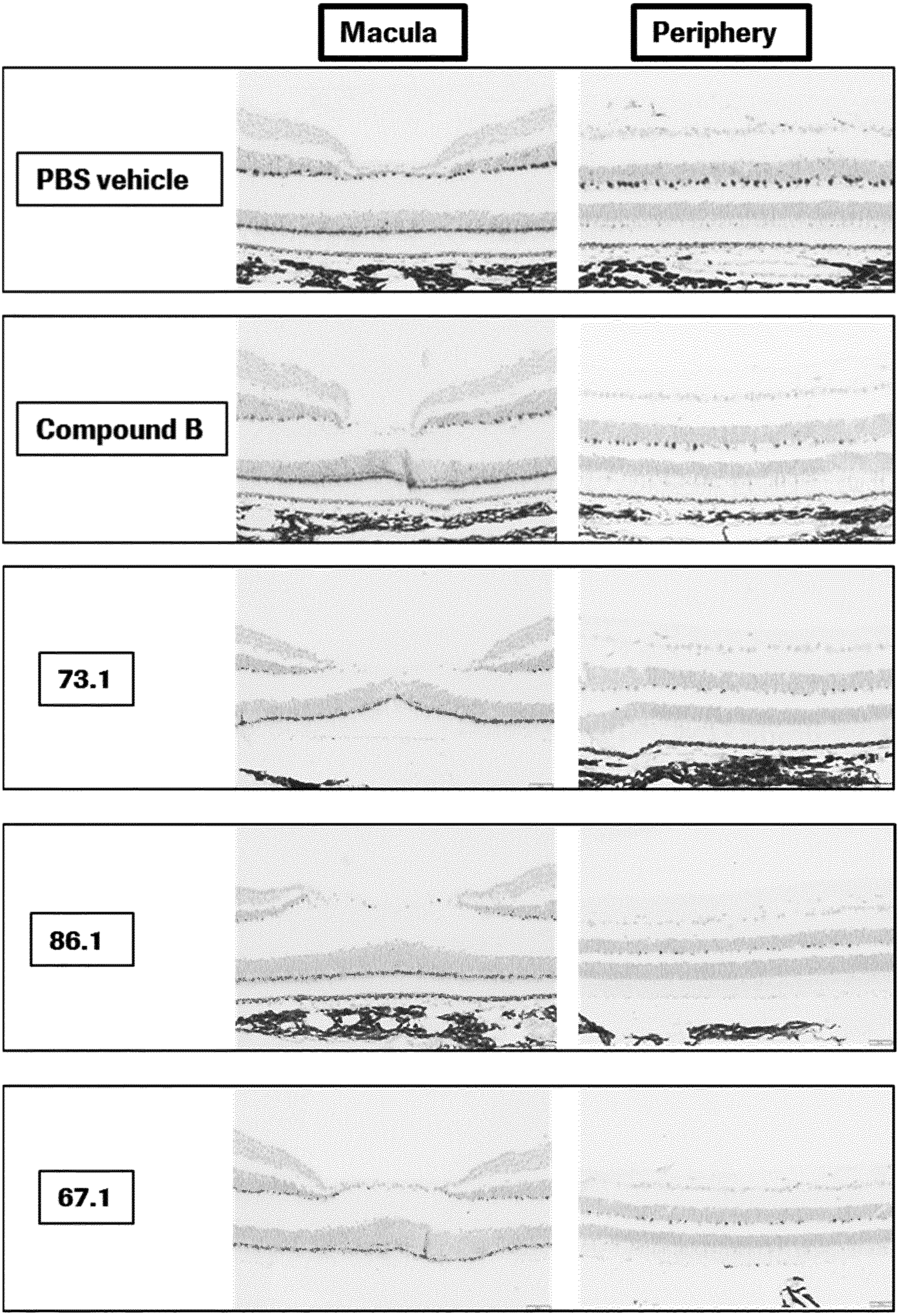

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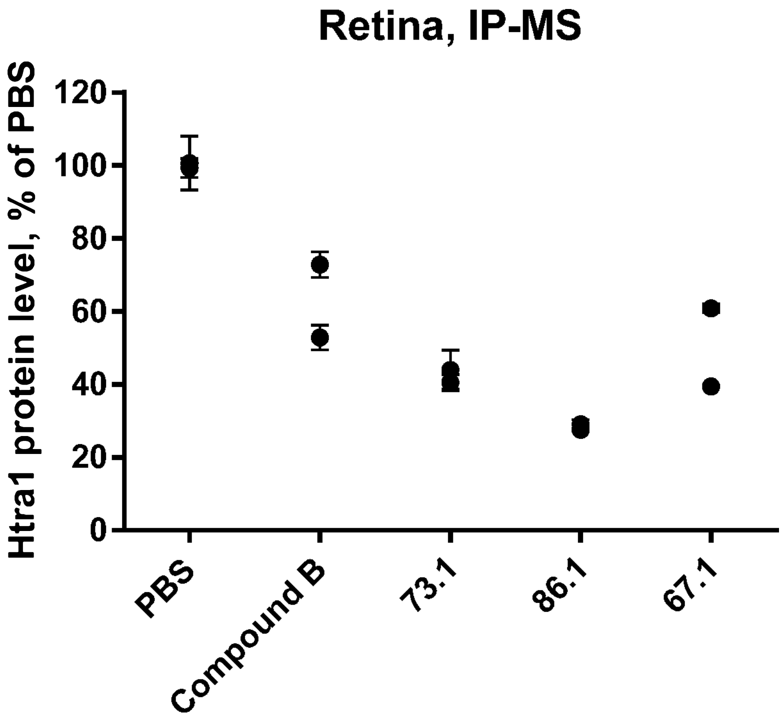

Figure 5E

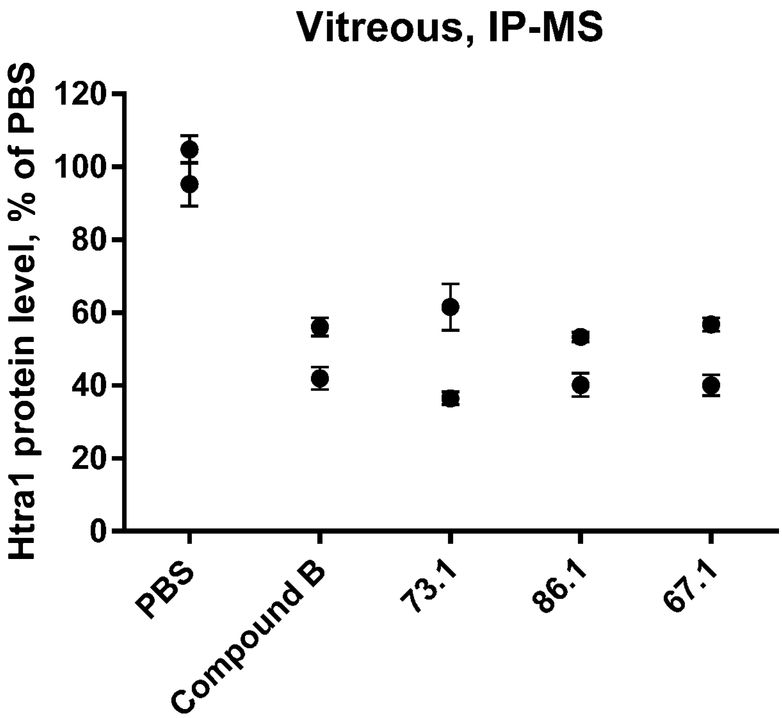

Figure 5F

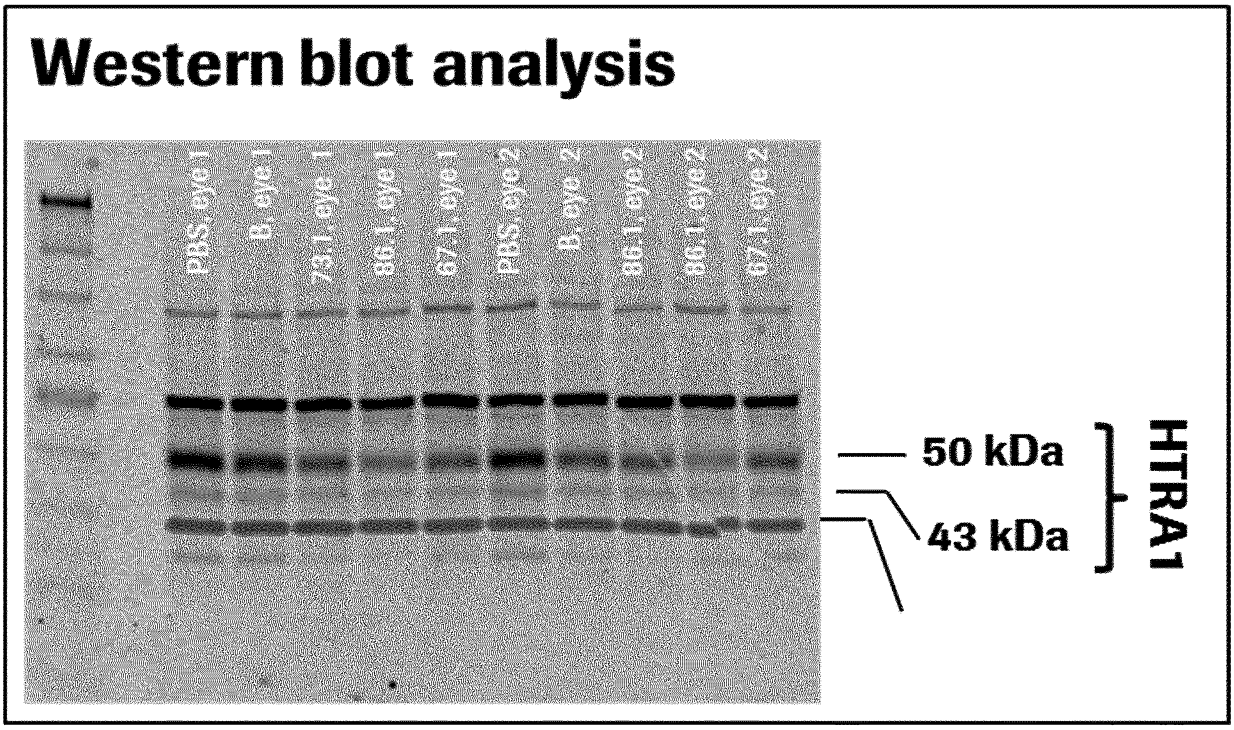

Figure 5G

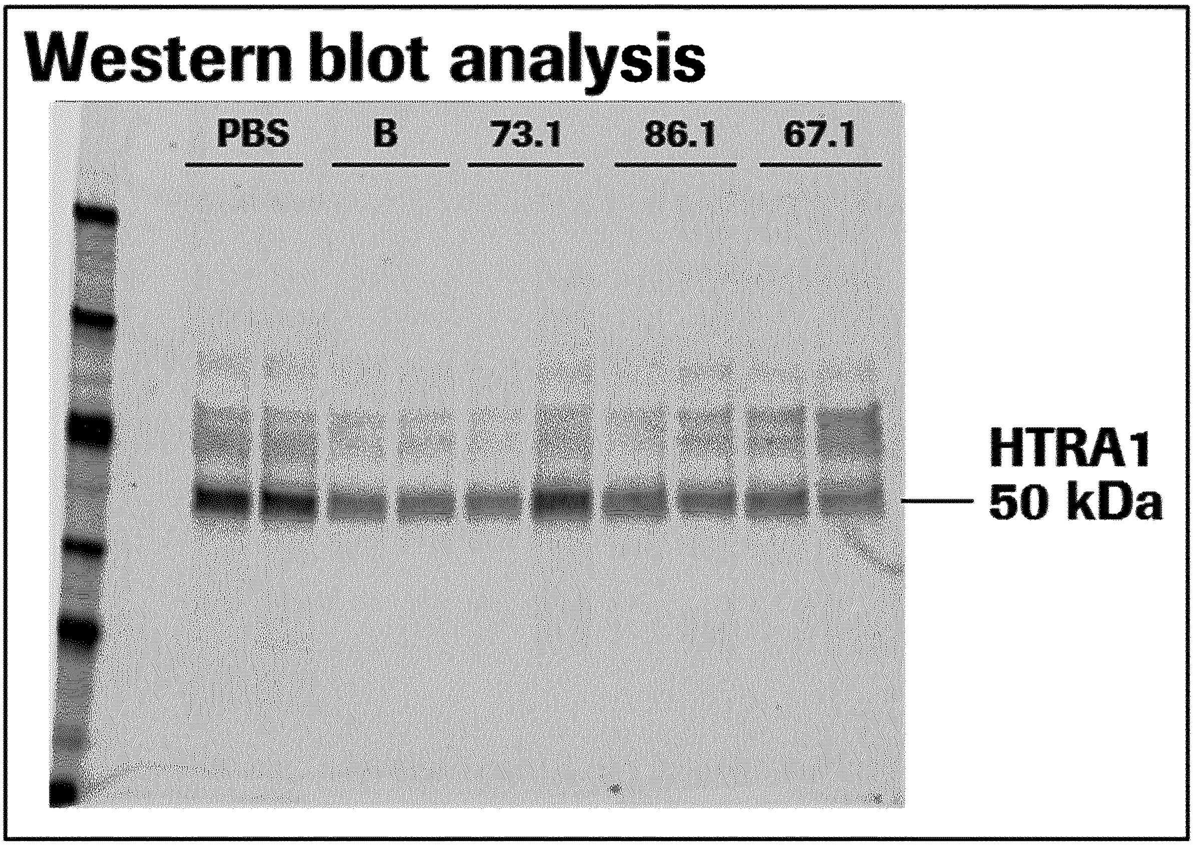

Figure 6

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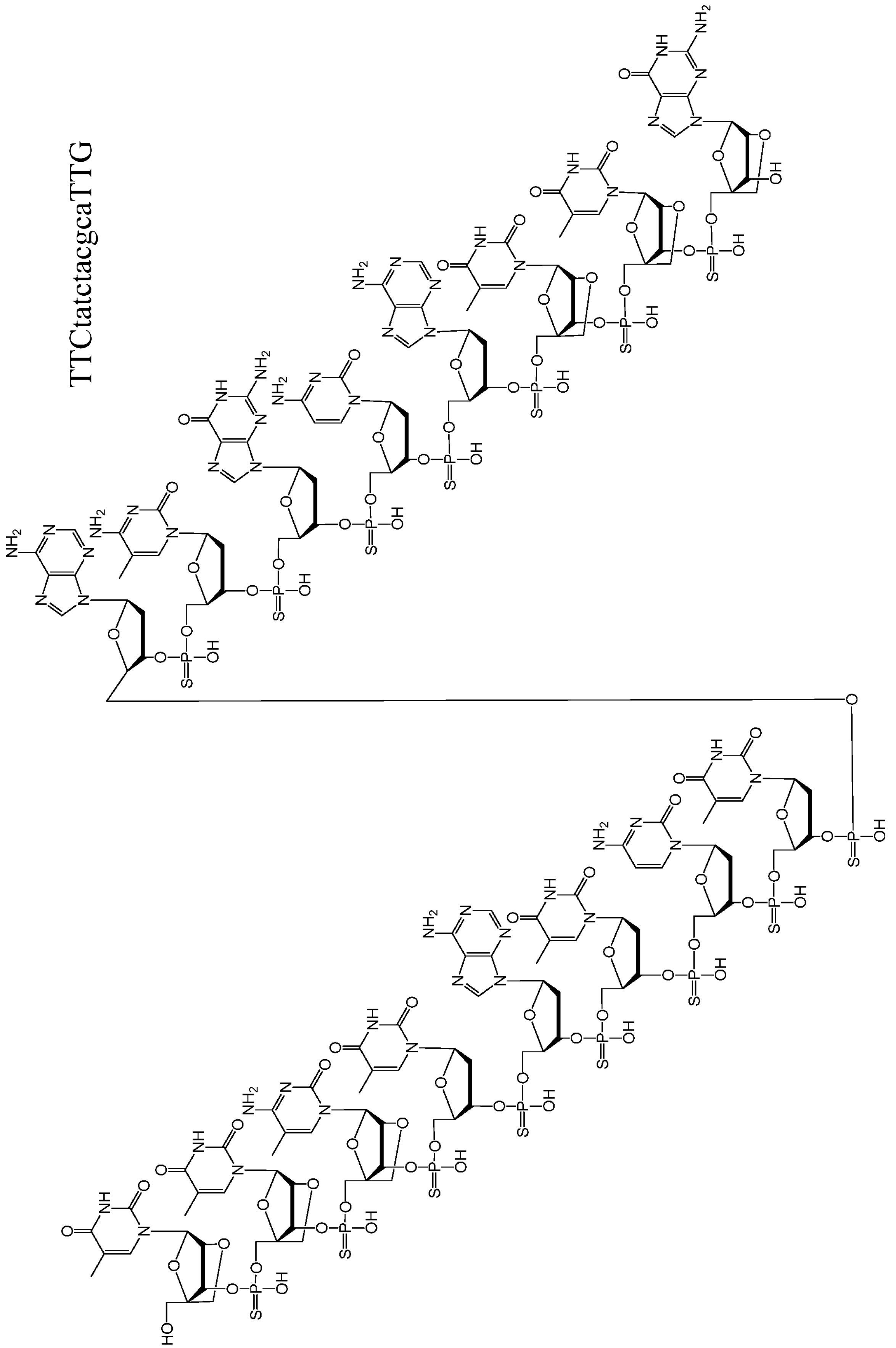

Figure 7

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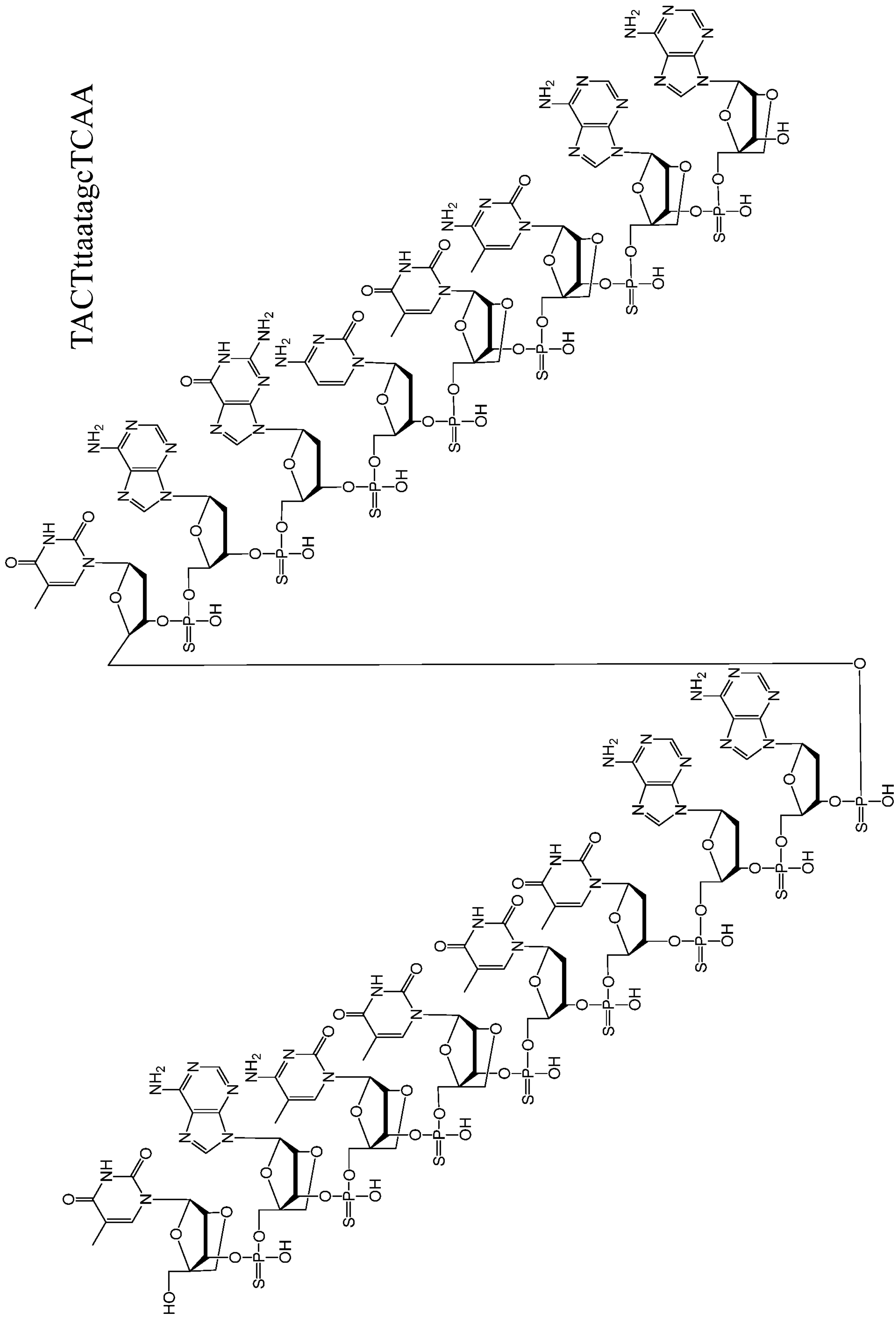

Figure 8

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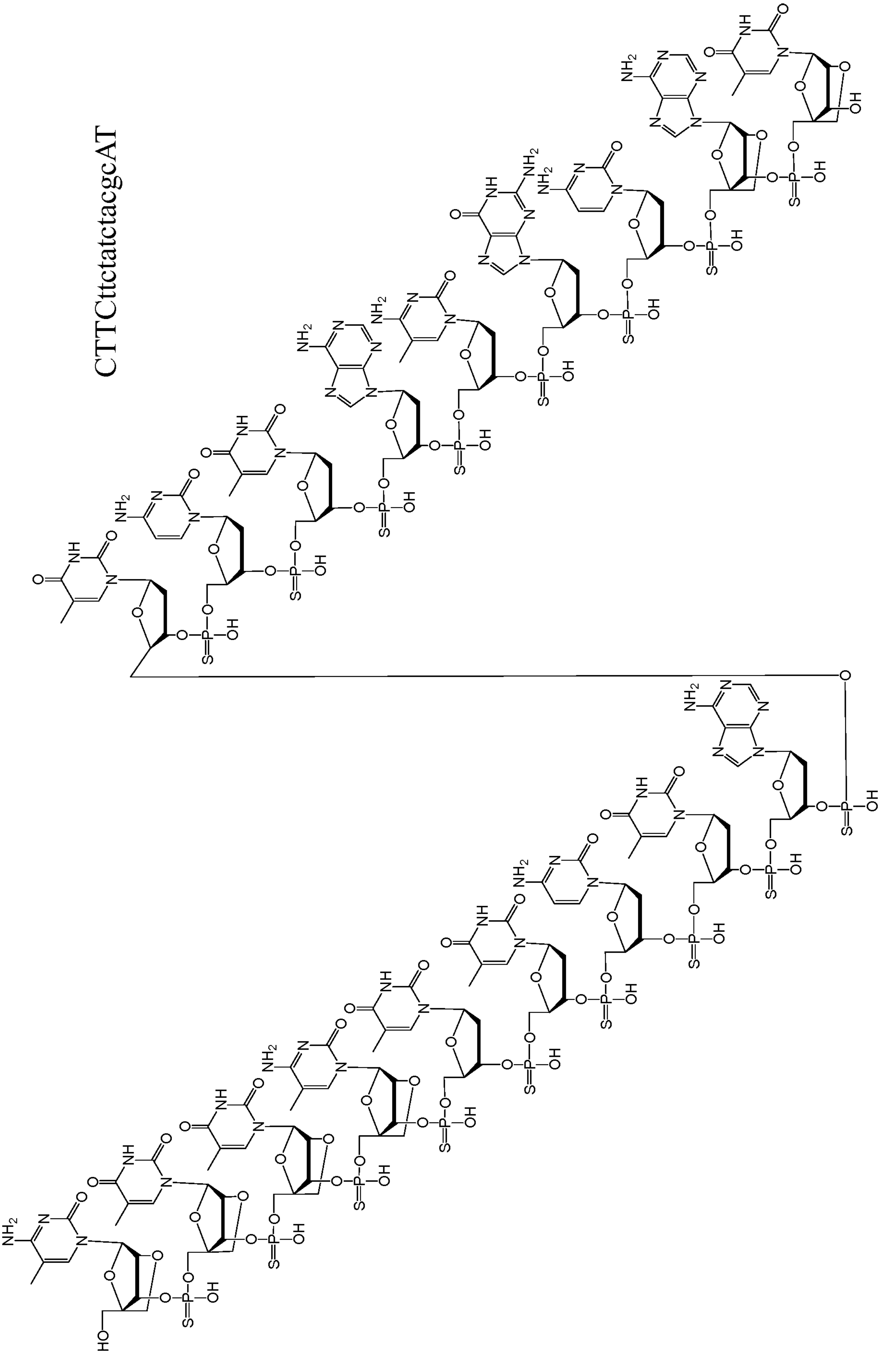

Figure 9

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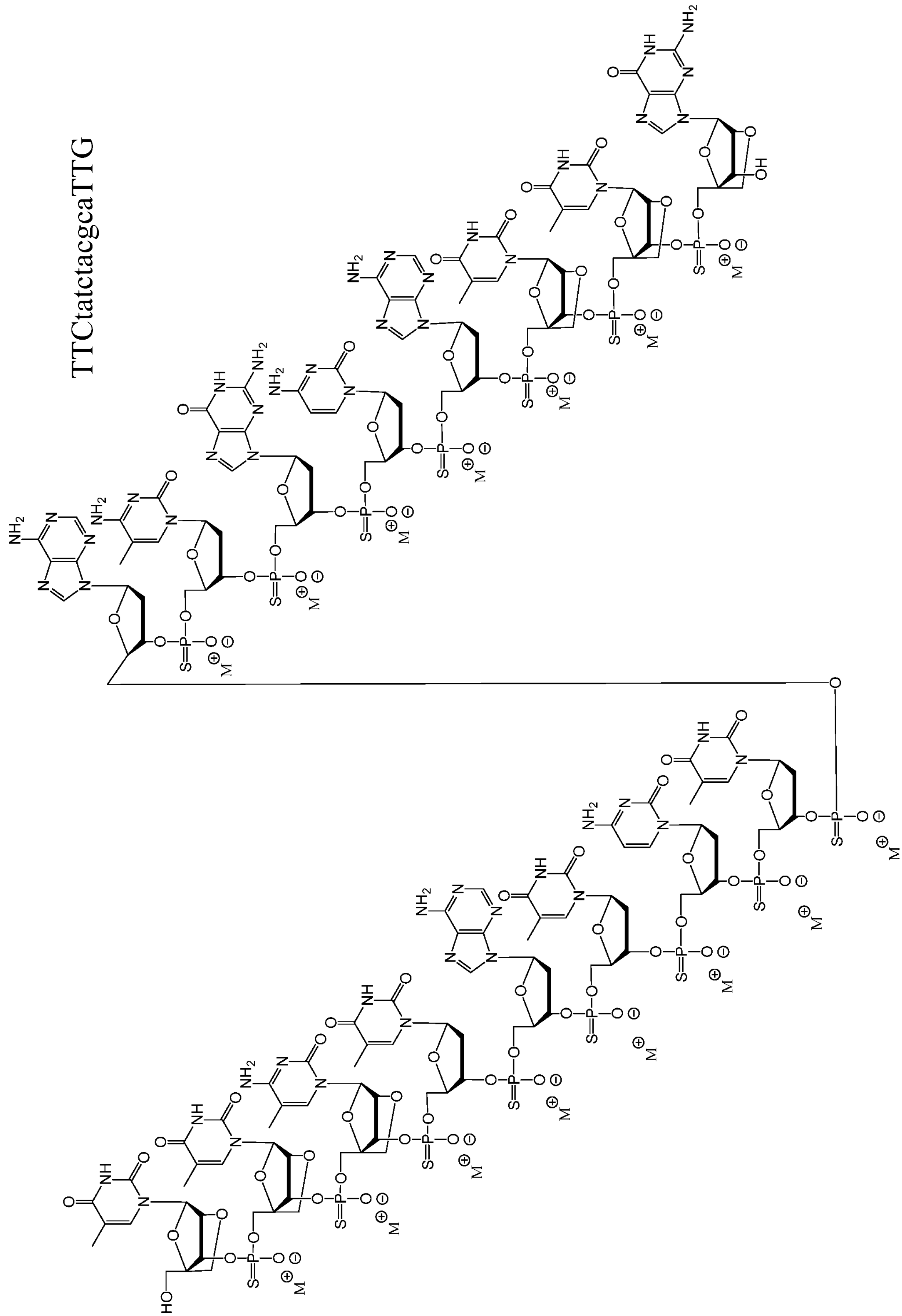

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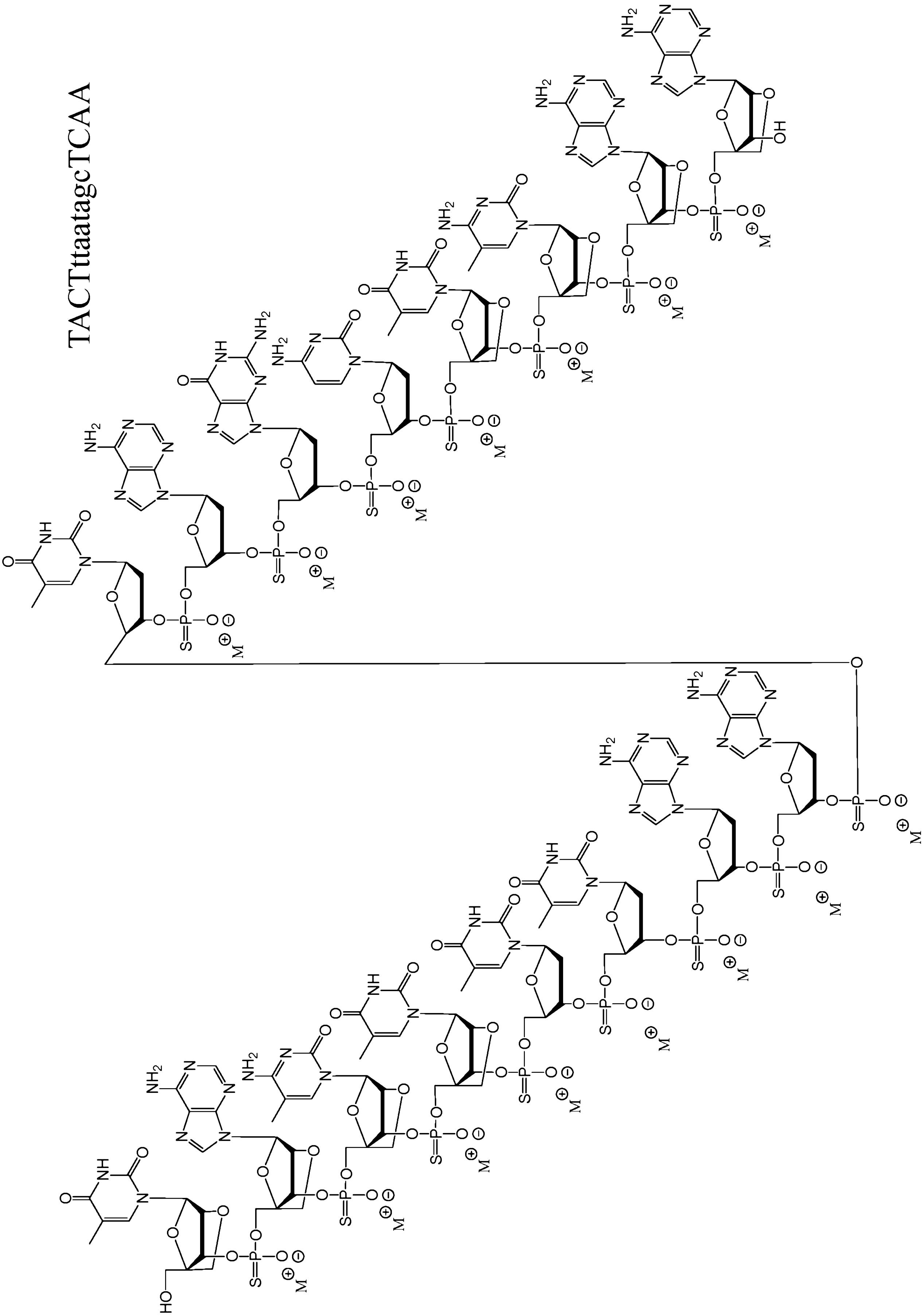

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Figure 11

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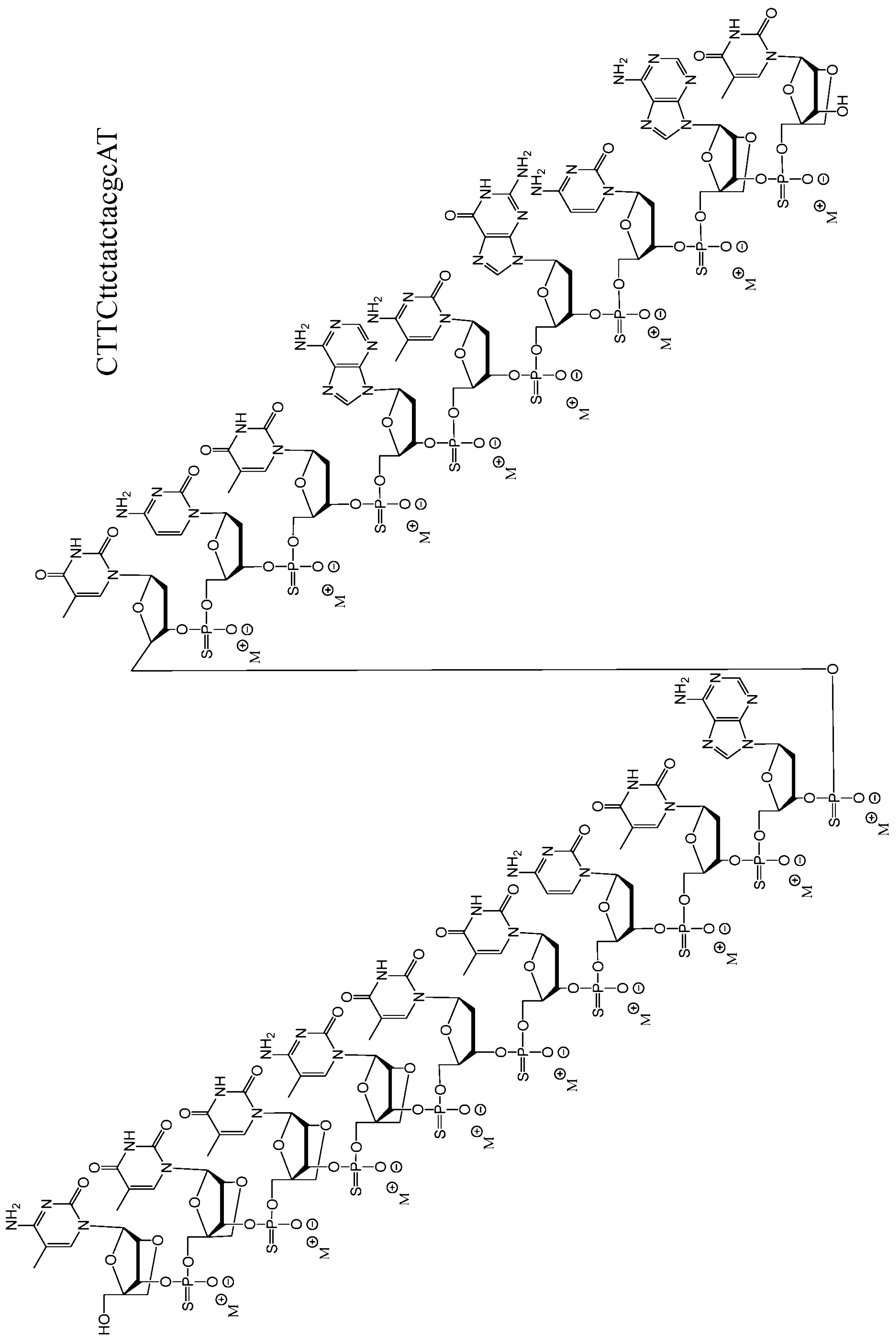


Figure 12A

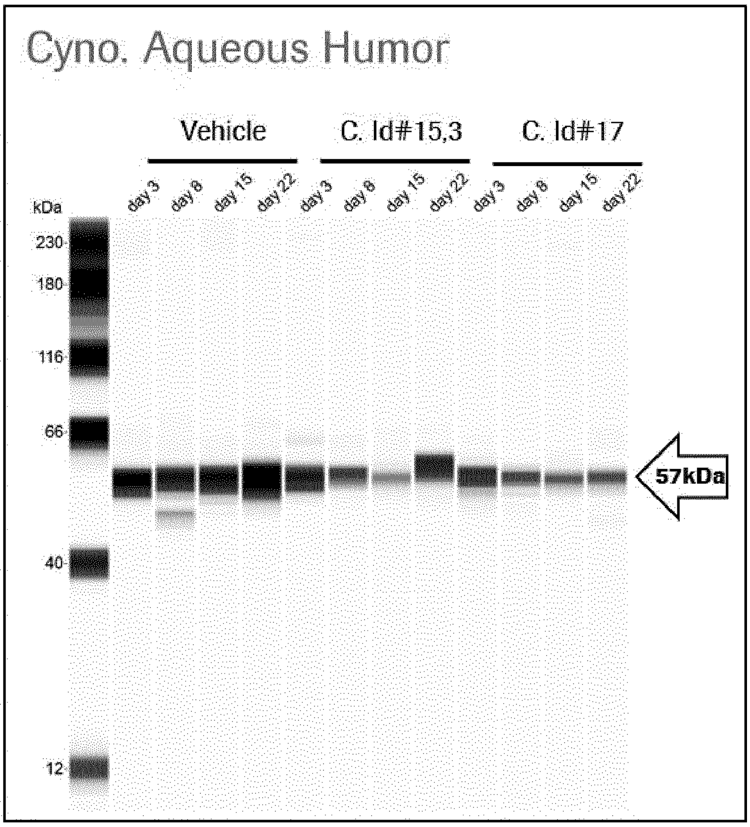


Figure 12B

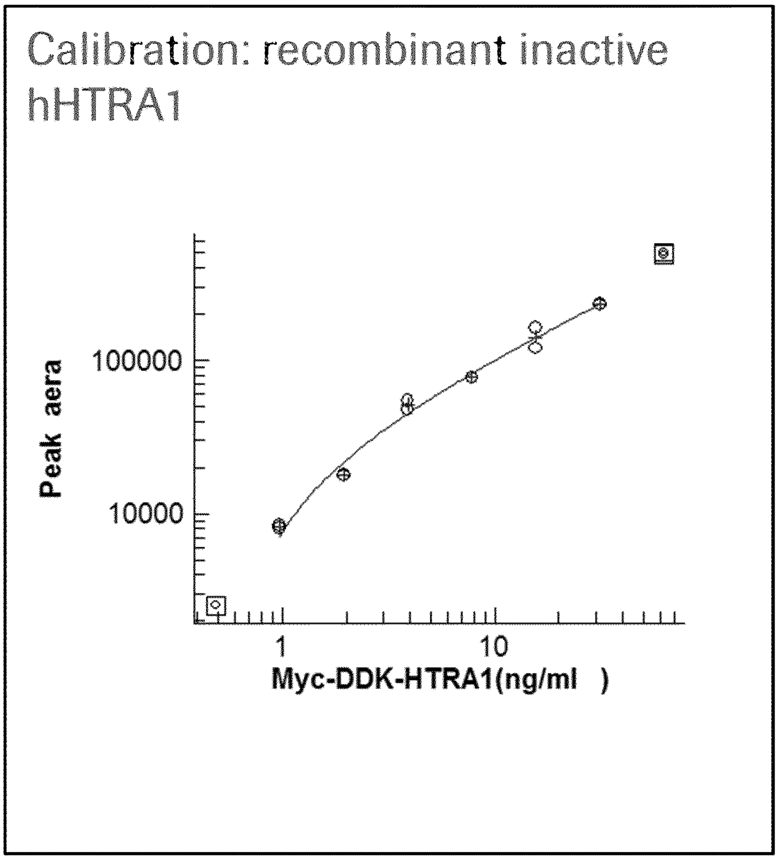
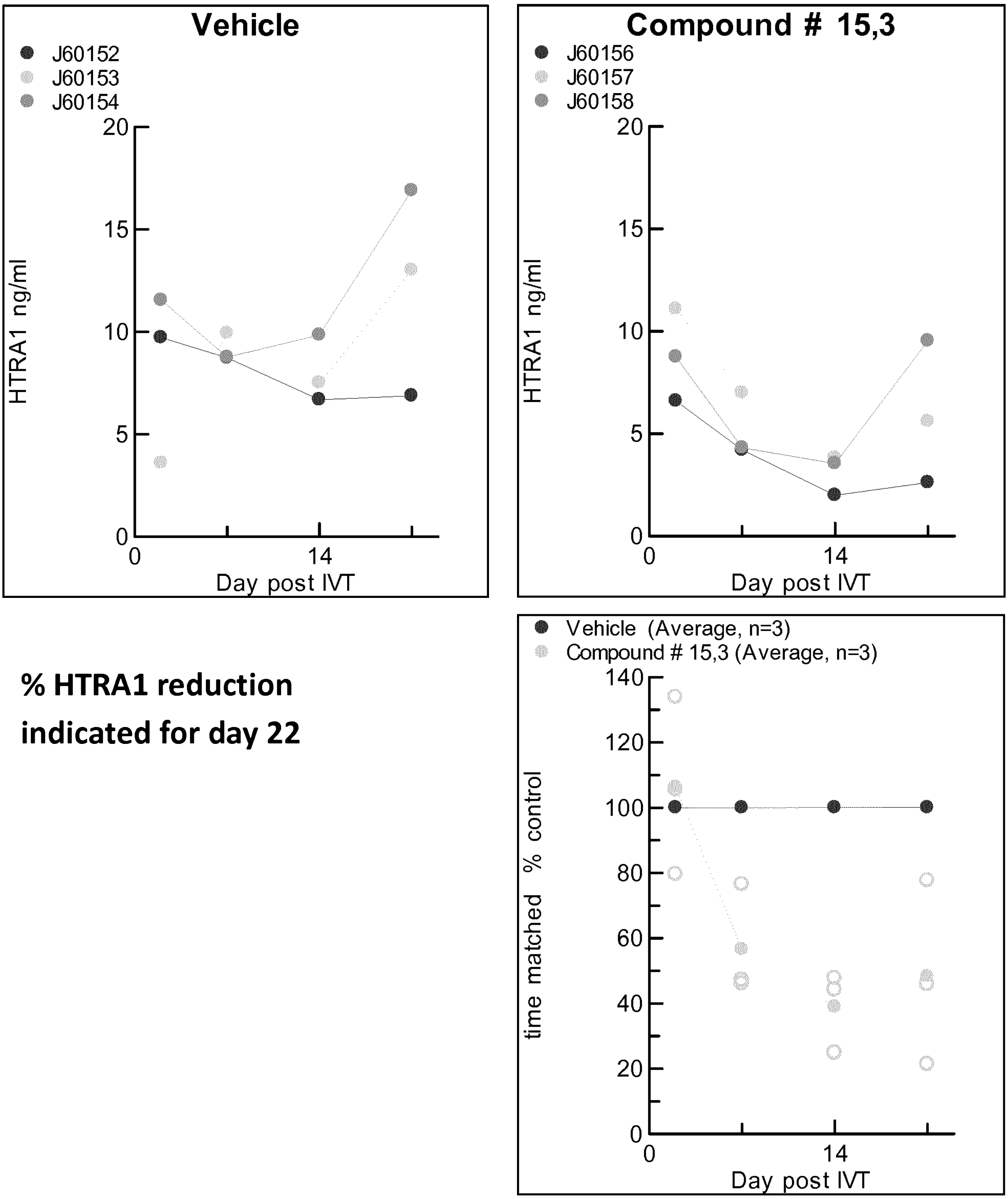
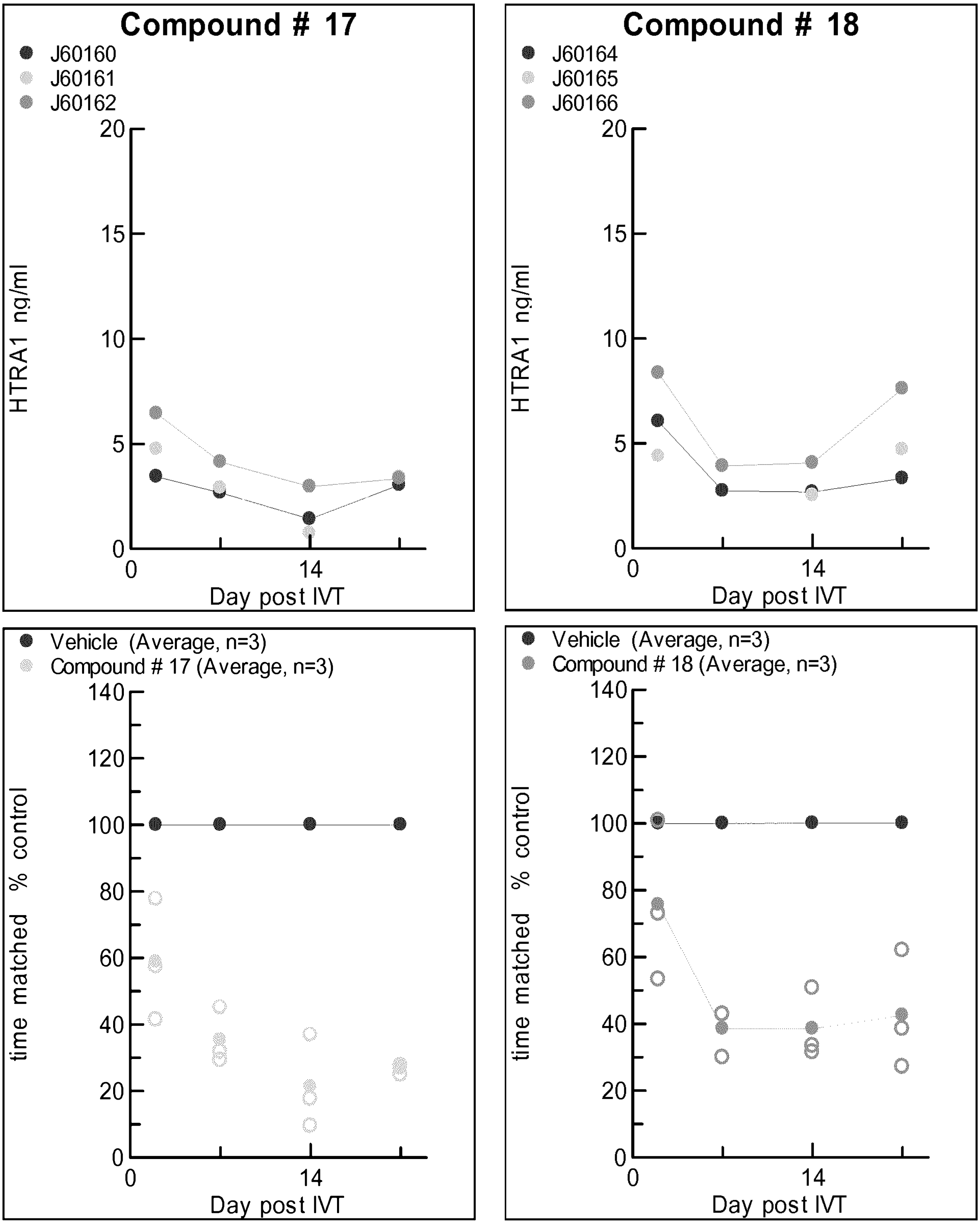


Figure 12C



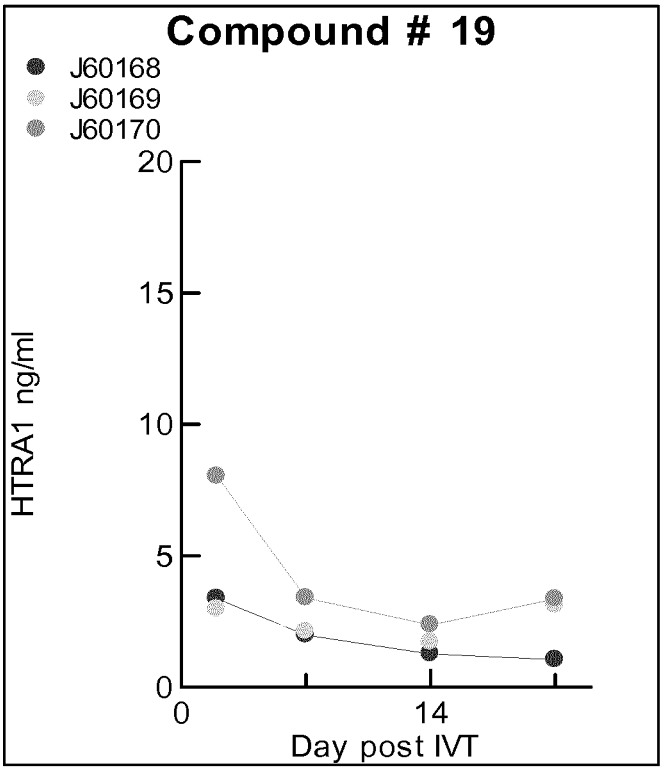
% HTRA1 reduction indicated for day 22

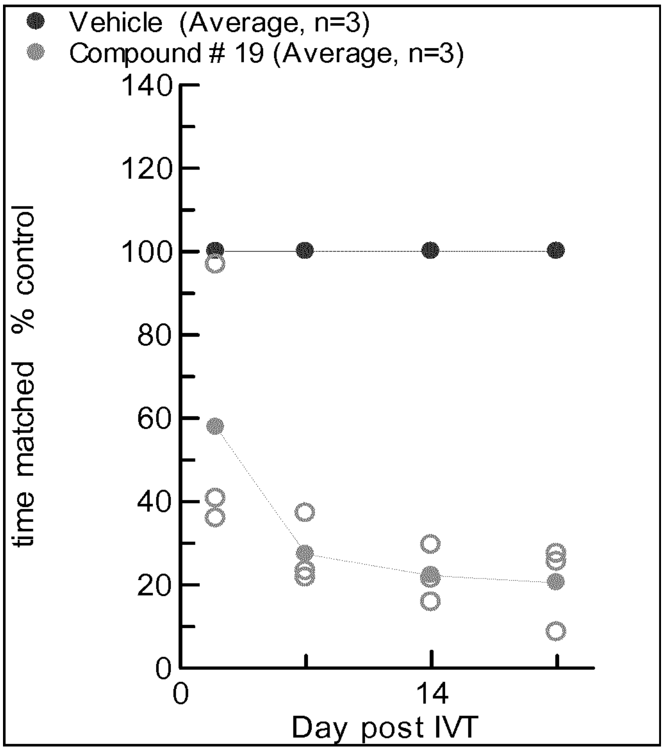
Figure 12C (cont)



% HTRA1 reduction indicated for day 22

Figure 12C (cont)





% HTRA1 reduction indicated for day 22

Figure 13

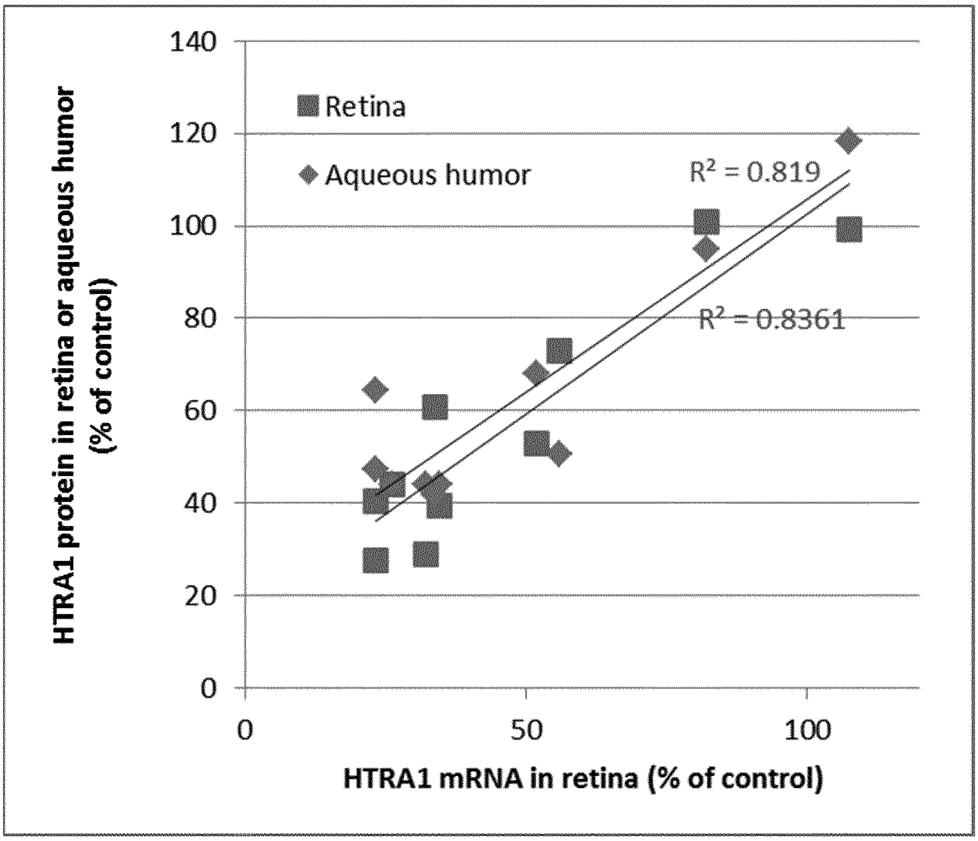
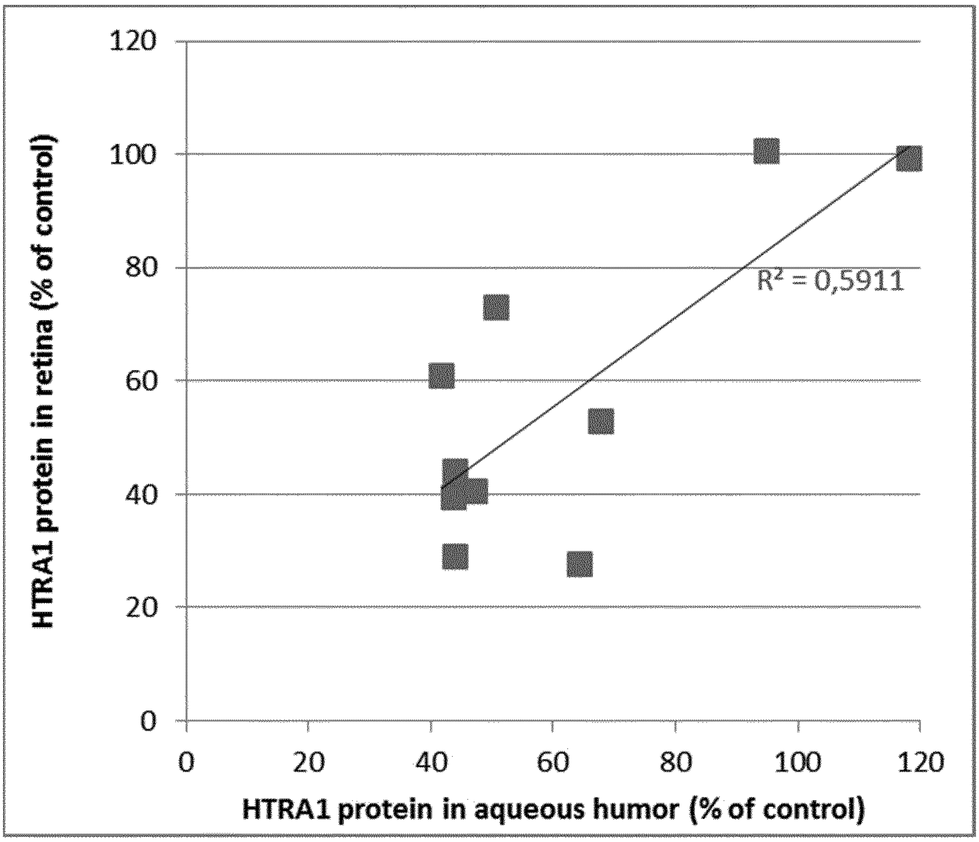


Figure 14



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       F. Hoffmann La Roche

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tgcttttctc caagtcagca cccaaaggtc aatgcacaga gaccccgggt gggtgagcgc   180

tggcttctca aacggccgaa gttgcctctt ttaggaatct ctttggaatt gggagcacga   240

tgactctgag tttgagctat taaagtactt cttac   275

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tgcttttctc caagtcagca cccaaaggtc aatgcacaga gaccccgggt gggtgagcgc 180

tggcttctca aacggccgaa gttgcctctt ttaggaatct ctttggaatt gggagcacga 240

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tgcttttctc caagtcagca cccaaaggtc aatgcacaga gaccccgggt gggtgagcgc 180

tggcttctca aacggccgaa gttgcctctt ttaggaatct ctttggaatt gggagcacga 240

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gcattgacct ttgggtgctg acttggagaa aagcacaaac acgaccagtc ccatcctggc 180

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tctctgtgca ttgacctttg ggtgctgact tggagaaaag cacaaacacg accagtccca 180

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tttgggtgct gacttggaga aaagcacaaa cacgaccagt cccatcctgg ctcccgtggg   180

gcttcttcta tctacgcatt gtatcgactg cattagttgg actaagatga tgactcagtt   240

aaaggaggag acaaatgctg actgtc   266

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tctctgtgca ttgacctttg ggtgctgact tggagaaaag cacaaacacg accagtccca   180

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tgcattgacc tttgggtgct gacttggaga aaagcacaaa cacgaccagt cccatcctgg   180

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