OLIGONUCLEOTIDES FOR MODULATING TAU EXPRESSION

FIELD OF INVENTION

The present invention relates to oligonucleotides (oligomers) that are complementary to microtubule-associated protein Tau (*MAPT*) transcript, leading to reduction of the expression of Tau. Reduction of *MAPT* transcripts and/or Tau protein expression is beneficial for a range of medical disorders, such as such as Tauopathies, Alzheimzer's disease, fronto-temporal dementia (FTD), FTDP-17, progressive supranuclear palsy (PSP), chronic traumatic encephalopathy (CTE), corticobasal ganglionic degeneration (CBD), epilepsy, Dravet syndrome, depression, seizure disorders and movement disorders.

BACKGROUND

Tau is a microtubule-associated protein (MAP) that interacts with tubulin and is involved in microtubule assembly and stabilization. Microtubules are critical structural components of the cellular cytoskeleton and are involved in various cellular processes, including mitosis, cytokinesis, and vesicular transport. Tau protein is present in multiple cell and tissue types, but is particularly abundant in neurons where it plays a critical role in regulating axonal transport and function.

Alterations in Tau expression levels and/or function contribute to the pathophysiology of various neurodegenerative disorders. For example, aggregates of misfolded and hyperphosphorylated Tau are found in the neurofibrillary inclusions associated with Alzheimer's disease (AD) and related Tauopathies such as progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBD), chronic traumatic encephalopathy (CTE), fronto- temporal dementia FTD) and FTD with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), tangle-predominant senile dementia (TPSD), primary age-related Tauopathy (PART), Down syndrome and lytico-bodig disease. Upregulation of pathological Tau is associated with infantile Tauopathies including hemimegalencephaly (HME), tuberous sclerosis complex; focal cortical dysplasia type 2b; and ganglioglioma. In addition, abnormal Tau expression and/or function may also be associated with other diseases such as Hallervorden-Spatz syndrome, also known as neurodegeneration with brain iron accumulation type 1 (NBIA1), gangliocytomas, and subacute sclerosing panencephalitis. Tau may also play a role in seizure disorders (e.g., epilepsy), network dysfunction (e.g., depression), and movement disorders (e.g., Parkinson's disease).

Antisense molecules as well as siRNA molecules have that can reduce Tau protein levels by targeting *MAPT* pre-mRNA or mRNA transcripts have been described, see for example De Vos et al 2013 Journal of Neuroscience Vol 33 pp 12887, WO2013/148260, WO2014/153236, WO2015/010135, WO2016/126995, WO2016/151523, WO2017/09679 and WO2018/064593.

Antisense oligonucleotides than can induce splice modulation of the *MAPT* transcript have also been described in Sud et al 2014 Mol Ther Nucl Acid 3 e180 and WO2016/019063.

Tau-associated disorders such as AD are the most common cause of dementia in the elderly, and robust and effective agents for the treatment of AD and related neurodegenerative diseases, including Tauopathies, seizure disorders, and movement disorders, are greatly needed.

OBJECTIVE OF THE INVENTION

The present invention provides antisense oligonucleotides which reduce Tau both *in vivo* and *in vitro*. The invention identified three specific target regions in the *MAPT* pre-mRNA located in intron 1 or 2 of the human *MAPT* pre-mRNA which may be targeted by antisense oligonucleotides to give effective Tau inhibition. In particular targeting position 12051 to 12111, 39562 to 39593 and or 72837 to 72940 of SEQ ID NO: 1 is advantageous in terms of reducing Tau. The invention also provides effective antisense oligonucleotide sequences and compounds which are capable of reducing Tau, and their use in treatment of diseases or disorders such as neurodegenerative diseases including Tauopathies, Alzheimer's disease, FTDP-17, seizure disorders and movement disorders.

SUMMARY OF INVENTION

The present invention relates to oligonucleotides targeting a Tau encoding nucleic acid which is capable of modulating the expression of Tau and the use of the oligonucleotide to treat or prevent diseases related to the functioning of the Tau.

Accordingly, in a first aspect the invention provides oligonucleotides 10 to 30 nucleotides in length which comprise a contiguous nucleotide sequence of at least 10 nucleotides in length with at least 90% complementarity to specific regions of MAPT represented by SEQ ID NO: 3, 4 and 5.

The oligonucleotide can be an antisense oligonucleotide, preferably with a gapmer design. Preferably, the oligonucleotide is capable of inhibiting the expression of Tau by cleavage of a target nucleic acid. The cleavage is preferably achieved via nuclease recruitment.

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

In a further aspect, the invention provides methods for *in vivo* or *in vitro* method for modulation of Tau expression in a target cell which is expressing Tau, by administering an oligonucleotide 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 Tau comprising administering a therapeutically or prophylactically effective amount of the oligonucleotide of the invention 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 Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto-temporal dementia (FTD) or FTDP-17.

BRIEF DESCRIPTION OF FIGURES

Figure 1: Screening result from oligonucleotide library (example 1) covering all intron regions on MAPT. Each dot represents an oligonucleotide compound, the x-axis illustrates its position on the MAPT transcript and the y- axis shows the amount of MAPT mRNA reminaing when compared to control (low number correspond to large reduction of MAPT). A, B and C indicate three regions on the MAPT transcript selected as target regions for further oligonucleotide compounds.

Figure 2: Compound 9_103 (sequence of nucleobases is shown in SEQ ID NO 9)

Figure 3: Compound 9_104 (sequence of nucleobases is shown in SEQ ID NO 9)

Figure 4: Compound 11_1 (sequence of nucleobases is shown in SEQ ID NO 11)

Figure 5: Compound 49_38 (sequence of nucleobases is shown in SEQ ID NO 49)

Figure 6: Compound 49_189 (sequence of nucleobases is shown in SEQ ID NO 49)

The compounds illustrated in figures 2, 3, 4, 5 and 6 are shown in the protonated form - the S atom on the phosphorothioate linkage is protonated – it will be understood that the presence of the proton will depend on the acidity of the environment of the molecule, and the presence of an alternative cation (e.g. when the oligonucleotide is in salt form). Protonated phosphorothioates exist in tautomeric forms.

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 and isolation. 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, such as 2' sugar modified nucleosides.

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 or shRNAs. Preferably, the antisense oligonucleotides of the present invention are single stranded. It is understood that single stranded oligonucleotides of the present invention can form hairpins or intermolecular duplex structures (duplex between two molecules of the same oligonucleotide), as long as the degree of intra or inter self-complementarity is less than 50% across of the full length of the oligonucleotide.

Advantageously, the single stranded antisense oligonucleotide of the invention does not contain RNA nucleosides, since this will decrease nuclease resistance.

Advantageously, the antisense oligonucleotide of the invention comprises one or more modified nucleosides or nucleotides, such as 2' sugar modified nucleosides. Furthermore, it is advantageous that the nucleosides which are not modified are DNA nucleosides.

Contiguous Nucleotide Sequence

The term "contiguous nucleotide sequence" refers to the region of the oligonucleotide which is complementary to the target nucleic acid or target sequence. The term is used interchangeably herein with the term "contiguous nucleobase sequence" and the term "oligonucleotide motif sequence". In some embodiments all the nucleotides of the oligonucleotide constitute the contiguous nucleotide sequence. In some embodiments the oligonucleotide comprises the contiguous nucleotide sequence, such as a F-G-F' gapmer 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. It is understood that the contiguous nucleotide sequence of the oligonucleotide cannot be longer than the oligonucleotide as such and that the oligonucleotide cannot be shorter than the contiguous nucleotide sequence.

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 comprises 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”. Nucleosides with an unmodified DNA or RNA sugar moiety are termed DNA or RNA nucleosides herein. Nucleosides with modifications in the base region of the DNA or RNA nucleoside are still generally termed DNA or RNA if they allow Watson Crick base pairing.

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. The oligonucleotides of the invention may therefore comprise modified internucleoside linkages. 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 G of a gapmer oligonucleotide, as well as in regions of modified nucleosides, such as region F and F’.

In an embodiment, the oligonucleotide comprises one or more internucleoside linkages modified from the natural phosphodiester, such as one or more modified internucleoside linkages 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 at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified, such as at least 60%, such as at least 70%, such as at least 75%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified. 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.

Modified internucleoside linkages may be selected from the group comprising phosphorothioate, diphosphorothioate and boranophosphate. In some embodiments, the modified internucleoside linkages are compatible with the RNaseH recruitment of the oligonucleotide of the invention, for example phosphorothioate, diphosphorothioate or boranophosphate.

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

With the oligonucleotides of the invention it is advantageous to use phosphorothioate internucleoside linkages.

Phosphorothioate internucleoside linkages are particularly useful due to nuclease resistance, beneficial pharmacokinetics and ease of manufacture. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate, such as at least 60%, such as at least 70%, such as at least 75%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate.

In some embodiments, the oligonucleotide of the invention comprises both phosphorothioate internucleoside linkages and at least one phosphodiester linkage, such as 2, 3 or 4 phosphodiester linkages, in addition to the phosphorodithioate linkage(s). In a gapmer oligonucleotide, phosphodiester linkages, when present, are suitably not located between contiguous DNA nucleosides in the gap region G.

In some embodiments, the oligonucleotide comprises one or more neutral internucleoside linkage, particularly a internucleoside linkage selected from phosphotriester, methylphosphonate, MMI, amide-3, formacetal or thioformacetal.

Further internucleoside linkages are disclosed in WO2009/124238 (incorporated herein by reference). In an embodiment the internucleoside linkage is selected from linkers disclosed in WO2007/031091 (incorporated herein by reference). Particularly, the internucleoside linkage may be selected from -O-P(O)$_2$-O-, -O-P(O,S)-O-, -O-P(S)$_2$-O-, -S-P(O)$_2$-O-, -S-P(O,S)-O-, -S-P(S)$_2$-O-, -O-P(O)$_2$-S-, -O-P(O,S)-S-, -S-P(O)$_2$-S-, -O-PO(R^H)-O-, 0-PO(OCH$_3$)-0-, -O-PO(NR^H)-O-, -O-PO(OCH$_2$CH$_2$S-R)-O-, -O-PO(BH$_3$)-O-, -O-PO(NHR^H)-O-, -O-P(O)$_2$-NR^H-, -NR^H-P(O)$_2$-O-

, -NR^H-CO-O-, -NR^H-CO-NR^H-, and/or the internucleoside linker may be selected form the group consisting of: -O-CO-O-, -O-CO-NR^H-, -NR^H-CO-CH_2-, -O-CH_2-CO-NR^H-, -O-CH_2-CH_2-NR^H-, -CO-NR^H-CH_2-, -CH_2-NR^HCO-, -O-CH_2-CH_2-S-, -S-CH_2-CH_2-O-, -S-CH_2-CH_2-S-, -CH_2-SO_2-CH_2-, -CH_2-CO-NR^H-, -O-CH_2-CH_2-NR^H-CO -, -CH_2-NCH_3-O-CH_2-, where R^H is selected from hydrogen and C1 -4-alkyl.

Nuclease resistant linkages, such as phosphorthioate linkages, are particularly useful in oligonucleotide regions capable of recruiting nuclease when forming a duplex with the target nucleic acid, such as region G for gapmers. Phosphorothioate linkages may, however, also be useful in non-nuclease recruiting regions and/or affinity enhancing regions such as regions F and F' for gapmers. Gapmer oligonucleotides may, in some embodiments comprise one or more phosphodiester linkages in region F or F', or both region F and F', where all the internucleoside linkages in region G may be phosphorothioate.

Advantageously, all the internucleoside linkages of the contiguous nucleotide sequence of the oligonucleotide are phosphorothioate, or all the internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

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.

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 proportion of nucleotides (in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are complementary to a reference sequence (e.g. a target sequence or sequence motif). The percentage of complementarity is thus calculated by counting the number of aligned nucleobases that are complementary (from Watson Crick base pair) between the two sequences (when aligned with the target sequence 5'-3' and the oligonucleotide sequence from 3'-5'), dividing that number 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. Insertions and deletions are not allowed in the calculation of % complementarity of a contiguous nucleotide sequence. It will be understood that in determining complementarity, chemical modifications of the nucleobases are disregarded as long as the functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5'-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

The term "fully complementary", refers to 100% complementarity.

The following is an example of an oligonucleotide that is fully complementary to the target nucleic acid.

The following is an example of an oligonucleotide (SEQ ID NO: 49) that is fully complementary to the target nucleic acid (SEQ ID NO: 4).

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5' gaaggttgaaatgagaattgatttgagttaaa 3' (SEQ ID NO: 4)
3'            actcttaactaaactcaatt  5' (SEQ ID NO: 49)
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Identity

The term "Identity" as used herein, refers to the proportion of nucleotides (expressed in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are identical to a reference sequence (e.g. a sequence motif). The percentage of identity is thus calculated by counting the number of aligned nucleobases that are identical (a Match) between two sequences (in the contiguous nucleotide sequence of the compound of the invention and in the reference sequence), dividing that number by the total number of nucleotides in the oligonucleotide and multiplying by 100. Therefore, Percentage of Identity = (Matches x 100)/Length of aligned region (e.g. the contiguous nucleotide sequence). Insertions and deletions are not allowed in the calculation the percentage of identity of a contiguous nucleotide sequence. It will be understood that in determining identity, chemical modifications of the nucleobases are disregarded as long as the functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

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 $\Delta G^\circ = -RT\ln(K_d)$, 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 nucleic acid

According to the present invention, the target nucleic acid is a nucleic acid which encodes mammalian Tau 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 a Tau target nucleic acid or MAPT target nucleic acid, these terms can be used interchangeably. The oligonucleotide of the invention may for example target exon regions of a mammalian MAPT, or may for example target intron region in the MAPT pre-mRNA (see Table 1).

Table 1. human MAPT Exons and Introns

Exonic regions in the human Tau premRNA (SEQ ID NO 2)			Intronic regions in the human Tau premRNA (SEQ ID NO 2)		
ID	**start**	**end**	**ID**	**start**	**end**
e1	1	303	i1	304	67979
e2	67980	68129	i2	68130	77517
e3	77518	77604	i3	77605	80043
e4	80044	80130	i4	80131	84033
e5	84034	84099	i5	84100	88837
e6	88838	89590	i6	89591	92699
e7	92700	92755	i7	92756	95537
e8	95538	95735	i8	95736	97119
e9	97120	97246	i8	97247	102058
e10	102059	102324	i9	102325	115969
e11	115970	116062	i10	116063	119902
e12	119903	119984	i11	119985	124287
e13	124288	124400	i12	124401	129623
e14	129624	134004			

Suitably, the target nucleic acid encodes a Tau protein, in particular mammalian Tau, such as human Tau (See for example tables 2 and 3) which provides pre-mRNA sequences for human, and monkey Tau).

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

For *in vivo* or *in vitro* application, the oligonucleotide of the invention is typically capable of inhibiting the expression of the Tau protein in a cell which is expressing the MAPT target nucleic acid. The contiguous sequence of nucleobases of the oligonucleotide of the invention is typically complementary to the MAPT 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' or 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 Tau protein, such as human Tau, e.g. the human MAPTpre- mRNA sequence, such as that disclosed as SEQ ID NO 1. Further information on exemplary target nucleic acids is provided in tables 2 and 3.

Table 2. Genome and assembly information for Tau across species.

Species	**Chr.**	**Strand**	**Genomic coordinates Start**	**End**	**Assembly**	**NCBI reference sequence* accession number for mRNA**
Human	17	fwd	45894382	46028334	GRCh38.p12	NG_007398.1
Cynomolgus monkey	16	fwd	58257786	58390183	Macaca_fascicularis_5.0	From 58257786 to 58390183 in NC_022287.1

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.

Table 3. Sequence details for Tau/ MAPT across species.

Species	**RNA type**	**Length (nt)**	**SEQ ID NO**
Human	premRNA	134004	1
Monkey	premRNA	132218	2

Target Sequence

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 oligonucleotide of the invention. In some embodiments, the target sequence consists of a

region on the target nucleic acid with a nucleobase sequence that is complementary to the contiguous nucleotide sequence of the oligonucleotide of the invention. This region of the target nucleic acid may interchangeably be referred to as the target nucleotide sequence, target sequence or target region. 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.

In some embodiments the target sequence is a sequence selected from any region in table 4 (R_1-R_2254). In particular, the target sequence may be selected from one of the region within the group of regions consisting of R_223, R_738 or R_1298.

Table 4. Regions (reg.) on SEQ ID NO: 1 which may be targeted using an oligonucleotide of the invention

Reg.	length (nt)	Position on SEQ ID NO: 1 start	end	Reg.	length (nt)	Position on SEQ ID NO: 1 start	end	Reg.	length (nt)	Position on SEQ ID NO: 1 start	end
R_1	32	4	35	R_752	23	40118	40140	R_1503	88	85545	85632
R_2	32	37	68	R_753	40	40209	40248	R_1504	20	85662	85681
R_3	32	70	101	R_754	24	40273	40296	R_1505	75	85710	85784
R_4	25	103	127	R_755	63	40301	40363	R_1506	35	85786	85820
R_5	187	156	342	R_756	35	40461	40495	R_1507	24	85822	85845
R_6	33	344	376	R_757	27	40497	40523	R_1508	24	85864	85887
R_7	37	385	421	R_758	33	40547	40579	R_1509	20	85879	85898
R_8	47	440	486	R_759	42	40587	40628	R_1510	41	85889	85929
R_9	22	488	509	R_760	41	40630	40670	R_1511	25	85964	85988
R_10	38	511	548	R_761	34	40697	40730	R_1512	23	85994	86016
R_11	63	580	642	R_762	57	40772	40828	R_1513	56	86064	86119
R_12	20	649	668	R_763	36	40831	40866	R_1514	71	86189	86259
R_13	32	710	741	R_764	60	40868	40927	R_1515	32	86266	86297
R_14	37	743	779	R_765	28	40941	40968	R_1516	54	86319	86372
R_15	27	792	818	R_766	29	40971	40999	R_1517	38	86383	86420
R_16	23	814	836	R_767	96	41031	41126	R_1518	31	86427	86457
R_17	115	839	953	R_768	43	41128	41170	R_1519	33	86478	86510
R_18	25	955	979	R_769	22	41218	41239	R_1520	36	86676	86711
R_19	80	981	1060	R_770	28	41266	41293	R_1521	20	86715	86734
R_20	23	1071	1093	R_771	25	41311	41335	R_1522	20	86742	86761
R_21	26	1095	1120	R_772	50	41356	41405	R_1523	29	86809	86837
R_22	32	1177	1208	R_773	55	41425	41479	R_1524	51	86873	86923
R_23	78	1239	1316	R_774	23	41483	41505	R_1525	48	86939	86986
R_24	34	1334	1367	R_775	47	41518	41564	R_1526	21	86989	87009
R_25	68	1401	1468	R_776	36	41586	41621	R_1527	46	87080	87125
R_26	82	1470	1551	R_777	77	41641	41717	R_1528	23	87140	87162

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_27	95	1566	1660	R_778	48	41762	41809	R_1529	24	87164	87187
R_28	43	1708	1750	R_779	42	41830	41871	R_1530	45	87209	87253
R_29	71	1762	1832	R_780	57	41888	41944	R_1531	21	87261	87281
R_30	37	1841	1877	R_781	25	41964	41988	R_1532	37	87297	87333
R_31	26	1878	1903	R_782	30	42005	42034	R_1533	61	87367	87427
R_32	21	1960	1980	R_783	31	42096	42126	R_1534	69	87595	87663
R_33	20	1982	2001	R_784	30	42141	42170	R_1535	29	87665	87693
R_34	27	2018	2044	R_785	32	42172	42203	R_1536	20	87679	87698
R_35	22	2061	2082	R_786	56	42279	42334	R_1537	20	87760	87779
R_36	24	2196	2219	R_787	63	42336	42398	R_1538	21	87915	87935
R_37	30	2237	2266	R_788	44	42439	42482	R_1539	21	87952	87972
R_38	27	2334	2360	R_789	29	42486	42514	R_1540	20	87962	87981
R_39	22	2362	2383	R_790	30	42518	42547	R_1541	47	88017	88063
R_40	22	2419	2440	R_791	24	42581	42604	R_1542	32	88099	88130
R_41	31	2472	2502	R_792	32	42631	42662	R_1543	33	88133	88165
R_42	21	2506	2526	R_793	24	42681	42704	R_1544	22	88176	88197
R_43	21	2541	2561	R_794	21	42712	42732	R_1545	36	88216	88251
R_44	31	2565	2595	R_795	49	42745	42793	R_1546	35	88279	88313
R_45	21	2598	2618	R_796	35	42841	42875	R_1547	30	88353	88382
R_46	28	2725	2752	R_797	45	42877	42921	R_1548	38	88384	88421
R_47	38	2769	2806	R_798	22	42937	42958	R_1549	37	88439	88475
R_48	59	2915	2973	R_799	20	42969	42988	R_1550	54	88493	88546
R_49	50	2978	3027	R_800	45	42976	43020	R_1551	29	88561	88589
R_50	21	3035	3055	R_801	20	43035	43054	R_1552	21	88594	88614
R_51	24	3072	3095	R_802	72	43047	43118	R_1553	23	88617	88639
R_52	22	3171	3192	R_803	23	43136	43158	R_1554	24	88648	88671
R_53	28	3207	3234	R_804	56	43188	43243	R_1555	30	88678	88707
R_54	25	3236	3260	R_805	20	43239	43258	R_1556	27	88715	88741
R_55	33	3262	3294	R_806	20	43279	43298	R_1557	24	88774	88797
R_56	58	3302	3359	R_807	27	43304	43330	R_1558	48	88820	88867
R_57	21	3364	3384	R_808	30	43346	43375	R_1559	35	88877	88911
R_58	36	3417	3452	R_809	64	43408	43471	R_1560	52	88919	88970
R_59	56	3476	3531	R_810	52	43481	43532	R_1561	26	88978	89003
R_60	20	3533	3552	R_811	22	43538	43559	R_1562	32	89011	89042
R_61	20	3554	3573	R_812	29	43561	43589	R_1563	26	89044	89069
R_62	22	3648	3669	R_813	37	43593	43629	R_1564	51	89100	89150
R_63	21	3681	3701	R_814	24	43637	43660	R_1565	34	89196	89229
R_64	20	3756	3775	R_815	21	43697	43717	R_1566	28	89231	89258
R_65	24	3808	3831	R_816	21	43719	43739	R_1567	24	89261	89284
R_66	35	3833	3867	R_817	34	43772	43805	R_1568	24	89286	89309
R_67	46	3869	3914	R_818	21	43818	43838	R_1569	42	89374	89415

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_68	27	3916	3942	R_819	72	43916	43987	R_1570	24	89430	89453
R_69	21	3956	3976	R_820	23	44002	44024	R_1571	48	89466	89513
R_70	41	4009	4049	R_821	26	44041	44066	R_1572	31	89528	89558
R_71	29	4069	4097	R_822	43	44103	44145	R_1573	46	89563	89608
R_72	37	4117	4153	R_823	44	44167	44210	R_1574	24	89610	89633
R_73	23	4160	4182	R_824	73	44216	44288	R_1575	28	89725	89752
R_74	38	4191	4228	R_825	23	44284	44306	R_1576	25	89754	89778
R_75	24	4263	4286	R_826	38	44298	44335	R_1577	21	89780	89800
R_76	75	4288	4362	R_827	56	44380	44435	R_1578	27	89802	89828
R_77	40	4388	4427	R_828	20	44449	44468	R_1579	38	89833	89870
R_78	46	4429	4474	R_829	50	44463	44512	R_1580	23	89882	89904
R_79	44	4525	4568	R_830	21	44530	44550	R_1581	20	89961	89980
R_80	28	4600	4627	R_831	25	44543	44567	R_1582	35	89982	90016
R_81	38	4646	4683	R_832	38	44552	44589	R_1583	44	90049	90092
R_82	26	4696	4721	R_833	28	44610	44637	R_1584	27	90129	90155
R_83	32	4732	4763	R_834	25	44629	44653	R_1585	21	90264	90284
R_84	35	4787	4821	R_835	45	44651	44695	R_1586	35	90287	90321
R_85	20	4837	4856	R_836	28	44763	44790	R_1587	40	90444	90483
R_86	36	4900	4935	R_837	21	44820	44840	R_1588	73	90558	90630
R_87	27	5033	5059	R_838	32	44857	44888	R_1589	20	90632	90651
R_88	28	5066	5093	R_839	47	44888	44934	R_1590	28	90702	90729
R_89	46	5098	5143	R_840	20	44994	45013	R_1591	35	90771	90805
R_90	24	5145	5168	R_841	21	45032	45052	R_1592	27	90794	90820
R_91	20	5184	5203	R_842	23	45054	45076	R_1593	24	90814	90837
R_92	40	5205	5244	R_843	22	45078	45099	R_1594	30	90827	90856
R_93	28	5246	5273	R_844	38	45129	45166	R_1595	21	90839	90859
R_94	20	5329	5348	R_845	21	45203	45223	R_1596	21	90876	90896
R_95	58	5366	5423	R_846	66	45238	45303	R_1597	26	90901	90926
R_96	41	5425	5465	R_847	33	45304	45336	R_1598	29	90972	91000
R_97	58	5524	5581	R_848	37	45338	45374	R_1599	24	91032	91055
R_98	20	5583	5602	R_849	35	45391	45425	R_1600	42	91057	91098
R_99	30	5635	5664	R_850	24	45526	45549	R_1601	30	91135	91164
R_100	51	5694	5744	R_851	25	45551	45575	R_1602	25	91189	91213
R_101	42	5775	5816	R_852	27	45673	45699	R_1603	26	91247	91272
R_102	53	5838	5890	R_853	69	45708	45776	R_1604	21	91274	91294
R_103	32	5892	5923	R_854	48	45821	45868	R_1605	29	91296	91324
R_104	53	5925	5977	R_855	37	45907	45943	R_1606	20	91396	91415
R_105	28	6001	6028	R_856	42	45987	46028	R_1607	31	91471	91501
R_106	21	6039	6059	R_857	37	46043	46079	R_1608	71	91521	91591
R_107	64	6106	6169	R_858	36	46104	46139	R_1609	48	91667	91714
R_108	65	6176	6240	R_859	30	46146	46175	R_1610	23	91755	91777

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
		start	end			start	end			start	end
R_109	35	6242	6276	R_860	25	46178	46202	R_1611	29	91788	91816
R_110	29	6276	6304	R_861	21	46261	46281	R_1612	32	91858	91889
R_111	38	6306	6343	R_862	50	46304	46353	R_1613	28	91915	91942
R_112	22	6374	6395	R_863	40	46373	46412	R_1614	35	91965	91999
R_113	22	6422	6443	R_864	29	46435	46463	R_1615	29	92052	92080
R_114	28	6464	6491	R_865	27	46465	46491	R_1616	20	92131	92150
R_115	23	6524	6546	R_866	36	46522	46557	R_1617	20	92152	92171
R_116	23	6574	6596	R_867	37	46590	46626	R_1618	32	92181	92212
R_117	54	6615	6668	R_868	22	46663	46684	R_1619	43	92227	92269
R_118	28	6725	6752	R_869	60	46686	46745	R_1620	29	92271	92299
R_119	49	6738	6786	R_870	34	46811	46844	R_1621	98	92306	92403
R_120	25	6788	6812	R_871	28	46845	46872	R_1622	22	92420	92441
R_121	59	6819	6877	R_872	85	46896	46980	R_1623	31	92463	92493
R_122	22	6908	6929	R_873	23	47027	47049	R_1624	23	92495	92517
R_123	26	6931	6956	R_874	69	47051	47119	R_1625	27	92574	92600
R_124	24	6958	6981	R_875	62	47178	47239	R_1626	134	92643	92776
R_125	35	6984	7018	R_876	42	47430	47471	R_1627	57	92793	92849
R_126	32	7020	7051	R_877	20	47473	47492	R_1628	43	92866	92908
R_127	23	7097	7119	R_878	38	47519	47556	R_1629	45	92910	92954
R_128	83	7121	7203	R_879	33	47605	47637	R_1630	26	92956	92981
R_129	21	7205	7225	R_880	34	47652	47685	R_1631	23	92983	93005
R_130	32	7242	7273	R_881	33	47699	47731	R_1632	46	93007	93052
R_131	20	7289	7308	R_882	29	47733	47761	R_1633	30	93022	93051
R_132	21	7376	7396	R_883	36	47769	47804	R_1634	22	93094	93115
R_133	20	7397	7416	R_884	22	47806	47827	R_1635	21	93117	93137
R_134	23	7439	7461	R_885	28	47848	47875	R_1636	39	93139	93177
R_135	23	7463	7485	R_886	31	47999	48029	R_1637	117	93214	93330
R_136	28	7492	7519	R_887	36	48043	48078	R_1638	37	93359	93395
R_137	26	7569	7594	R_888	37	48080	48116	R_1639	46	93409	93454
R_138	38	7622	7659	R_889	42	48118	48159	R_1640	32	93508	93539
R_139	25	7705	7729	R_890	78	48195	48272	R_1641	28	93541	93568
R_140	20	7705	7724	R_891	70	48294	48363	R_1642	33	93570	93602
R_141	28	7774	7801	R_892	28	48377	48404	R_1643	22	93647	93668
R_142	20	7855	7874	R_893	20	48406	48425	R_1644	26	93674	93699
R_143	23	7885	7907	R_894	22	48438	48459	R_1645	28	93716	93743
R_144	35	7933	7967	R_895	20	48485	48504	R_1646	72	93770	93841
R_145	21	7937	7957	R_896	23	48532	48554	R_1647	36	93897	93932
R_146	20	7937	7956	R_897	32	48564	48595	R_1648	25	94007	94031
R_147	23	7948	7970	R_898	43	48627	48669	R_1649	25	94121	94145
R_148	26	7952	7977	R_899	32	48671	48702	R_1650	20	94227	94246
R_149	25	7953	7977	R_900	30	48744	48773	R_1651	69	94295	94363

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
		start	end			start	end			start	end
R_150	30	8009	8038	R_901	24	48782	48805	R_1652	49	94371	94419
R_151	31	8043	8073	R_902	21	48797	48817	R_1653	40	94426	94465
R_152	20	8125	8144	R_903	22	48802	48823	R_1654	73	94478	94550
R_153	21	8146	8166	R_904	54	48808	48861	R_1655	35	94571	94605
R_154	36	8168	8203	R_905	38	48924	48961	R_1656	63	94607	94669
R_155	44	8245	8288	R_906	20	48966	48985	R_1657	41	94788	94828
R_156	29	8324	8352	R_907	25	49010	49034	R_1658	73	94844	94916
R_157	43	8355	8397	R_908	21	49067	49087	R_1659	21	94929	94949
R_158	23	8399	8421	R_909	61	49145	49205	R_1660	21	94979	94999
R_159	26	8457	8482	R_910	81	49207	49287	R_1661	31	95087	95117
R_160	54	8486	8539	R_911	35	49289	49323	R_1662	25	95173	95197
R_161	43	8541	8583	R_912	41	49325	49365	R_1663	23	95244	95266
R_162	26	8585	8610	R_913	99	49400	49498	R_1664	38	95278	95315
R_163	26	8637	8662	R_914	30	49507	49536	R_1665	28	95355	95382
R_164	37	8678	8714	R_915	24	49538	49561	R_1666	95	95390	95484
R_165	24	8742	8765	R_916	23	49563	49585	R_1667	159	95486	95644
R_166	37	8812	8848	R_917	27	49612	49638	R_1668	30	95646	95675
R_167	37	8868	8904	R_918	33	49654	49686	R_1669	101	95695	95795
R_168	21	9015	9035	R_919	37	49697	49733	R_1670	33	95807	95839
R_169	28	9065	9092	R_920	28	49751	49778	R_1671	24	95863	95886
R_170	20	9180	9199	R_921	20	49870	49889	R_1672	22	95888	95909
R_171	23	9191	9213	R_922	42	49890	49931	R_1673	31	95915	95945
R_172	24	9203	9226	R_923	38	49964	50001	R_1674	30	95951	95980
R_173	28	9215	9242	R_924	106	50003	50108	R_1675	28	96033	96060
R_174	21	9244	9264	R_925	29	50110	50138	R_1676	37	96057	96093
R_175	23	9260	9282	R_926	24	50394	50417	R_1677	28	96159	96186
R_176	25	9266	9290	R_927	42	50473	50514	R_1678	40	96287	96326
R_177	23	9266	9288	R_928	27	50578	50604	R_1679	43	96331	96373
R_178	24	9267	9290	R_929	42	50606	50647	R_1680	39	96450	96488
R_179	21	9267	9287	R_930	42	50692	50733	R_1681	30	96492	96521
R_180	22	9267	9288	R_931	20	50763	50782	R_1682	44	96523	96566
R_181	23	9268	9290	R_932	34	50808	50841	R_1683	22	96589	96610
R_182	21	9270	9290	R_933	48	50847	50894	R_1684	22	96655	96676
R_183	23	9289	9311	R_934	55	50955	51009	R_1685	52	96714	96765
R_184	20	9292	9311	R_935	21	51011	51031	R_1686	23	96776	96798
R_185	22	9330	9351	R_936	58	51071	51128	R_1687	25	96798	96822
R_186	20	9334	9353	R_937	85	51138	51222	R_1688	36	96838	96873
R_187	22	10083	10104	R_938	22	51273	51294	R_1689	44	96895	96938
R_188	23	10092	10114	R_939	40	51330	51369	R_1690	21	96940	96960
R_189	38	10119	10156	R_940	20	51343	51362	R_1691	24	96993	97016
R_190	20	10255	10274	R_941	71	51498	51568	R_1692	24	97038	97061

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_191	21	10257	10277	R_942	35	51570	51604	R_1693	22	97073	97094
R_192	28	10305	10332	R_943	20	51639	51658	R_1694	25	97106	97130
R_193	63	10358	10420	R_944	31	51680	51710	R_1695	20	97132	97151
R_194	28	10498	10525	R_945	75	51712	51786	R_1696	23	97162	97184
R_195	27	10597	10623	R_946	57	51788	51844	R_1697	38	97186	97223
R_196	24	10625	10648	R_947	57	51846	51902	R_1698	32	97225	97256
R_197	56	10666	10721	R_948	33	51928	51960	R_1699	41	97258	97298
R_198	27	10741	10767	R_949	33	51962	51994	R_1700	34	97300	97333
R_199	21	10777	10797	R_950	20	52012	52031	R_1701	20	97342	97361
R_200	38	10799	10836	R_951	52	52024	52075	R_1702	21	97486	97506
R_201	30	10840	10869	R_952	20	52183	52202	R_1703	24	97532	97555
R_202	24	10871	10894	R_953	31	52316	52346	R_1704	20	97592	97611
R_203	30	10911	10940	R_954	54	52348	52401	R_1705	21	97606	97626
R_204	49	10942	10990	R_955	24	52408	52431	R_1706	20	97690	97709
R_205	21	10992	11012	R_956	25	52433	52457	R_1707	43	97694	97736
R_206	69	11018	11086	R_957	68	52452	52519	R_1708	26	97740	97765
R_207	30	11089	11118	R_958	42	52521	52562	R_1709	28	97767	97794
R_208	42	11127	11168	R_959	41	52569	52609	R_1710	64	97820	97883
R_209	25	11193	11217	R_960	21	52626	52646	R_1711	32	97928	97959
R_210	68	11279	11346	R_961	21	52676	52696	R_1712	40	98008	98047
R_211	42	11367	11408	R_962	71	52704	52774	R_1713	49	98103	98151
R_212	43	11410	11452	R_963	31	52784	52814	R_1714	33	98166	98198
R_213	54	11458	11511	R_964	22	52826	52847	R_1715	26	98200	98225
R_214	79	11556	11634	R_965	25	52874	52898	R_1716	32	98324	98355
R_215	37	11648	11684	R_966	80	52915	52994	R_1717	21	98333	98353
R_216	31	11691	11721	R_967	21	53027	53047	R_1718	21	98467	98487
R_217	28	11724	11751	R_968	44	53130	53173	R_1719	22	98506	98527
R_218	81	11800	11880	R_969	21	53175	53195	R_1720	31	98577	98607
R_219	20	11905	11924	R_970	24	53181	53204	R_1721	32	98681	98712
R_220	21	11928	11948	R_971	22	53233	53254	R_1722	23	98751	98773
R_221	50	11950	11999	R_972	20	53262	53281	R_1723	37	98789	98825
R_222	20	12030	12049	R_973	22	53315	53336	R_1724	37	98930	98966
R_223	61	12051	12111	R_974	20	53352	53371	R_1725	40	98969	99008
R_224	23	12147	12169	R_975	72	53390	53461	R_1726	21	99015	99035
R_225	25	12171	12195	R_976	42	53473	53514	R_1727	45	99231	99275
R_226	23	12197	12219	R_977	25	53534	53558	R_1728	38	99345	99382
R_227	45	12221	12265	R_978	30	53560	53589	R_1729	46	99387	99432
R_228	43	12304	12346	R_979	23	53600	53622	R_1730	25	99434	99458
R_229	51	12353	12403	R_980	28	53637	53664	R_1731	21	99515	99535
R_230	23	12405	12427	R_981	24	53696	53719	R_1732	23	99565	99587
R_231	62	12475	12536	R_982	21	53738	53758	R_1733	21	99658	99678

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_232	28	12538	12565	R_983	22	53753	53774	R_1734	43	99718	99760
R_233	28	12587	12614	R_984	23	53759	53781	R_1735	30	99762	99791
R_234	21	12615	12635	R_985	30	53793	53822	R_1736	62	99820	99881
R_235	29	12637	12665	R_986	23	53895	53917	R_1737	21	99933	99953
R_236	38	12684	12721	R_987	25	53910	53934	R_1738	26	99986	100011
R_237	34	12746	12779	R_988	21	53979	53999	R_1739	29	100013	100041
R_238	20	12799	12818	R_989	20	53996	54015	R_1740	71	100063	100133
R_239	33	12822	12854	R_990	21	54027	54047	R_1741	32	100169	100200
R_240	37	12856	12892	R_991	28	54049	54076	R_1742	21	100248	100268
R_241	20	12894	12913	R_992	40	54162	54201	R_1743	30	100263	100292
R_242	23	12933	12955	R_993	20	54218	54237	R_1744	38	100296	100333
R_243	50	13057	13106	R_994	77	54239	54315	R_1745	22	100359	100380
R_244	37	13133	13169	R_995	50	54317	54366	R_1746	23	100375	100397
R_245	51	13227	13277	R_996	21	54368	54388	R_1747	23	100384	100406
R_246	22	13348	13369	R_997	32	54406	54437	R_1748	24	100639	100662
R_247	29	13380	13408	R_998	33	54439	54471	R_1749	24	100645	100668
R_248	41	13410	13450	R_999	20	54507	54526	R_1750	20	100666	100685
R_249	32	13452	13483	R_1000	55	54528	54582	R_1751	23	100695	100717
R_250	45	13483	13527	R_1001	21	54584	54604	R_1752	20	100746	100765
R_251	32	13529	13560	R_1002	42	54606	54647	R_1753	34	100771	100804
R_252	21	13569	13589	R_1003	118	54651	54768	R_1754	21	100801	100821
R_253	50	13591	13640	R_1004	23	54833	54855	R_1755	26	100823	100848
R_254	88	13770	13857	R_1005	28	54857	54884	R_1756	20	100857	100876
R_255	20	13861	13880	R_1006	57	54887	54943	R_1757	34	100899	100932
R_256	32	13882	13913	R_1007	29	54973	55001	R_1758	21	100965	100985
R_257	55	13936	13990	R_1008	21	55014	55034	R_1759	32	101017	101048
R_258	39	13992	14030	R_1009	28	55074	55101	R_1760	21	101085	101105
R_259	34	14033	14066	R_1010	21	55134	55154	R_1761	26	101195	101220
R_260	35	14068	14102	R_1011	38	55171	55208	R_1762	23	101227	101249
R_261	27	14104	14130	R_1012	31	55210	55240	R_1763	30	101324	101353
R_262	20	14140	14159	R_1013	80	55248	55327	R_1764	20	101357	101376
R_263	51	14180	14230	R_1014	25	55329	55353	R_1765	21	101415	101435
R_264	20	14232	14251	R_1015	23	55365	55387	R_1766	20	101444	101463
R_265	107	14253	14359	R_1016	43	55424	55466	R_1767	37	101465	101501
R_266	72	14367	14438	R_1017	51	55539	55589	R_1768	25	101497	101521
R_267	69	14503	14571	R_1018	27	55591	55617	R_1769	42	101523	101564
R_268	27	14595	14621	R_1019	29	55619	55647	R_1770	26	101576	101601
R_269	35	14629	14663	R_1020	30	55653	55682	R_1771	34	101620	101653
R_270	58	14732	14789	R_1021	29	55724	55752	R_1772	36	101679	101714
R_271	25	14805	14829	R_1022	33	55778	55810	R_1773	39	101734	101772
R_272	56	14851	14906	R_1023	76	55848	55923	R_1774	24	101779	101802

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_273	53	14954	15006	R_1024	33	55992	56024	R_1775	71	101817	101887
R_274	39	15026	15064	R_1025	29	56026	56054	R_1776	67	101913	101979
R_275	21	15066	15086	R_1026	59	56080	56138	R_1777	28	101989	102016
R_276	22	15138	15159	R_1027	26	56155	56180	R_1778	28	102025	102052
R_277	107	15157	15263	R_1028	22	56196	56217	R_1779	33	102054	102086
R_278	24	15249	15272	R_1029	21	56225	56245	R_1780	23	102088	102110
R_279	22	15277	15298	R_1030	31	56274	56304	R_1781	44	102112	102155
R_280	38	15300	15337	R_1031	24	56338	56361	R_1782	22	102161	102182
R_281	24	15414	15437	R_1032	22	56410	56431	R_1783	65	102202	102266
R_282	21	15476	15496	R_1033	36	56433	56468	R_1784	23	102268	102290
R_283	23	15617	15639	R_1034	22	56521	56542	R_1785	35	102292	102326
R_284	58	15671	15728	R_1035	30	56567	56596	R_1786	32	102352	102383
R_285	36	15730	15765	R_1036	55	56641	56695	R_1787	29	102385	102413
R_286	29	15840	15868	R_1037	44	56697	56740	R_1788	29	102526	102554
R_287	27	15870	15896	R_1038	43	56761	56803	R_1789	77	102579	102655
R_288	50	15926	15975	R_1039	72	56805	56876	R_1790	39	102744	102782
R_289	27	16008	16034	R_1040	30	56885	56914	R_1791	32	102841	102872
R_290	46	16109	16154	R_1041	44	56916	56959	R_1792	22	103017	103038
R_291	27	16159	16185	R_1042	67	56961	57027	R_1793	20	103118	103137
R_292	30	16245	16274	R_1043	30	57033	57062	R_1794	20	103196	103215
R_293	44	16296	16339	R_1044	20	57167	57186	R_1795	23	103346	103368
R_294	20	16316	16335	R_1045	49	57211	57259	R_1796	24	103400	103423
R_295	48	16371	16418	R_1046	24	57348	57371	R_1797	27	103456	103482
R_296	36	16447	16482	R_1047	43	57434	57476	R_1798	54	103494	103547
R_297	36	16485	16520	R_1048	73	57536	57608	R_1799	21	103557	103577
R_298	26	16532	16557	R_1049	86	57641	57726	R_1800	34	103637	103670
R_299	21	16582	16602	R_1050	27	57754	57780	R_1801	58	103683	103740
R_300	83	16604	16686	R_1051	20	57786	57805	R_1802	25	103782	103806
R_301	63	16688	16750	R_1052	21	57807	57827	R_1803	20	103851	103870
R_302	75	16766	16840	R_1053	27	57829	57855	R_1804	26	103876	103901
R_303	24	16918	16941	R_1054	41	57857	57897	R_1805	21	103997	104017
R_304	32	16947	16978	R_1055	51	57899	57949	R_1806	49	104093	104141
R_305	31	17007	17037	R_1056	26	57981	58006	R_1807	61	104143	104203
R_306	45	17039	17083	R_1057	48	58008	58055	R_1808	28	104263	104290
R_307	25	17085	17109	R_1058	26	58057	58082	R_1809	22	104331	104352
R_308	30	17111	17140	R_1059	32	58097	58128	R_1810	24	104354	104377
R_309	29	17179	17207	R_1060	40	58138	58177	R_1811	36	104379	104414
R_310	34	17292	17325	R_1061	38	58192	58229	R_1812	72	104416	104487
R_311	28	17292	17319	R_1062	26	58235	58260	R_1813	23	104504	104526
R_312	28	17309	17336	R_1063	57	58375	58431	R_1814	54	104544	104597
R_313	21	17316	17336	R_1064	25	58444	58468	R_1815	20	104599	104618

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_314	21	17319	17339	R_1065	55	58484	58538	R_1816	22	104632	104653
R_315	22	17326	17347	R_1066	26	58555	58580	R_1817	25	104710	104734
R_316	52	17349	17400	R_1067	20	58582	58601	R_1818	22	104738	104759
R_317	20	17416	17435	R_1068	23	58604	58626	R_1819	40	104783	104822
R_318	39	17445	17483	R_1069	32	58650	58681	R_1820	42	104824	104865
R_319	43	17485	17527	R_1070	70	58740	58809	R_1821	21	104919	104939
R_320	74	17587	17660	R_1071	32	58889	58920	R_1822	23	105014	105036
R_321	38	17667	17704	R_1072	25	58927	58951	R_1823	58	105040	105097
R_322	25	17706	17730	R_1073	22	58953	58974	R_1824	25	105111	105135
R_323	45	17796	17840	R_1074	35	58993	59027	R_1825	50	105137	105186
R_324	53	17855	17907	R_1075	48	59029	59076	R_1826	22	105188	105209
R_325	44	17909	17952	R_1076	45	59079	59123	R_1827	40	105283	105322
R_326	20	17954	17973	R_1077	31	59125	59155	R_1828	31	105393	105423
R_327	34	17975	18008	R_1078	31	59183	59213	R_1829	29	105427	105455
R_328	20	18010	18029	R_1079	20	59243	59262	R_1830	72	105457	105528
R_329	46	18031	18076	R_1080	35	59264	59298	R_1831	30	105544	105573
R_330	26	18078	18103	R_1081	24	59303	59326	R_1832	39	105683	105721
R_331	29	18136	18164	R_1082	39	59328	59366	R_1833	36	105732	105767
R_332	33	18208	18240	R_1083	31	59380	59410	R_1834	23	106011	106033
R_333	54	18261	18314	R_1084	20	59490	59509	R_1835	45	106334	106378
R_334	22	18333	18354	R_1085	39	59551	59589	R_1836	21	106380	106400
R_335	34	18410	18443	R_1086	76	59591	59666	R_1837	23	106407	106429
R_336	27	18446	18472	R_1087	46	59713	59758	R_1838	23	106475	106497
R_337	86	18474	18559	R_1088	26	59837	59862	R_1839	47	106562	106608
R_338	25	18590	18614	R_1089	40	59878	59917	R_1840	42	106645	106686
R_339	21	18627	18647	R_1090	23	59957	59979	R_1841	44	106677	106720
R_340	37	18650	18686	R_1091	37	59998	60034	R_1842	29	106677	106705
R_341	33	18688	18720	R_1092	63	60133	60195	R_1843	22	106728	106749
R_342	30	18742	18771	R_1093	22	60201	60222	R_1844	40	106783	106822
R_343	20	18773	18792	R_1094	23	60281	60303	R_1845	22	106824	106845
R_344	32	18782	18813	R_1095	37	60291	60327	R_1846	31	106847	106877
R_345	20	18843	18862	R_1096	27	60360	60386	R_1847	31	106879	106909
R_346	24	18864	18887	R_1097	23	60429	60451	R_1848	64	106923	106986
R_347	24	18900	18923	R_1098	52	60536	60587	R_1849	35	106988	107022
R_348	35	18935	18969	R_1099	24	60605	60628	R_1850	35	107046	107080
R_349	38	18971	19008	R_1100	28	60656	60683	R_1851	26	107085	107110
R_350	23	19080	19102	R_1101	90	60703	60792	R_1852	25	107122	107146
R_351	51	19106	19156	R_1102	48	60794	60841	R_1853	40	107239	107278
R_352	21	19158	19178	R_1103	49	60841	60889	R_1854	57	107338	107394
R_353	25	19262	19286	R_1104	31	60921	60951	R_1855	36	107405	107440
R_354	22	19310	19331	R_1105	21	60953	60973	R_1856	22	107442	107463

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
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R_356	24	19362	19385	R_1107	23	61040	61062	R_1858	22	107506	107527
R_357	44	19394	19437	R_1108	20	61117	61136	R_1859	28	107553	107580
R_358	47	19493	19539	R_1109	22	61148	61169	R_1860	53	107582	107634
R_359	26	19569	19594	R_1110	106	61165	61270	R_1861	37	107639	107675
R_360	34	19624	19657	R_1111	21	61274	61294	R_1862	34	107679	107712
R_361	38	19659	19696	R_1112	25	61392	61416	R_1863	36	107775	107810
R_362	32	19713	19744	R_1113	22	61447	61468	R_1864	25	107868	107892
R_363	56	19746	19801	R_1114	25	61486	61510	R_1865	24	107893	107916
R_364	43	19839	19881	R_1115	23	61495	61517	R_1866	24	108016	108039
R_365	24	19894	19917	R_1116	27	61518	61544	R_1867	42	108071	108112
R_366	24	19960	19983	R_1117	23	61586	61608	R_1868	21	108176	108196
R_367	21	19985	20005	R_1118	32	61646	61677	R_1869	30	108213	108242
R_368	30	20006	20035	R_1119	34	61784	61817	R_1870	72	108263	108334
R_369	21	20037	20057	R_1120	23	61870	61892	R_1871	32	108390	108421
R_370	20	20069	20088	R_1121	43	61904	61946	R_1872	27	108441	108467
R_371	20	20151	20170	R_1122	22	61948	61969	R_1873	31	108479	108509
R_372	25	20182	20206	R_1123	33	61997	62029	R_1874	21	108524	108544
R_373	22	20237	20258	R_1124	21	62076	62096	R_1875	58	108546	108603
R_374	22	20267	20288	R_1125	22	62103	62124	R_1876	33	108669	108701
R_375	27	20363	20389	R_1126	20	62133	62152	R_1877	26	108721	108746
R_376	25	20375	20399	R_1127	26	62162	62187	R_1878	30	108822	108851
R_377	21	20482	20502	R_1128	20	62239	62258	R_1879	32	108859	108890
R_378	27	20485	20511	R_1129	24	62243	62266	R_1880	30	108909	108938
R_379	22	20497	20518	R_1130	20	62266	62285	R_1881	41	108996	109036
R_380	24	20566	20589	R_1131	24	62307	62330	R_1882	43	109038	109080
R_381	22	20591	20612	R_1132	27	62332	62358	R_1883	22	109104	109125
R_382	20	20610	20629	R_1133	22	62433	62454	R_1884	41	109145	109185
R_383	22	20679	20700	R_1134	22	62561	62582	R_1885	25	109237	109261
R_384	28	20702	20729	R_1135	50	62600	62649	R_1886	41	109263	109303
R_385	35	20741	20775	R_1136	29	62678	62706	R_1887	34	109306	109339
R_386	43	20790	20832	R_1137	32	62708	62739	R_1888	48	109355	109402
R_387	35	20880	20914	R_1138	20	62846	62865	R_1889	20	109404	109423
R_388	22	20892	20913	R_1139	46	62871	62916	R_1890	28	109425	109452
R_389	21	21011	21031	R_1140	23	62945	62967	R_1891	31	109454	109484
R_390	26	21138	21163	R_1141	52	62978	63029	R_1892	20	109494	109513
R_391	20	21158	21177	R_1142	43	63043	63085	R_1893	25	109519	109543
R_392	24	21248	21271	R_1143	31	63087	63117	R_1894	60	109554	109613
R_393	26	21324	21349	R_1144	35	63119	63153	R_1895	34	109631	109664
R_394	35	21351	21385	R_1145	31	63155	63185	R_1896	26	109666	109691
R_395	29	21441	21469	R_1146	54	63193	63246	R_1897	22	109693	109714

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R_397	31	21611	21641	R_1148	29	63362	63390	R_1899	34	109822	109855
R_398	38	21645	21682	R_1149	33	63404	63436	R_1900	23	109866	109888
R_399	40	21743	21782	R_1150	33	63462	63494	R_1901	140	109935	110074
R_400	59	21819	21877	R_1151	27	63501	63527	R_1902	20	110077	110096
R_401	20	21949	21968	R_1152	29	63569	63597	R_1903	29	110137	110165
R_402	27	22001	22027	R_1153	36	63599	63634	R_1904	29	110216	110244
R_403	63	22041	22103	R_1154	20	63634	63653	R_1905	32	110254	110285
R_404	53	22125	22177	R_1155	46	63769	63814	R_1906	33	110294	110326
R_405	48	22179	22226	R_1156	20	63826	63845	R_1907	31	110328	110358
R_406	20	22247	22266	R_1157	24	63848	63871	R_1908	44	110383	110426
R_407	48	22277	22324	R_1158	54	63873	63926	R_1909	24	110421	110444
R_408	31	22334	22364	R_1159	48	63941	63988	R_1910	20	110563	110582
R_409	105	22370	22474	R_1160	45	63990	64034	R_1911	32	110584	110615
R_410	37	22475	22511	R_1161	20	64059	64078	R_1912	28	110598	110625
R_411	32	22644	22675	R_1162	20	64322	64341	R_1913	54	110612	110665
R_412	34	22686	22719	R_1163	20	64382	64401	R_1914	29	110781	110809
R_413	28	22763	22790	R_1164	24	64487	64510	R_1915	51	110823	110873
R_414	34	22792	22825	R_1165	34	64532	64565	R_1916	22	110875	110896
R_415	22	22844	22865	R_1166	27	64550	64576	R_1917	27	110899	110925
R_416	23	22875	22897	R_1167	24	65195	65218	R_1918	25	110992	111016
R_417	27	22959	22985	R_1168	20	65195	65214	R_1919	38	111036	111073
R_418	22	22990	23011	R_1169	28	65736	65763	R_1920	26	111108	111133
R_419	23	23019	23041	R_1170	30	65810	65839	R_1921	20	111141	111160
R_420	49	23066	23114	R_1171	26	65850	65875	R_1922	21	111162	111182
R_421	35	23131	23165	R_1172	32	65877	65908	R_1923	35	111184	111218
R_422	22	23168	23189	R_1173	29	65917	65945	R_1924	22	111234	111255
R_423	46	23191	23236	R_1174	55	66048	66102	R_1925	20	111298	111317
R_424	45	23238	23282	R_1175	41	66123	66163	R_1926	26	111319	111344
R_425	23	23318	23340	R_1176	37	66165	66201	R_1927	61	111403	111463
R_426	21	23497	23517	R_1177	66	66203	66268	R_1928	57	111467	111523
R_427	24	23518	23541	R_1178	49	66291	66339	R_1929	23	111525	111547
R_428	22	23562	23583	R_1179	34	66392	66425	R_1930	24	111567	111590
R_429	26	23585	23610	R_1180	45	66469	66513	R_1931	26	111592	111617
R_430	46	23626	23671	R_1181	23	66545	66567	R_1932	24	111631	111654
R_431	34	23637	23670	R_1182	27	66591	66617	R_1933	22	111666	111687
R_432	21	23650	23670	R_1183	24	66635	66658	R_1934	21	111692	111712
R_433	28	23718	23745	R_1184	22	66660	66681	R_1935	49	111732	111780
R_434	87	23748	23834	R_1185	49	66690	66738	R_1936	31	111815	111845
R_435	41	23836	23876	R_1186	29	66755	66783	R_1937	21	111908	111928
R_436	30	23889	23918	R_1187	36	66789	66824	R_1938	39	111934	111972

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R_438	99	24059	24157	R_1189	23	66865	66887	R_1940	58	112001	112058
R_439	37	24219	24255	R_1190	27	66889	66915	R_1941	28	112064	112091
R_440	33	24319	24351	R_1191	48	66991	67038	R_1942	24	112066	112089
R_441	20	24342	24361	R_1192	24	67116	67139	R_1943	21	112122	112142
R_442	71	24354	24424	R_1193	24	67155	67178	R_1944	24	112157	112180
R_443	28	24447	24474	R_1194	27	67185	67211	R_1945	21	112221	112241
R_444	21	24515	24535	R_1195	35	67231	67265	R_1946	26	112253	112278
R_445	31	24536	24566	R_1196	20	67316	67335	R_1947	23	112428	112450
R_446	20	24552	24571	R_1197	23	67337	67359	R_1948	26	112444	112469
R_447	26	24592	24617	R_1198	31	67361	67391	R_1949	30	112501	112530
R_448	26	24656	24681	R_1199	37	67467	67503	R_1950	20	112511	112530
R_449	25	24716	24740	R_1200	27	67498	67524	R_1951	69	112757	112825
R_450	20	24721	24740	R_1201	23	67499	67521	R_1952	20	112884	112903
R_451	57	24817	24873	R_1202	37	67517	67553	R_1953	44	112905	112948
R_452	41	24903	24943	R_1203	26	67604	67629	R_1954	28	112979	113006
R_453	26	24958	24983	R_1204	25	67624	67648	R_1955	62	113062	113123
R_454	20	24985	25004	R_1205	26	67708	67733	R_1956	36	113141	113176
R_455	48	25014	25061	R_1206	21	67806	67826	R_1957	23	113172	113194
R_456	55	25122	25176	R_1207	27	67877	67903	R_1958	26	113203	113228
R_457	29	25178	25206	R_1208	43	67905	67947	R_1959	37	113277	113313
R_458	25	25249	25273	R_1209	36	67987	68022	R_1960	32	113364	113395
R_459	30	25279	25308	R_1210	50	68024	68073	R_1961	43	113397	113439
R_460	40	25310	25349	R_1211	92	68092	68183	R_1962	118	113452	113569
R_461	53	25369	25421	R_1212	24	68216	68239	R_1963	46	113572	113617
R_462	52	25427	25478	R_1213	52	68257	68308	R_1964	21	113628	113648
R_463	66	25514	25579	R_1214	32	68390	68421	R_1965	21	113662	113682
R_464	21	25618	25638	R_1215	48	68442	68489	R_1966	36	113690	113725
R_465	51	25679	25729	R_1216	20	68486	68505	R_1967	32	113729	113760
R_466	39	25731	25769	R_1217	21	68546	68566	R_1968	28	113782	113809
R_467	28	25825	25852	R_1218	25	68556	68580	R_1969	21	113997	114017
R_468	72	25881	25952	R_1219	20	68561	68580	R_1970	22	114007	114028
R_469	23	25964	25986	R_1220	23	68610	68632	R_1971	57	114039	114095
R_470	59	25988	26046	R_1221	25	68679	68703	R_1972	32	114174	114205
R_471	25	26061	26085	R_1222	35	68736	68770	R_1973	28	114235	114262
R_472	34	26088	26121	R_1223	62	68806	68867	R_1974	21	114349	114369
R_473	24	26162	26185	R_1224	22	68885	68906	R_1975	38	114395	114432
R_474	30	26194	26223	R_1225	22	68908	68929	R_1976	31	114434	114464
R_475	28	26233	26260	R_1226	20	68931	68950	R_1977	20	114529	114548
R_476	38	26335	26372	R_1227	29	68950	68978	R_1978	34	114624	114657
R_477	24	26395	26418	R_1228	34	69017	69050	R_1979	65	114711	114775

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R_479	27	26480	26506	R_1230	20	69083	69102	R_1981	42	114930	114971
R_480	42	26521	26562	R_1231	27	69123	69149	R_1982	22	114982	115003
R_481	67	26684	26750	R_1232	30	69160	69189	R_1983	20	115005	115024
R_482	24	26752	26775	R_1233	35	69210	69244	R_1984	42	115026	115067
R_483	35	26822	26856	R_1234	53	69248	69300	R_1985	28	115092	115119
R_484	22	26937	26958	R_1235	23	69304	69326	R_1986	57	115121	115177
R_485	38	26984	27021	R_1236	34	69393	69426	R_1987	28	115179	115206
R_486	24	27022	27045	R_1237	29	69428	69456	R_1988	31	115228	115258
R_487	54	27053	27106	R_1238	45	69458	69502	R_1989	24	115263	115286
R_488	91	27154	27244	R_1239	43	69547	69589	R_1990	37	115306	115342
R_489	35	27283	27317	R_1240	20	69601	69620	R_1991	44	115361	115404
R_490	25	27339	27363	R_1241	20	69633	69652	R_1992	20	115467	115486
R_491	75	27386	27460	R_1242	29	69656	69684	R_1993	30	115628	115657
R_492	41	27493	27533	R_1243	39	69705	69743	R_1994	26	115665	115690
R_493	22	27602	27623	R_1244	42	69769	69810	R_1995	34	115687	115720
R_494	33	27631	27663	R_1245	22	69829	69850	R_1996	28	115804	115831
R_495	23	27691	27713	R_1246	28	69912	69939	R_1997	26	115833	115858
R_496	33	27736	27768	R_1247	32	69941	69972	R_1998	27	115937	115963
R_497	24	27752	27775	R_1248	31	70029	70059	R_1999	119	115965	116083
R_498	26	27777	27802	R_1249	41	70065	70105	R_2000	23	116085	116107
R_499	20	27777	27796	R_1250	27	70162	70188	R_2001	42	116121	116162
R_500	23	27778	27800	R_1251	43	70200	70242	R_2002	33	116193	116225
R_501	30	27859	27888	R_1252	20	70217	70236	R_2003	24	116276	116299
R_502	38	27909	27946	R_1253	20	70345	70364	R_2004	26	116356	116381
R_503	49	27956	28004	R_1254	35	70366	70400	R_2005	29	116405	116433
R_504	45	28071	28115	R_1255	57	70433	70489	R_2006	46	116441	116486
R_505	33	28124	28156	R_1256	21	70515	70535	R_2007	29	116488	116516
R_506	20	28152	28171	R_1257	26	70537	70562	R_2008	40	116518	116557
R_507	24	28181	28204	R_1258	40	70583	70622	R_2009	46	116653	116698
R_508	25	28251	28275	R_1259	20	70657	70676	R_2010	28	116700	116727
R_509	33	28295	28327	R_1260	22	70688	70709	R_2011	46	116729	116774
R_510	28	28345	28372	R_1261	34	70723	70756	R_2012	43	116927	116969
R_511	51	28383	28433	R_1262	23	70758	70780	R_2013	32	116997	117028
R_512	38	28441	28478	R_1263	21	70782	70802	R_2014	23	117043	117065
R_513	24	28553	28576	R_1264	21	70808	70828	R_2015	35	117068	117102
R_514	37	28598	28634	R_1265	26	70818	70843	R_2016	28	117148	117175
R_515	35	28669	28703	R_1266	31	70912	70942	R_2017	36	117195	117230
R_516	23	28733	28755	R_1267	22	71039	71060	R_2018	20	117243	117262
R_517	31	28758	28788	R_1268	25	71104	71128	R_2019	37	117273	117309
R_518	21	28857	28877	R_1269	24	71195	71218	R_2020	32	117329	117360

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R_520	58	29019	29076	R_1271	36	71519	71554	R_2022	21	117509	117529
R_521	22	29115	29136	R_1272	24	71560	71583	R_2023	23	117557	117579
R_522	66	29198	29263	R_1273	30	71606	71635	R_2024	65	117580	117644
R_523	24	29297	29320	R_1274	21	71637	71657	R_2025	27	117646	117672
R_524	41	29335	29375	R_1275	22	71672	71693	R_2026	22	117708	117729
R_525	21	29386	29406	R_1276	56	71744	71799	R_2027	47	117730	117776
R_526	22	29433	29454	R_1277	35	71827	71861	R_2028	37	117778	117814
R_527	40	29473	29512	R_1278	21	71863	71883	R_2029	24	117881	117904
R_528	29	29531	29559	R_1279	32	71913	71944	R_2030	40	117904	117943
R_529	41	29586	29626	R_1280	25	71946	71970	R_2031	30	117945	117974
R_530	29	29635	29663	R_1281	23	72022	72044	R_2032	28	117993	118020
R_531	36	29665	29700	R_1282	28	72092	72119	R_2033	48	118064	118111
R_532	93	29750	29842	R_1283	22	72095	72116	R_2034	27	118113	118139
R_533	35	29853	29887	R_1284	21	72121	72141	R_2035	27	118141	118167
R_534	22	29907	29928	R_1285	50	72147	72196	R_2036	29	118169	118197
R_535	77	29964	30040	R_1286	31	72204	72234	R_2037	33	118210	118242
R_536	38	30093	30130	R_1287	23	72230	72252	R_2038	45	118386	118430
R_537	30	30169	30198	R_1288	36	72236	72271	R_2039	48	118446	118493
R_538	32	30210	30241	R_1289	31	72285	72315	R_2040	24	118532	118555
R_539	20	30243	30262	R_1290	85	72314	72398	R_2041	46	118634	118679
R_540	20	30303	30322	R_1291	52	72400	72451	R_2042	44	118774	118817
R_541	23	30324	30346	R_1292	37	72443	72479	R_2043	54	118841	118894
R_542	27	30362	30388	R_1293	31	72482	72512	R_2044	20	118912	118931
R_543	30	30390	30419	R_1294	40	72566	72605	R_2045	21	118999	119019
R_544	31	30462	30492	R_1295	49	72607	72655	R_2046	44	119283	119326
R_545	22	30534	30555	R_1296	86	72657	72742	R_2047	33	119353	119385
R_546	28	30557	30584	R_1297	63	72752	72814	R_2048	39	119392	119430
R_547	24	30596	30619	R_1298	125	72816	72940	R_2049	65	119441	119505
R_548	30	30626	30655	R_1299	31	72955	72985	R_2050	21	119566	119586
R_549	41	30675	30715	R_1300	20	72987	73006	R_2051	55	119604	119658
R_550	33	30726	30758	R_1301	40	73008	73047	R_2052	24	119660	119683
R_551	29	30787	30815	R_1302	24	73049	73072	R_2053	42	119685	119726
R_552	62	30819	30880	R_1303	37	73118	73154	R_2054	33	119736	119768
R_553	79	30972	31050	R_1304	26	73163	73188	R_2055	32	119770	119801
R_554	67	31053	31119	R_1305	29	73212	73240	R_2056	34	119804	119837
R_555	56	31121	31176	R_1306	22	73279	73300	R_2057	116	119885	120000
R_556	22	31178	31199	R_1307	22	73315	73336	R_2058	59	120128	120186
R_557	22	31207	31228	R_1308	30	73338	73367	R_2059	34	120317	120350
R_558	27	31227	31253	R_1309	23	73387	73409	R_2060	24	120530	120553
R_559	27	31255	31281	R_1310	52	73411	73462	R_2061	22	120571	120592

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R_562	20	31419	31438	R_1313	83	73562	73644	R_2064	20	120924	120943
R_563	36	31440	31475	R_1314	36	73646	73681	R_2065	22	121093	121114
R_564	26	31503	31528	R_1315	20	73703	73722	R_2066	29	121117	121145
R_565	34	31530	31563	R_1316	27	73725	73751	R_2067	39	121244	121282
R_566	23	31585	31607	R_1317	62	73776	73837	R_2068	48	121365	121412
R_567	21	31611	31631	R_1318	20	73845	73864	R_2069	37	121414	121450
R_568	21	31614	31634	R_1319	61	73894	73954	R_2070	25	121649	121673
R_569	32	31675	31706	R_1320	91	73955	74045	R_2071	40	121687	121726
R_570	23	31708	31730	R_1321	32	74079	74110	R_2072	45	121728	121772
R_571	39	31737	31775	R_1322	28	74115	74142	R_2073	22	121795	121816
R_572	68	31763	31830	R_1323	62	74144	74205	R_2074	24	121939	121962
R_573	27	31763	31789	R_1324	27	74214	74240	R_2075	28	122038	122065
R_574	20	31803	31822	R_1325	62	74244	74305	R_2076	30	122218	122247
R_575	23	31832	31854	R_1326	28	74320	74347	R_2077	27	122273	122299
R_576	50	31952	32001	R_1327	24	74350	74373	R_2078	21	122301	122321
R_577	22	32110	32131	R_1328	46	74386	74431	R_2079	30	122318	122347
R_578	20	32114	32133	R_1329	23	74433	74455	R_2080	32	122356	122387
R_579	35	32143	32177	R_1330	31	74463	74493	R_2081	21	122428	122448
R_580	45	32179	32223	R_1331	48	74497	74544	R_2082	21	122432	122452
R_581	26	32208	32233	R_1332	40	74546	74585	R_2083	24	123020	123043
R_582	49	32225	32273	R_1333	20	74604	74623	R_2084	30	123038	123067
R_583	27	32289	32315	R_1334	65	74648	74712	R_2085	26	123052	123077
R_584	34	32317	32350	R_1335	29	74725	74753	R_2086	22	123258	123279
R_585	32	32352	32383	R_1336	35	74764	74798	R_2087	28	123291	123318
R_586	25	32390	32414	R_1337	57	74805	74861	R_2088	22	123402	123423
R_587	46	32416	32461	R_1338	56	74863	74918	R_2089	27	123644	123670
R_588	37	32497	32533	R_1339	37	74936	74972	R_2090	20	123819	123838
R_589	37	32691	32727	R_1340	28	74974	75001	R_2091	26	123841	123866
R_590	23	32753	32775	R_1341	53	75003	75055	R_2092	25	123965	123989
R_591	38	32794	32831	R_1342	22	75019	75040	R_2093	24	123997	124020
R_592	24	32835	32858	R_1343	30	75097	75126	R_2094	35	124034	124068
R_593	55	32890	32944	R_1344	51	75126	75176	R_2095	44	124075	124118
R_594	52	32959	33010	R_1345	28	75362	75389	R_2096	50	124156	124205
R_595	37	33025	33061	R_1346	29	75417	75445	R_2097	75	124247	124321
R_596	23	33063	33085	R_1347	54	75482	75535	R_2098	23	124353	124375
R_597	62	33087	33148	R_1348	27	75552	75578	R_2099	34	124377	124410
R_598	23	33160	33182	R_1349	27	75580	75606	R_2100	84	124472	124555
R_599	21	33190	33210	R_1350	26	75593	75618	R_2101	20	124557	124576
R_600	24	33222	33245	R_1351	41	75815	75855	R_2102	32	124648	124679

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R_602	26	33317	33342	R_1353	20	75944	75963	R_2104	20	124700	124719
R_603	25	33344	33368	R_1354	37	75964	76000	R_2105	35	124712	124746
R_604	20	33379	33398	R_1355	20	76123	76142	R_2106	70	124748	124817
R_605	22	33395	33416	R_1356	30	76156	76185	R_2107	21	124824	124844
R_606	20	33395	33414	R_1357	80	76199	76278	R_2108	23	124859	124881
R_607	22	33400	33421	R_1358	23	76296	76318	R_2109	35	124883	124917
R_608	22	33457	33478	R_1359	21	76327	76347	R_2110	20	124919	124938
R_609	22	33512	33533	R_1360	24	76341	76364	R_2111	57	124940	124996
R_610	23	33532	33554	R_1361	61	76366	76426	R_2112	38	125015	125052
R_611	24	33532	33555	R_1362	26	76467	76492	R_2113	21	125032	125052
R_612	28	33535	33562	R_1363	35	76520	76554	R_2114	29	125064	125092
R_613	21	33547	33567	R_1364	58	76571	76628	R_2115	37	125107	125143
R_614	20	33548	33567	R_1365	57	76697	76753	R_2116	42	125198	125239
R_615	23	33582	33604	R_1366	22	76755	76776	R_2117	50	125241	125290
R_616	20	33588	33607	R_1367	23	76822	76844	R_2118	42	125292	125333
R_617	24	33618	33641	R_1368	42	76863	76904	R_2119	31	125346	125376
R_618	26	33675	33700	R_1369	26	76906	76931	R_2120	22	125378	125399
R_619	29	33726	33754	R_1370	51	76944	76994	R_2121	46	125401	125446
R_620	47	33775	33821	R_1371	69	77037	77105	R_2122	33	125700	125732
R_621	20	33835	33854	R_1372	26	77153	77178	R_2123	32	125734	125765
R_622	49	33856	33904	R_1373	85	77180	77264	R_2124	48	125803	125850
R_623	64	33948	34011	R_1374	35	77271	77305	R_2125	35	125912	125946
R_624	20	34025	34044	R_1375	41	77307	77347	R_2126	45	125948	125992
R_625	20	34072	34091	R_1376	27	77433	77459	R_2127	73	126012	126084
R_626	31	34139	34169	R_1377	24	77462	77485	R_2128	60	126087	126146
R_627	78	34179	34256	R_1378	30	77508	77537	R_2129	32	126341	126372
R_628	49	34258	34306	R_1379	36	77561	77596	R_2130	22	126374	126395
R_629	29	34379	34407	R_1380	39	77615	77653	R_2131	25	126388	126412
R_630	21	34417	34437	R_1381	50	77655	77704	R_2132	20	126473	126492
R_631	27	34449	34475	R_1382	20	77719	77738	R_2133	22	126484	126505
R_632	24	34495	34518	R_1383	26	77762	77787	R_2134	24	126660	126683
R_633	21	34516	34536	R_1384	29	77807	77835	R_2135	23	126691	126713
R_634	21	34562	34582	R_1385	23	77837	77859	R_2136	34	126715	126748
R_635	21	34572	34592	R_1386	26	77861	77886	R_2137	22	126822	126843
R_636	22	34576	34597	R_1387	22	77910	77931	R_2138	20	126885	126904
R_637	32	34612	34643	R_1388	45	77933	77977	R_2139	38	127054	127091
R_638	24	34646	34669	R_1389	36	78017	78052	R_2140	40	127111	127150
R_639	65	34681	34745	R_1390	24	78074	78097	R_2141	30	127201	127230
R_640	139	34765	34903	R_1391	47	78136	78182	R_2142	21	127232	127252
R_641	60	34943	35002	R_1392	93	78184	78276	R_2143	76	127258	127333

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
		start	end			start	end			start	end
R_642	52	35012	35063	R_1393	24	78282	78305	R_2144	59	127359	127417
R_643	83	35065	35147	R_1394	99	78319	78417	R_2145	33	127419	127451
R_644	21	35160	35180	R_1395	42	78420	78461	R_2146	52	127567	127618
R_645	29	35188	35216	R_1396	23	78478	78500	R_2147	38	127620	127657
R_646	21	35218	35238	R_1397	21	78647	78667	R_2148	49	127656	127704
R_647	59	35269	35327	R_1398	34	78736	78769	R_2149	37	127706	127742
R_648	26	35330	35355	R_1399	20	78891	78910	R_2150	60	127761	127820
R_649	44	35372	35415	R_1400	26	78926	78951	R_2151	25	127953	127977
R_650	20	35417	35436	R_1401	21	78953	78973	R_2152	30	128097	128126
R_651	43	35442	35484	R_1402	69	78997	79065	R_2153	40	128187	128226
R_652	22	35482	35503	R_1403	21	79067	79087	R_2154	58	128237	128294
R_653	74	35505	35578	R_1404	25	79091	79115	R_2155	20	128323	128342
R_654	20	35599	35618	R_1405	21	79122	79142	R_2156	32	128408	128439
R_655	25	35620	35644	R_1406	24	79160	79183	R_2157	37	128425	128461
R_656	39	35654	35692	R_1407	31	79187	79217	R_2158	22	128463	128484
R_657	26	35697	35722	R_1408	75	79219	79293	R_2159	56	128500	128555
R_658	30	35724	35753	R_1409	27	79308	79334	R_2160	21	128565	128585
R_659	23	35756	35778	R_1410	71	79366	79436	R_2161	29	128586	128614
R_660	22	35777	35798	R_1411	34	79469	79502	R_2162	53	128631	128683
R_661	40	35838	35877	R_1412	41	79534	79574	R_2163	59	128685	128743
R_662	24	35879	35902	R_1413	28	79576	79603	R_2164	99	128738	128836
R_663	20	35887	35906	R_1414	23	79605	79627	R_2165	23	128850	128872
R_664	21	35894	35914	R_1415	24	79712	79735	R_2166	20	128896	128915
R_665	62	35928	35989	R_1416	35	79738	79772	R_2167	63	128922	128984
R_666	27	36002	36028	R_1417	37	79793	79829	R_2168	25	129031	129055
R_667	20	36025	36044	R_1418	38	79847	79884	R_2169	28	129071	129098
R_668	21	36030	36050	R_1419	48	79924	79971	R_2170	69	129104	129172
R_669	64	36099	36162	R_1420	31	80108	80138	R_2171	27	129196	129222
R_670	30	36171	36200	R_1421	34	80140	80173	R_2172	38	129235	129272
R_671	39	36202	36240	R_1422	77	80211	80287	R_2173	30	129330	129359
R_672	56	36242	36297	R_1423	55	80307	80361	R_2174	33	129345	129377
R_673	47	36307	36353	R_1424	26	80366	80391	R_2175	40	129401	129440
R_674	34	36404	36437	R_1425	38	80419	80456	R_2176	24	129427	129450
R_675	22	36439	36460	R_1426	20	80472	80491	R_2177	22	129443	129464
R_676	20	36493	36512	R_1427	21	80505	80525	R_2178	34	129488	129521
R_677	24	36514	36537	R_1428	40	80527	80566	R_2179	79	129540	129618
R_678	20	36568	36587	R_1429	37	80571	80607	R_2180	69	129617	129685
R_679	32	36589	36620	R_1430	40	80618	80657	R_2181	29	129705	129733
R_680	25	36622	36646	R_1431	29	80671	80699	R_2182	65	129735	129799
R_681	22	36654	36675	R_1432	36	80732	80767	R_2183	48	129801	129848
R_682	26	36678	36703	R_1433	39	80791	80829	R_2184	37	129884	129920

Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1		Reg.	length (nt)	Position on SEQ ID NO: 1	
		start	end			start	end			start	end
R_683	28	36728	36755	R_1434	37	80830	80866	R_2185	42	129918	129959
R_684	41	36790	36830	R_1435	53	80868	80920	R_2186	38	129988	130025
R_685	60	36862	36921	R_1436	30	80996	81025	R_2187	26	130084	130109
R_686	37	36940	36976	R_1437	25	81027	81051	R_2188	24	130125	130148
R_687	55	37002	37056	R_1438	55	81053	81107	R_2189	36	130150	130185
R_688	44	37124	37167	R_1439	68	81109	81176	R_2190	21	130247	130267
R_689	29	37169	37197	R_1440	24	81225	81248	R_2191	80	130269	130348
R_690	25	37232	37256	R_1441	68	81264	81331	R_2192	30	130384	130413
R_691	21	37258	37278	R_1442	23	81344	81366	R_2193	21	130424	130444
R_692	75	37280	37354	R_1443	64	81377	81440	R_2194	37	130564	130600
R_693	93	37399	37491	R_1444	26	81481	81506	R_2195	21	130663	130683
R_694	22	37465	37486	R_1445	31	81571	81601	R_2196	43	130690	130732
R_695	21	37491	37511	R_1446	44	81608	81651	R_2197	61	130735	130795
R_696	20	37543	37562	R_1447	47	81694	81740	R_2198	109	130797	130905
R_697	23	37582	37604	R_1448	27	81757	81783	R_2199	51	130941	130991
R_698	31	37608	37638	R_1449	36	81780	81815	R_2200	23	131025	131047
R_699	21	37660	37680	R_1450	25	81817	81841	R_2201	21	131064	131084
R_700	21	37720	37740	R_1451	46	81866	81911	R_2202	35	131119	131153
R_701	35	37778	37812	R_1452	23	81916	81938	R_2203	62	131155	131216
R_702	72	37825	37896	R_1453	27	81946	81972	R_2204	39	131269	131307
R_703	35	37926	37960	R_1454	20	82028	82047	R_2205	22	131309	131330
R_704	42	37962	38003	R_1455	55	82049	82103	R_2206	32	131350	131381
R_705	20	38119	38138	R_1456	71	82122	82192	R_2207	52	131432	131483
R_706	28	38162	38189	R_1457	32	82216	82247	R_2208	43	131501	131543
R_707	23	38215	38237	R_1458	47	82278	82324	R_2209	20	131565	131584
R_708	22	38249	38270	R_1459	25	82498	82522	R_2210	90	131606	131695
R_709	79	38284	38362	R_1460	27	82549	82575	R_2211	79	131697	131775
R_710	30	38419	38448	R_1461	48	82606	82653	R_2212	69	131758	131826
R_711	25	38476	38500	R_1462	26	82655	82680	R_2213	20	131877	131896
R_712	21	38486	38506	R_1463	27	82699	82725	R_2214	21	131898	131918
R_713	22	38520	38541	R_1464	67	82735	82801	R_2215	23	131951	131973
R_714	47	38548	38594	R_1465	56	82833	82888	R_2216	37	131975	132011
R_715	22	38603	38624	R_1466	29	82898	82926	R_2217	25	132017	132041
R_716	27	38623	38649	R_1467	26	82928	82953	R_2218	29	132061	132089
R_717	22	38709	38730	R_1468	45	82990	83034	R_2219	22	132091	132112
R_718	21	38734	38754	R_1469	73	83083	83155	R_2220	32	132138	132169
R_719	46	38777	38822	R_1470	39	83180	83218	R_2221	36	132182	132217
R_720	33	38853	38885	R_1471	70	83255	83324	R_2222	26	132253	132278
R_721	27	38897	38923	R_1472	35	83346	83380	R_2223	48	132280	132327
R_722	23	38982	39004	R_1473	23	83409	83431	R_2224	33	132403	132435
R_723	26	39007	39032	R_1474	111	83433	83543	R_2225	58	132437	132494

Reg.	lengt h (nt)	Position on SEQ ID NO: 1		Reg.	lengt h (nt)	Position on SEQ ID NO: 1		Reg.	lengt h (nt)	Position on SEQ ID NO: 1	
		start	end			start	end			start	end
R_724	23	39007	39029	R_1475	39	83553	83591	R_2226	33	132496	132528
R_725	20	39016	39035	R_1476	54	83628	83681	R_2227	60	132541	132600
R_726	21	39026	39046	R_1477	36	83710	83745	R_2228	22	132619	132640
R_727	30	39048	39077	R_1478	32	83776	83807	R_2229	23	132656	132678
R_728	31	39140	39170	R_1479	23	83809	83831	R_2230	21	132758	132778
R_729	24	39161	39184	R_1480	53	83854	83906	R_2231	39	132780	132818
R_730	36	39188	39223	R_1481	20	83960	83979	R_2232	47	132827	132873
R_731	28	39235	39262	R_1482	43	83995	84037	R_2233	27	132893	132919
R_732	39	39264	39302	R_1483	73	84051	84123	R_2234	65	132917	132981
R_733	52	39328	39379	R_1484	40	84142	84181	R_2235	20	132983	133002
R_734	59	39391	39449	R_1485	52	84217	84268	R_2236	67	133014	133080
R_735	30	39463	39492	R_1486	28	84270	84297	R_2237	46	133082	133127
R_736	20	39492	39511	R_1487	20	84354	84373	R_2238	39	133129	133167
R_737	20	39519	39538	R_1488	21	84440	84460	R_2239	31	133169	133199
R_738	37	39557	39593	R_1489	31	84488	84518	R_2240	34	133201	133234
R_739	34	39595	39628	R_1490	22	84653	84674	R_2241	27	133251	133277
R_740	34	39639	39672	R_1491	29	84727	84755	R_2242	20	133282	133301
R_741	26	39682	39707	R_1492	38	84851	84888	R_2243	37	133343	133379
R_742	20	39709	39728	R_1493	21	84887	84907	R_2244	30	133404	133433
R_743	23	39746	39768	R_1494	58	84932	84989	R_2245	77	133435	133511
R_744	23	39753	39775	R_1495	35	84991	85025	R_2246	48	133528	133575
R_745	20	39777	39796	R_1496	24	85109	85132	R_2247	22	133676	133697
R_746	20	39798	39817	R_1497	60	85135	85194	R_2248	54	133710	133763
R_747	41	39833	39873	R_1498	27	85206	85232	R_2249	20	133765	133784
R_748	20	39876	39895	R_1499	26	85239	85264	R_2250	29	133786	133814
R_749	36	39907	39942	R_1500	32	85327	85358	R_2251	40	133816	133855
R_750	47	39990	40036	R_1501	24	85390	85413	R_2252	42	133857	133898
R_751	36	40074	40109	R_1502	24	85520	85543	R_2253	63	133900	133962
								R_2254	40	133964	134003

In some embodiments the target sequence is a sequence selected from a human MAPT mRNA intron, such as a Tau human mRNA intron 1 or 2 (see table 1 above).

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

The target sequence to which the oligonucleotide is complementary or hybridizes to generally comprises a contiguous nucleobases sequence of at least 10 nucleotides. The contiguous nucleotide sequence is between 10 to 100 nucleotides, such as 12 to 60, such as 13 to 50, such as 14 to 30, such as 15 to 25, such as 16 to 20 contiguous nucleotides.

In one embodiment of the invention the target sequence is SEQ ID NO: 3, corresponding to region A. In certain embodiments the target sequence is selected from position 12051 – 12111 of SEQ ID NO: 1 such as positon 12051 – 12079, position 12085-12111 or position 12060 – 12078 of SEQ ID NO: 1.

In another embodiment of the invention the target sequence is SEQ ID NO: 4, corresponding to region B. In certain embodiments the target sequence is selected from position 39562-39593 of SEQ ID NO: 1 such as positon 39573-39592 of SEQ ID NO: 1.

In another embodiment of the invention the target sequence is SEQ ID NO: 5, corresponding to region C. In certain embodiments the target sequence is selected from position 72837-72940 of SEQ ID NO: 1 such as positon 72861-72891 or position 72862-72890 of SEQ ID NO: 1.

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 rodent cell, such as a mouse cell or a rat cell, or a primate cell such as a monkey cell or a human cell.

In preferred embodiments the target cell expresses Tau mRNA, such as the Tau pre-mRNA or Tau mature mRNA. The poly A tail of Tau mRNA is typically disregarded for antisense oligonucleotide targeting.

Naturally occurring variant

The term "naturally occurring variant" refers to variants of MAPT 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 (SNPs), 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 MAPT target nucleic acid, such as a target nucleic acid selected form the group consisting of SEQ ID NO 1 and 2. In some embodiments the naturally occurring variants have at least 99% homology to the human MAPT target nucleic acid of SEQ ID NO: 1.

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 Tau when compared to the amount of Tau before administration of the oligonucleotide. Alternatively, modulation of expression may be

determined by reference to a control experiment. It is generally understood that the control is an individual or target cell treated with a saline composition or an individual or target cell treated with a non-targeting oligonucleotide (mock).

One type of modulation is the ability of an oligonucleotide to inhibit, down-regulate, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of Tau, e.g. by degradation of mRNA or blockage of transcription. Another type of modulation is an oligonucleotide's ability to restore, increase or enhance expression of Tau, e.g. by repair of splice sites or prevention of splicing or removal or blockage of inhibitory mechanisms such as microRNA repression.

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.

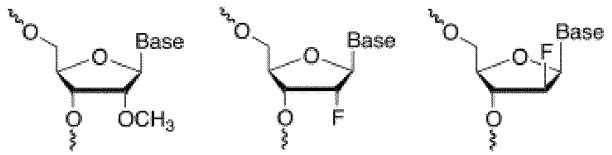
Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between 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.

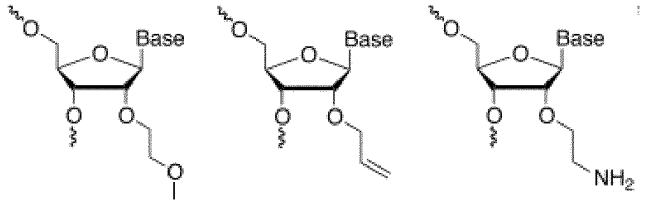
2' sugar modified nucleosides

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 capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2' – 4' biradicle bridged) nucleosides.

Indeed, much focus has been spent on developing 2' sugar substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides. 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.



2'-*O*-Me 2'F-RNA 2'F-ANA



2'-*O*-MOE 2'-*O*-Allyl 2'-*O*-Ethylamine

In relation to the present invention 2' substituted sugar modified nucleosides does not include 2' bridged nucleosides like LNA.

Locked Nucleic Acid Nucleosides (LNA nucleoside)

A "LNA nucleoside" is a 2'-sugar modified nucleoside which comprises a biradical linking the C2' and C4' of the ribose sugar ring of said nucleoside (also referred to as a "2'- 4' bridge"),

which restricts or locks the conformation of the ribose ring. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature. The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex.

Non limiting, exemplary LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352, WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita et al., Bioorganic & Med.Chem. Lett. 12, 73-76, Seth et al. J. Org. Chem. 2010, Vol 75(5) pp. 1569-81, Mitsuoka et al., Nucleic Acids Research 2009, 37(4), 1225-1238, and Wan and Seth, J. Medical Chemistry 2016, 59, 9645−9667.

The 2'-4' bridge comprises 2 to 4 bridging atoms and is in particular of formula -X-Y- wherein

X is oxygen, sulfur, $-CR^aR^b-$, $-C(R^a)=C(R^b)-$, $-C(=CR^aR^b)-$, $-C(R^a)=N-$, $-Si(R^a)_2-$, $-SO_2-$, $-NR^a-$; $-O-NR^a-$, $-NR^a-O-$, $-C(=J)-$, Se, $-O-NR^a-$, $-NR^a-CR^aR^b-$, $-N(R^a)-O-$ or $-O-CR^aR^b-$;

Y is oxygen, sulfur, $-(CR^aR^b)_n-$, $-CR^aR^b-O-CR^aR^b-$, $-C(R^a)=C(R^b)-$, $-C(R^a)=N-$, $-Si(R^a)_2-$, $-SO_2-$, $-NR^a-$, $-C(=J)-$, Se, $-O-NR^a-$, $-NR^a-CR^aR^b-$, $-N(R^a)-O-$ or $-O-CR^aR^b-$;

with the proviso that -X-Y- is not -O-O-, $Si(R^a)_2-Si(R^a)_2-$, $-SO_2-SO_2-$, $-C(R^a)=C(R^b)-C(R^a)=C(R^b)$, $-C(R^a)=N-C(R^a)=N-$, $-C(R^a)=N-C(R^a)=C(R^b)$, $-C(R^a)=C(R^b)-C(R^a)=N-$ or -Se-Se-;

J is oxygen, sulfur, $=CH_2$ or $=N(R^a)$;

R^a and R^b are independently selected from hydrogen, halogen, hydroxyl, cyano, thiohydroxyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl, formyl, aryl, heterocyclyl, amino, alkylamino, carbamoyl, alkylaminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, alkylcarbonylamino, carbamido, alkanoyloxy, sulfonyl, alkylsulfonyloxy, nitro, azido, thiohydroxylsulfidealkylsulfanyl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, $-OC(=X^a)R^c$, $-OC(=X^a)NR^cR^d$ and $-NR^eC(=X^a)NR^cR^d$;

or two geminal R^a and R^b together form optionally substituted methylene;

or two geminal R^a and R^b, together with the carbon atom to which they are attached, form cycloalkyl or halocycloalkyl, with only one carbon atom of -X-Y-;

wherein substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkoxy and substituted methylene are alkyl, alkenyl, alkynyl and methylene substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl, formyl, heterocylyl, aryl and heteroaryl;

X^a is oxygen, sulfur or $-NR^c$;

R^c, R^d and R^e are independently selected from hydrogen and alkyl; and

n is 1, 2 or 3.

In a further particular embodiment of the invention, X is oxygen, sulfur, $-NR^a-$, $-CR^aR^b-$ or $-C(=CR^aR^b)-$, particularly oxygen, sulfur, -NH-, $-CH_2-$ or $-C(=CH_2)-$, more particularly oxygen.

In another particular embodiment of the invention, Y is $-CR^aR^b-$, $-CR^aR^b-CR^aR^b-$ or $-CR^aR^b-CR^aR^b-CR^aR^b-$, particularly $-CH_2-CHCH_3-$, $-CHCH_3-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$.

In a particular embodiment of the invention, -X-Y- is $-O-(CR^aR^b)_n-$, $-S-CR^aR^b-$, $-N(R^a)CR^aR^b-$, $-CR^aR^b-CR^aR^b-$, $-O-CR^aR^b-O-CR^aR^b-$, $-CR^aR^b-O-CR^aR^b-$, $-C(=CR^aR^b)-CR^aR^b-$, $-N(R^a)CR^aR^b-$, $-O-N(R^a)-CR^aR^b-$ or $-N(R^a)-O-CR^aR^b-$.

In a particular embodiment of the invention, R^a and R^b are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl and alkoxyalkyl, in particular hydrogen, halogen, alkyl and alkoxyalkyl.

In another embodiment of the invention, R^a and R^b are independently selected from the group consisting of hydrogen, fluoro, hydroxyl, methyl and $-CH_2-O-CH_3$, in particular hydrogen, fluoro, methyl and $-CH_2-O-CH_3$.

Advantageously, one of R^a and R^b of -X-Y- is as defined above and the other ones are all hydrogen at the same time.

In a further particular embodiment of the invention, R^a is hydrogen or alkyl, in particular hydrogen or methyl.

In another particular embodiment of the invention, R^b is hydrogen or or alkyl, in particular hydrogen or methyl.

In a particular embodiment of the invention, one or both of R^a and R^b are hydrogen.

In a particular embodiment of the invention, only one of R^a and R^b is hydrogen.

In one particular embodiment of the invention, one of R^a and R^b is methyl and the other one is hydrogen.

In a particular embodiment of the invention, R^a and R^b are both methyl at the same time.

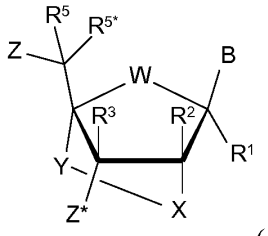
In a particular embodiment of the invention, -X-Y- is -O-CH_2-, -S-CH_2-, -S-$CH(CH_3)$-, -NH-CH_2-, -O-CH_2CH_2-, -O-$CH(CH_2$-O-$CH_3)$-, -O-$CH(CH_2CH_3)$-, -O-$CH(CH_3)$-, -O-CH_2-O-CH_2-, -O-CH_2-O-CH_2-, -CH_2-O-CH_2-, -$C(=CH_2)CH_2$-, -$C(=CH_2)CH(CH_3)$-, -$N(OCH_3)CH_2$- or -$N(CH_3)CH_2$-;

In a particular embodiment of the invention, -X-Y- is -O-CR^aR^b- wherein R^a and R^b are independently selected from the group consisting of hydrogen, alkyl and alkoxyalkyl, in particular hydrogen, methyl and -CH_2-O-CH_3.

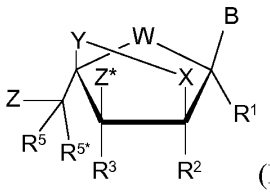
In a particular embodiment, -X-Y- is -O-CH_2- or -O-$CH(CH_3)$-, particularly -O-CH_2-.

The 2'- 4' bridge may be positioned either below the plane of the ribose ring (beta-D-configuration), or above the plane of the ring (alpha-L- configuration), as illustrated in formula (A) and formula (B) respectively.

The LNA nucleoside according to the invention is in particular of formula (A) or (B)



(A);



(B);

wherein

W is oxygen, sulfur, -N(R^a)- or -CR^aR^b-, in particular oxygen;

B is a nucleobase or a modified nucleobase;

Z is an internucleoside linkage to an adjacent nucleoside or a 5'-terminal group;

Z* is an internucleoside linkage to an adjacent nucleoside or a 3'-terminal group;

R^1, R^2, R^3, R^5 and R^{5*} are independently selected from hydrogen, halogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxy, alkoxy, alkoxyalkyl, azido, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl, formyl and aryl; and

X, Y, R^a and R^b are as defined above.

In a particular embodiment, in the definition of -X-Y-, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In another particular embodiment, in the definition of -X-Y-, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In a further particular embodiment, in the definition of -X-Y-, one or both of R^a and R^b are hydrogen. In a particular embodiment, in the definition of -X-Y-, only one of R^a and R^b is hydrogen. In one particular embodiment, in the definition of -X-Y-, one of R^a and R^b is methyl and the other one is hydrogen. In a particular embodiment, in the definition of -X-Y-, R^a and R^b are both methyl at the same time.

In a further particular embodiment, in the definition of X, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In another particular embodiment, in the definition of X, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In a particular embodiment, in the definition of X, one or both of R^a and R^b are hydrogen. In a particular embodiment, in the definition of X, only one of R^a and R^b is hydrogen. In one particular embodiment, in the definition of X, one of R^a and R^b is methyl and the other one is hydrogen. In a particular embodiment, in the definition of X, R^a and R^b are both methyl at the same time.

In a further particular embodiment, in the definition of Y, R^a is hydrogen or alkyl, in particular hydrogen or methyl. In another particular embodiment, in the definition of Y, R^b is hydrogen or alkyl, in particular hydrogen or methyl. In a particular embodiment, in the definition of Y, one or both of R^a and R^b are hydrogen. In a particular embodiment, in the definition of Y, only one of R^a and R^b is hydrogen. In one particular embodiment, in the definition of Y, one of R^a and R^b is methyl and the other one is hydrogen. In a particular embodiment, in the definition of Y, R^a and R^b are both methyl at the same time.

In a particular embodiment of the invention R^1, R^2, R^3, R^5 and R^{5*} are independently selected from hydrogen and alkyl, in particular hydrogen and methyl.

In a further particular advantageous embodiment of the invention, R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time.

In another particular embodiment of the invention, R^1, R^2, R^3, are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is as defined above, in particular alkyl, more particularly methyl.

In a particular embodiment of the invention, R^5 and R^{5*} are independently selected from hydrogen, halogen, alkyl, alkoxyalkyl and azido, in particular from hydrogen, fluoro, methyl, methoxyethyl and azido. In particular advantageous embodiments of the invention, one of R^5 and R^{5*} is hydrogen and the other one is alkyl, in particular methyl, halogen, in particular fluoro, alkoxyalkyl, in particular methoxyethyl or azido; or R^5 and R^{5*} are both hydrogen or halogen at the same time, in particular both hydrogen of fluoro at the same time. In such particular embodiments, W can advantageously be oxygen, and -X-Y- advantageously -O-CH_2-.

In a particular embodiment of the invention, -X-Y- is -O-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352 and WO 2004/046160 which are all hereby incorporated by reference, and include what are commonly known in the art as beta-D-oxy LNA and alpha-L-oxy LNA nucleosides.

In another particular embodiment of the invention, -X-Y- is -S-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such thio LNA nucleosides are disclosed in WO 99/014226 and WO 2004/046160 which are hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -NH-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such amino LNA nucleosides are disclosed in WO 99/014226 and WO 2004/046160 which are hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -O-CH_2CH_2- or -O$CH_2CH_2CH_2$-, W is oxygen, and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are disclosed in WO 00/047599 and Morita *et al.*, Bioorganic & Med.Chem. Lett. 12, 73-76, which are hereby incorporated by reference, and include what are commonly known in the art as 2'-O-4'C-ethylene bridged nucleic acids (ENA).

In another particular embodiment of the invention, -X-Y- is -O-CH_2-, W is oxygen, R^1, R^2, R^3 are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is not hydrogen, such as alkyl, for example methyl. Such 5' substituted LNA nucleosides are disclosed in WO 2007/134181 which is hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -O-CR^aR^b-, wherein one or both of R^a and R^b are not hydrogen, in particular alkyl such as methyl, W is oxygen, R^1, R^2, R^3 are all hydrogen at the same time, one of R^5 and R^{5*} is hydrogen and the other one is not hydrogen, in particular alkyl, for example methyl. Such bis modified LNA nucleosides are disclosed in WO 2010/077578 which is hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -O-CHR^a-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such 6'-substituted LNA nucleosides are disclosed in WO 2010/036698 and WO 2007/090071 which are both hereby incorporated by reference. In such 6'-substituted LNA nucleosides, R^a is in particular C_1-C_6 alkyl, such as methyl.

In another particular embodiment of the invention, -X-Y- is -O-CH(CH_2-O-CH_3)- ("2' O-methoxyethyl bicyclic nucleic acid", Seth *et al.* J. Org. Chem. 2010, Vol 75(5) pp. 1569-81).

In another particular embodiment of the invention, -X-Y- is -O-CH(CH_2CH_3)- ("2'O-ethyl bicyclic nucleic acid", *Seth at al.*, J. Org. Chem. 2010, Vol 75(5) pp. 1569-81).

In another particular embodiment of the invention, -X-Y- is -O-CH(CH_2-O-CH_3)-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such LNA nucleosides are also known in the art as cyclic MOEs (cMOE) and are disclosed in WO 2007/090071.

In another particular embodiment of the invention, -X-Y- is -O-CH(CH_3)-.

In another particular embodiment of the invention, -X-Y- is -O-CH_2-O-CH_2- (Seth *et al.*, J. Org. Chem 2010 op. cit.)

In another particular embodiment of the invention, -X-Y- is -O-$CH(CH_3)$-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such 6'-methyl LNA nucleosides are also known in the art as cET nucleosides, and may be either (S)-cET or (R)-cET diastereoisomers, as disclosed in WO 2007/090071 (beta-D) and WO 2010/036698 (alpha-L) which are both hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -O-CR^aR^b-, wherein neither R^a nor R^b is hydrogen, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. In a particular embodiment, R^a and R^b are both alkyl at the same time, in particular both methyl at the same time. Such 6'-di-substituted LNA nucleosides are disclosed in WO 2009/006478 which is hereby incorporated by reference.

In another particular embodiment of the invention, -X-Y- is -S-CHR^a-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. Such 6'-substituted thio LNA nucleosides are disclosed in WO 2011/156202 which is hereby incorporated by reference. In a particular embodiment of such 6'-substituted thio LNA, R^a is alkyl, in particular methyl.

In a particular embodiment of the invention, -X-Y- is -C(=CH_2)C(R^aR^b)-, -C(=CHF)C(R^aR^b)- or -C(=CF_2)C(R^aR^b)-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. R^a and R^b are advantagesously independently selected from hydrogen, halogen, alkyl and alkoxyalkyl, in particular hydrogen, methyl, fluoro and methoxymethyl. R^a and R^b are in particular both hydrogen or methyl at the same time or one of R^a and R^b is hydrogen and the other one is methyl. Such vinyl carbo LNA nucleosides are disclosed in WO 2008/154401 and WO 2009/067647 which are both hereby incorporated by reference.

In a particular embodiment of the invention, -X-Y- is -N(OR^a)-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. In a particular embodiment, R^a is alkyl such as methyl. Such LNA nucleosides are also known as N substituted LNAs and are disclosed in WO 2008/150729 which is hereby incorporated by reference.

In a particular embodiment of the invention, -X-Y- is -O-N(R^a)-, -N(R^a)-O-, -NR^a-CR^aR^b-CR^aR^b- or -NR^a-CR^aR^b-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. R^a and R^b are advantagesously independently selected from hydrogen, halogen, alkyl and alkoxyalkyl, in particular hydrogen, methyl, fluoro and methoxymethyl. In a particular embodiment, R^a is alkyl, such as methyl, R^b is hydrogen or methyl, in particular hydrogen. (Seth *et al.*, J. Org. Chem 2010 op. cit.).

In a particular embodiment of the invention, -X-Y- is -O-N(CH_3)- (Seth *et al.*, J. Org. Chem 2010 op. cit.).

In a particular embodiment of the invention, R^5 and R^{5*} are both hydrogen at the same time. In another particular embodiment of the invention, one of R^5 and R^{5*} is hydrogen and the other one is alkyl, such as methyl. In such embodiments, R^1, R^2 and R^3 can be in particular hydrogen and -X-Y- can be in particular -O-CH_2- or -O-CHC(R^a)$_3$-, such as -O-CH(CH_3)-.

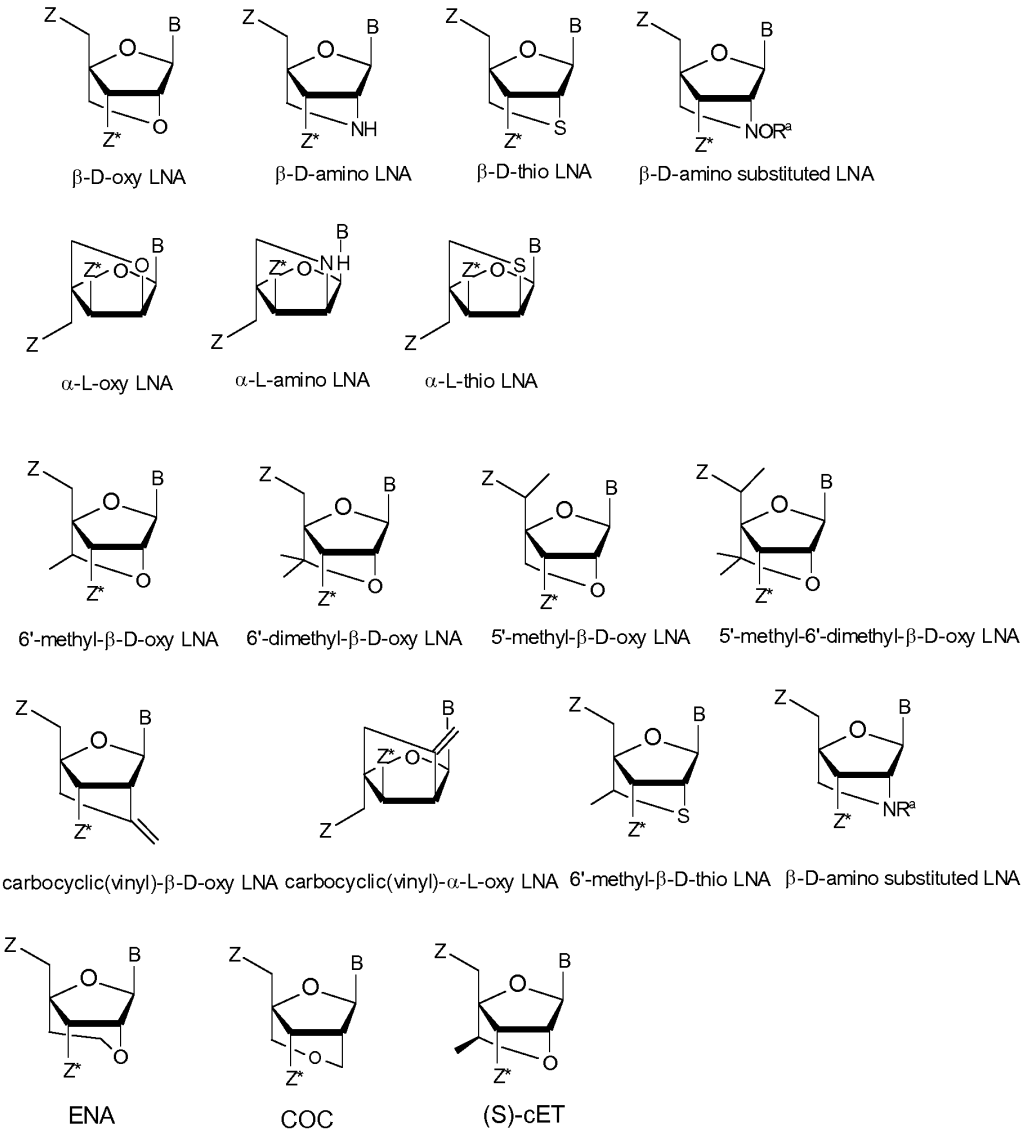
In a particular embodiment of the invention, -X-Y- is -CR^aR^b-O-CR^aR^b-, such as -CH_2-O-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. In such particular embodiments, R^a can be in particular alkyl such as methyl, R^b hydrogen or methyl, in particular hydrogen. Such LNA nucleosides are also known as conformationally restricted nucleotides (CRNs) and are disclosed in WO 2013/036868 which is hereby incorporated by reference.

In a particular embodiment of the invention, -X-Y- is -O-CR^aR^b-O-CR^aR^b-, such as -O-CH_2-O-CH_2-, W is oxygen and R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen at the same time. R^a and R^b are advantageously independently selected from hydrogen, halogen, alkyl and alkoxyalkyl, in particular hydrogen, methyl, fluoro and methoxymethyl. In such a particular embodiment, R^a can be in particular alkyl such as methyl, R^b hydrogen or methyl, in particular hydrogen. 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.

Particular examples of LNA nucleosides of the invention are presented in Scheme 1 (wherein B is as defined above).

Scheme 1



Particular LNA nucleosides are beta-D-oxy-LNA, 6'-methyl-beta-D-oxy LNA such as (S)-6'-methyl-beta-D-oxy-LNA (ScET) and ENA.

If one of the starting materials or compounds of the invention contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described e.g. in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wuts, 3rd Ed., 1999, Wiley, New York) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature. Examples of protecting groups are tert-butoxycarbonyl (Boc), 9-fluorenylmethyl

carbamate (Fmoc), 2-trimethylsilylethyl carbamate (Teoc), carbobenzyloxy (Cbz) and p-methoxybenzyloxycarbonyl (Moz).

The compounds described herein can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

The term “asymmetric carbon atom” means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention an asymmetric carbon atom can be of the “R” or “S” configuration.

Chemical group definitions

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C_1-C_8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl and propyl.

The term “cycloalkyl”, alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, more particularly cyclopropyl and cyclobutyl. A particular example of “cycloalkyl” is cyclopropyl.

The term “alkoxy”, alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy and tert.butoxy. Particular “alkoxy” are methoxy and ethoxy. Methoxyethoxy is a particular example of “alkoxyalkoxy”.

The term “oxy”, alone or in combination, signifies the -O- group.

The term “alkenyl”, alone or in combination, signifies a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl.

The term “alkynyl”, alone or in combination, signifies a straight-chain or branched hydrocarbon residue comprising a triple bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms.

The terms “halogen” or “halo”, alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine, chlorine or bromine, more particularly fluorine. The term “halo”, in combination with another group, denotes the substitution of said group with at least one halogen, particularly substituted with one to five halogens, particularly one to four halogens, i.e. one, two, three or four halogens.

The term “haloalkyl”, alone or in combination, denotes an alkyl group substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl or trifluoromethyl. Fluoromethyl, difluoromethyl and trifluoromethyl are particular “haloalkyl”.

The term “halocycloalkyl”, alone or in combination, denotes a cycloalkyl group as defined above substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. Particular example of “halocycloalkyl” are halocyclopropyl, in particular fluorocyclopropyl, difluorocyclopropyl and trifluorocyclopropyl.

The terms “hydroxyl” and “hydroxy”, alone or in combination, signify the -OH group.

The terms “thiohydroxyl” and “thiohydroxy”, alone or in combination, signify the -SH group.

The term “carbonyl”, alone or in combination, signifies the -C(O)- group.

The term “carboxy” or “carboxyl”, alone or in combination, signifies the -COOH group.

The term “amino”, alone or in combination, signifies the primary amino group ($-NH_2$), the secondary amino group (-NH-), or the tertiary amino group (-N-).

The term “alkylamino”, alone or in combination, signifies an amino group as defined above substituted with one or two alkyl groups as defined above.

The term “sulfonyl”, alone or in combination, means the $-SO_2$ group.

The term “sulfinyl”, alone or in combination, signifies the -SO- group.

The term “sulfanyl”, alone or in combination, signifies the -S- group.

The term “cyano”, alone or in combination, signifies the -CN group.

The term “azido”, alone or in combination, signifies the $-N_3$ group.

The term “nitro”, alone or in combination, signifies the NO_2 group.

The term “formyl”, alone or in combination, signifies the -C(O)H group.

The term “carbamoyl”, alone or in combination, signifies the $-C(O)NH_2$ group.

The term “cabamido”, alone or in combination, signifies the $-NH-C(O)-NH_2$ group.

The term “aryl”, alone or in combination, denotes a monovalent aromatic carbocyclic mono- or bicyclic ring system comprising 6 to 10 carbon ring atoms, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl. Examples of aryl include phenyl and naphthyl, in particular phenyl.

The term “heteroaryl”, alone or in combination, denotes a monovalent aromatic heterocyclic mono- or bicyclic ring system of 5 to 12 ring atoms, comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, the remaining ring atoms being carbon, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl. Examples of heteroaryl include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, triazinyl, azepinyl, diazepinyl, isoxazolyl, benzofuranyl, isothiazolyl, benzothienyl, indolyl, isoindolyl, isobenzofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzooxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl or acridinyl.

The term “heterocyclyl”, alone or in combination, signifies a monovalent saturated or partly unsaturated mono- or bicyclic ring system of 4 to 12, in particular 4 to 9 ring atoms, comprising 1, 2,3 or 4 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, alkenyloxy, carboxyl, alkoxycarbonyl, alkylcarbonyl and formyl. Examples for monocyclic saturated heterocyclyl are azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples for partly unsaturated heterocycloalkyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl or dihydropyranyl.

Pharmaceutically acceptable salts

The term “pharmaceutically acceptable salts” refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, particularly hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic

acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein. In addition these salts may be prepared form addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins. The compound of formula (I) can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula (I) are the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and methanesulfonic acid.

Protecting group

The term “protecting group”, alone or in combination, signifies a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site. Protecting groups can be removed. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups.

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 consecutive 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). For use in determining RHase H activity, recombinant human RNase H1 is available from Lubio Science GmbH, Lucerne, Switzerland.

Gapmer

The antisense oligonucleotide of the invention, or contiguous nucleotide sequence thereof, may be a gapmer, also termed gapmer oligonucleotide or gapmer designs. The antisense gapmers are commonly used to inhibit a target nucleic acid via RNase H mediated degradation. A gapmer oligonucleotide comprises at least three distinct structural regions a 5'-flank, a gap and a 3'-flank, F-G-F' in the '5 -> 3' orientation. The "gap" region (G) comprises a stretch of contiguous DNA nucleotides which enable the oligonucleotide to recruit RNase H. The gap region is flanked by a 5' flanking region (F) comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides, and by a 3' flanking region (F') comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides. The one or more sugar modified nucleosides in region F and F' enhance the affinity of the oligonucleotide for the target nucleic acid (*i.e.* are affinity enhancing sugar modified nucleosides). In some embodiments, the one or more sugar modified nucleosides in region F and F' are 2' sugar modified nucleosides, such as high affinity 2' sugar modifications, such as independently selected from LNA and 2'-MOE.

In a gapmer design, the 5' and 3' most nucleosides of the gap region are DNA nucleosides, and are positioned adjacent to a sugar modified nucleoside of the 5' (F) or 3' (F') region respectively. The flanks may further be defined by having at least one sugar modified nucleoside at the end most distant from the gap region, i.e. at the 5' end of the 5' flank and at the 3' end of the 3' flank.

Regions F-G-F' form a contiguous nucleotide sequence. Antisense oligonucleotides of the invention, or the contiguous nucleotide sequence thereof, may comprise a gapmer region of formula F-G-F'.

The overall length of the gapmer design F-G-F' may be, for example 12 to 32 nucleosides, such as 13 to 24, such as 14 to 22 nucleosides, Such as from 14 to17, such as 16 to18 nucleosides, such as 16 to 20 nuclotides.

By way of example, the gapmer oligonucleotide of the present invention can be represented by the following formulae:

F_{1-8}-G_{6-16}-F'_{2-8}, such as

F_{2-8}-G_{6-14}-F'_{2-8}, such as

F_{3-8}-G_{6-14}-F'_{2-8}

with the proviso that the overall length of the gapmer regions F-G-F' is at least 10, such as at least 12, such as at least 14 nucleotides in length.

In an aspect of the invention the antisense oligonucleotide or contiguous nucleotide sequence thereof consists of or comprises a gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise or consist of 1- 8 nucleosides, of which 2-4 are 2' sugar modified and defines the 5' and 3' end of the F and F' region, and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH.

Regions F, G and F' are further defined below and can be incorporated into the F-G-F' formula.

Gapmer - Region G

Region G (gap region) of the gapmer is a region of nucleosides which enables the oligonucleotide to recruit RNaseH, such as human RNase H1, typically DNA nucleosides. RNaseH is a cellular enzyme which recognizes the duplex between DNA and RNA, and enzymatically cleaves the RNA molecule. Suitably gapmers may have a gap region (G) of at least 5 or 6 contiguous DNA nucleosides, such as 5 – 16 contiguous DNA nucleosides, such as 6 – 15 contiguous DNA nucleosides, such as 7-14 contiguous DNA nucleosides, such as 8 – 12 contiguous DNA nucleotides, such as 8 – 12 contiguous DNA nucleotides in length. The gap region G may, in some embodiments consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous DNA nucleosides. Cytosine (C) DNA in the gap region may in some instances be methylated, such residues are either annotated as 5'-methyl-cytosine (^{me}C or with an e instead of a c). Methylation of cytosine DNA in the gap is advantageous if cg dinucleotides are present in the gap to reduce potential toxicity, the modification does not have significant impact on efficacy of the oligonucleotides. 5' substituted DNA nucleosides, such as 5' methyl DNA nucleoside have been reported for use in DNA gap regions (EP 2 742 136).

In some embodiments the gap region G may consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous phosphorothioate linked DNA nucleosides. In some embodiments, all internucleoside linkages in the gap are phosphorothioate linkages.

Whilst traditional gapmers have a DNA gap region, there are numerous examples of modified nucleosides which allow for RNaseH recruitment when they are used within the gap region. Modified nucleosides which have been reported as being capable of recruiting RNaseH when included within a gap region include, for example, alpha-L-LNA, C4' alkylated DNA (as described in PCT/EP2009/050349 and Vester *et al.*, Bioorg. Med. Chem. Lett. 18 (2008) 2296 – 2300, both incorporated herein by reference), arabinose derived nucleosides like ANA and 2'F-ANA (Mangos et al. 2003 J. AM. CHEM. SOC. 125, 654-661), UNA (unlocked nucleic acid) (as described in Fluiter *et al.*, Mol. Biosyst., 2009, 10, 1039 incorporated herein by reference). UNA is unlocked nucleic acid, typically where the bond between C2 and C3 of the ribose has been removed, forming an unlocked "sugar" residue. The modified nucleosides used in such gapmers

may be nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region, *i.e.* modifications which allow for RNaseH recruitment). In some embodiments the DNA Gap region (G) described herein may optionally contain 1 to 3 sugar modified nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region.

Region G - "Gap-breaker"

Alternatively, there are numerous reports of the insertion of a modified nucleoside which confers a 3' endo conformation into the gap region of gapmers, whilst retaining some RNaseH activity. Such gapmers with a gap region comprising one or more 3'endo modified nucleosides are referred to as "gap-breaker" or "gap-disrupted" gapmers, see for example WO2013/022984. Gap-breaker oligonucleotides retain sufficient region of DNA nucleosides within the gap region to allow for RNaseH recruitment. The ability of gapbreaker oligonucleotide design to recruit RNaseH is typically sequence or even compound specific – see Rukov et al. 2015 Nucl. Acids Res. Vol. 43 pp. 8476-8487, which discloses "gapbreaker" oligonucleotides which recruit RNaseH which in some instances provide a more specific cleavage of the target RNA. Modified nucleosides used within the gap region of gap-breaker oligonucleotides may for example be modified nucleosides which confer a 3'endo confirmation, such 2' –O-methyl (OMe) or 2'-O-MOE (MOE) nucleosides, or beta-D LNA nucleosides (the bridge between C2' and C4' of the ribose sugar ring of a nucleoside is in the beta conformation), such as beta-D-oxy LNA or ScET nucleosides.

As with gapmers containing region G described above, the gap region of gap-breaker or gap-disrupted gapmers, have a DNA nucleosides at the 5' end of the gap (adjacent to the 3' nucleoside of region F), and a DNA nucleoside at the 3' end of the gap (adjacent to the 5' nucleoside of region F'). Gapmers which comprise a disrupted gap typically retain a region of at least 3 or 4 contiguous DNA nucleosides at either the 5' end or 3' end of the gap region.

Exemplary designs for gap-breaker oligonucleotides include

F_{1-8}-[D_{3-4}-E_1- D_{3-4}].F'_{1-8}

F_{1-8}- [D_{1-4}-E_1- D_{3-4}]-F'_{1-8}

F_{1-8}- [D_{3-4}-E_1- D_{1-4}]-F'_{1-8}

wherein region G is within the brackets [D_n-E_r- D_m], D is a contiguous sequence of DNA nucleosides, E is a modified nucleoside (the gap-breaker or gap-disrupting nucleoside), and F and F' are the flanking regions as defined herein, and with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length.

In some embodiments, region G of a gap disrupted gapmer comprises at least 6 DNA nucleosides, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 DNA nucleosides. As described above, the DNA nucleosides may be contiguous or may optionally be interspersed with one or

more modified nucleosides, with the proviso that the gap region G is capable of mediating RNaseH recruitment.

Gapmer - flanking regions, F and F'

Region F is positioned immediately adjacent to the 5' DNA nucleoside of region G. The 3' most nucleoside of region F is a sugar modified nucleoside, such as a high affinity sugar modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F' is positioned immediately adjacent to the 3' DNA nucleoside of region G. The 5' most nucleoside of region F' is a sugar modified nucleoside, such as a high affinity sugar modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F is 1 – 8 contiguous nucleotides in length, such as 2-6, such as 3-4 contiguous nucleotides in length. Advantageously the 5' most nucleoside of region F is a sugar modified nucleoside. In some embodiments the two 5' most nucleoside of region F are sugar modified nucleoside. In some embodiments the 5' most nucleoside of region F is an LNA nucleoside. In some embodiments the two 5' most nucleoside of region F are LNA nucleosides. In some embodiments the two 5' most nucleoside of region F are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 5' most nucleoside of region F is a 2' substituted nucleoside, such as a MOE nucleoside.

Region F' is 2 – 8 contiguous nucleotides in length, such as 3-6, such as 4-5 contiguous nucleotides in length. Advantageously, embodiments the 3' most nucleoside of region F' is a sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are LNA nucleosides. In some embodiments the 3' most nucleoside of region F' is an LNA nucleoside. In some embodiments the two 3' most nucleoside of region F' are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 3' most nucleoside of region F' is a 2' substituted nucleoside, such as a MOE nucleoside.

It should be noted that when the length of region F or F' is one, it is advantageously an LNA nucleoside.

In some embodiments, region F and F' independently consists of or comprises a contiguous sequence of sugar modified nucleosides. In some embodiments, the sugar modified nucleosides of region F may be independently 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 some embodiments, region F and F' independently comprises both LNA and a 2' substituted modified nucleosides (mixed wing design).

In some embodiments, region F and F' consists of only one type of sugar modified nucleosides, such as only MOE or only beta-D-oxy LNA or only ScET. Such designs are also termed uniform flanks or uniform gapmer design.

In some embodiments, all the nucleosides of region F or F', or F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides. In some embodiments region F consists of 1-5, such as 2-4, such as 3-4 such as 1, 2, 3, 4 or 5 contiguous LNA nucleosides. In some embodiments, all the nucleosides of region F and F' are beta-D-oxy LNA nucleosides.

In some embodiments, all the nucleosides of region F or F', or F and F' are 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments region F consists of 1, 2, 3, 4, 5, 6, 7, or 8 contiguous OMe or MOE nucleosides. In some embodiments only one of the flanking regions can consist of 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments it is the 5' (F) flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 3' (F') flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides. In some embodiments it is the 3' (F') flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 5' (F) flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides.

In some embodiments, all the modified nucleosides of region F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details). In some embodiments, all the modified nucleosides of region F and F' are beta-D-oxy LNA nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details).

In some embodiments the 5' most and the 3' most nucleosides of region F and F' are LNA nucleosides, such as beta-D-oxy LNA nucleosides or ScET nucleosides.

In some embodiments, the internucleoside linkage between region F and region G is a phosphorothioate internucleoside linkage. In some embodiments, the internucleoside linkage between region F' and region G is a phosphorothioate internucleoside linkage. In some embodiments, the internucleoside linkages between the nucleosides of region F or F', F and F' are phosphorothioate internucleoside linkages.

LNA Gapmer

An LNA gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of LNA nucleosides. A beta-D-oxy gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of beta-D-oxy LNA nucleosides.

In some embodiments the LNA gapmer is of formula: $[LNA]_{1-5}$-[region G] -$[LNA]_{1-5}$, wherein region G is as defined in the Gapmer region G definition.

In one embodiment the LNA gapmer is of the formula $[LNA]_4$-$[region\ G]_{10-12}$ -$[LNA]_4$

MOE Gapmers

A MOE gapmers is a gapmer wherein regions F and F' consist of MOE nucleosides. In some embodiments the MOE gapmer is of design $[MOE]_{1-8}$-$[Region\ G]_{5-16}$-$[MOE]_{1-8}$, such as $[MOE]_{2-7}$-$[Region\ G]_{6-14}$-$[MOE]_{2-7}$, such as $[MOE]_{3-6}$-$[Region\ G]_{8-12}$-$[MOE]_{3-6}$, wherein region G is as defined in the Gapmer definition. MOE gapmers with a 5-10-5 design (MOE-DNA-MOE) have been widely used in the art.

Mixed Wing Gapmer

A mixed wing gapmer is an LNA gapmer wherein one or both of region F and F' comprise a 2' substituted nucleoside, such as a 2' substituted nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units, such as MOE nucleosides. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least one LNA nucleoside, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least two LNA nucleosides, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some mixed wing embodiments, one or both of region F and F' may further comprise one or more DNA nucleosides.

Mixed wing gapmer designs are disclosed in WO2008/049085 and WO2012/109395, both of which are hereby incorporated by reference.

Alternating Flank Gapmers

Flanking regions may comprise both LNA and DNA nucleoside and are referred to as "alternating flanks" as they comprise an alternating motif of LNA-DNA-LNA nucleosides. Gapmers comprising such alternating flanks are referred to as "alternating flank gapmers". "Alternative flank gapmers" are LNA gapmer oligonucleotides where at least one of the flanks (F or F') comprises DNA in addition to the LNA nucleoside(s). In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or both F and F' comprise at

least three nucleosides, wherein the 5' and 3' most nucleosides of the F and/or F' region are LNA nucleosides.

Alternating flank LNA gapmers are disclosed in WO2016/127002.

An alternating flank region may comprise up to 3 contiguous DNA nucleosides, such as 1 to 2 or 1 or 2 or 3 contiguous DNA nucleosides.

The alternating flak can be annotated as a series of integers, representing a number of LNA nucleosides (L) followed by a number of DNA nucleosides (D), for example

$[L]_{1-3}$-$[D]_{1-4}$-$[L]_{1-3}$

$[L]_{1-2}$-$[D]_{1-2}$-$[L]_{1-2}$-$[D]_{1-2}$-$[L]_{1-2}$

In oligonucleotide designs these will often be represented as numbers such that 2-2-1 represents 5' $[L]_2$-$[D]_2$-[L] 3', and 1-1-1-1-1 represents 5' [L]-[D]-[L]-[D]-[L] 3'. The length of the flank (region F and F') in oligonucleotides with alternating flanks may independently be 3 to 10 nucleosides, such as 4 to 8, such as 5 to 6 nucleosides, such as 4, 5, 6 or 7 modified nucleosides. In some embodiments only one of the flanks in the gapmer oligonucleotide is alternating while the other is constituted of LNA nucleotides. It may be advantageous to have at least two LNA nucleosides at the 3' end of the 3' flank (F'), to confer additional exonuclease resistance. In one embodiment the flanks in the alternating flank gapmer have an overall length from 5-to 8 nucleosides of which 3 to 5 are LNA nucleosides. Some examples of oligonucleotides with alternating flanks are:

$[L]_{1-5}$-$[D]_{1-4}$-$[L]_{1-3}$-$[G]_{5-16}$-$[L]_{2-6}$

$[L]_{1-2}$-$[D]_{2-3}$-$[L]_{3-4}$--$[G]_{5-7}$-$[L]_{1-2}$-$[D]_{2-3}$-$[L]_{2-3}$

$[L]_{1-2}$-$[D]_{1-2}$-$[L]_{1-2}$-$[D]_{1-2}$-$[L]_{1-2}$-$[G]_{5-16}$-$[L]_{1-2}$-$[D]_{1-3}$-$[L]_{2-4}$

$[L]_{1-5}$-$[G]_{5-16}$-[L]-[D]-[L]-[D]-$[L]_2$

$[L]_4$-$[G]_{6-10}$-[L]-$[D]_3$-$[L]_2$

with the proviso that the overall length of the gapmer is at least 12, such as at least 14 nucleotides in length.

Region D' or D'' in an oligonucleotide

The oligonucleotide of the invention may in some embodiments comprise or consist of the contiguous nucleotide sequence of the oligonucleotide which is complementary to the target nucleic acid, such as the gapmer F-G-F', and further 5' and/or 3' nucleosides. The further 5' and/or 3' nucleosides may or may not be fully complementary to the target nucleic acid. Such further 5' and/or 3' nucleosides may be referred to as region D' and D'' herein.

The addition of region D' or D'' may be used for the purpose of joining the contiguous nucleotide sequence, such as the gapmer, to a conjugate moiety or another functional group. When used for joining the contiguous nucleotide sequence with a conjugate moiety is can serve as a biocleavable linker. Alternatively, it may be used to provide exonucleoase protection or for ease of synthesis or manufacture.

Region D' and D'' can be attached to the 5' end of region F or the 3' end of region F', respectively to generate designs of the following formulas D'-F-G-F', F-G-F'-D'' or D'-F-G-F'-D''. In this instance the F-G-F' is the gapmer portion of the oligonucleotide and region D' or D'' constitute a separate part of the oligonucleotide.

Region D' or D'' may independently comprise or consist of 1, 2, 3, 4 or 5 additional nucleotides, which may be complementary or non-complementary to the target nucleic acid. The nucleotide adjacent to the F or F' region is not a sugar-modified nucleotide, such as a DNA or RNA or base modified versions of these. The D' or D' region may serve as a nuclease susceptible biocleavable linker (see definition of linkers). In some embodiments the additional 5' and/or 3' end nucleotides are linked with phosphodiester linkages, and are DNA or RNA. Nucleotide based biocleavable linkers suitable for use as region D' or D'' are disclosed in WO2014/076195, which include by way of example a phosphodiester linked DNA dinucleotide. The use of biocleavable linkers in poly-oligonucleotide constructs is disclosed in WO2015/113922, where they are used to link multiple antisense constructs (e.g. gapmer regions) within a single oligonucleotide.

In one embodiment the oligonucleotide of the invention comprises a region D' and/or D'' in addition to the contiguous nucleotide sequence which constitutes the gapmer.

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

F-G-F'; in particular F_{2-8}-G_{6-16}-F'_{2-8}

D'-F-G-F', in particular D'_{2-3}-F_{1-8}-G_{6-16}-F'_{2-8}

F-G-F'-D'', in particular F_{2-8}-G_{6-16}-F'_{2-8}-D''_{1-3}

D'-F-G-F'-D'', in particular D'_{1-3}- F_{2-8}-G_{6-16}-F'_{2-8}-D''_{1-3}

In some embodiments the internucleoside linkage positioned between region D' and region F is a phosphodiester linkage. In some embodiments the internucleoside linkage positioned between region F' and region D'' is a phosphodiester linkage.

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).

Conjugation of the oligonucleotide of the invention to one or more non-nucleotide moieties may improve the pharmacology of the oligonucleotide, *e.g.* by affecting the activity, cellular distribution, cellular uptake or stability of the oligonucleotide. In some embodiments the conjugate moiety modify or enhance the pharmacokinetic properties of the oligonucleotide by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the oligonucleotide. In particular, the conjugate may target the oligonucleotide to a specific organ, tissue or cell type and thereby enhance the effectiveness of the oligonucleotide in that organ, tissue or cell type. At the same time the conjugate may serve to reduce activity of the oligonucleotide in non-target cell types, tissues or organs, e.g. off target activity or activity in non-target cell types, tissues or organs.

Oligonucleotide conjugates and their synthesis has also been reported in comprehensive reviews by Manoharan in Antisense Drug Technology, Principles, Strategies, and Applications, S.T. Crooke, ed., Ch. 16, Marcel Dekker, Inc., 2001 and Manoharan, Antisense and Nucleic Acid Drug Development, 2002, 12, 103, each of which is incorporated herein by reference in its entirety.

In an embodiment, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates (e.g. GalNAc), cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (e.g. bacterial toxins), vitamins, viral proteins (e.g. capsids) or combinations thereof.

In some embodiments, the conjugate is an antibody or an antibody fragment which has a specific affinity for a transferrin receptor, for example as disclosed in WO 2012/143379 herby incorporated by reference. In some embodiments the non-nucleotide moiety is an antibody or antibody fragment, such as an antibody or antibody fragment that facilitates delivery across the blood-brain-barrier, in particular an antibody or antibody fragment targeting the transferrin receptor.

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 (Region C), to a first region, e.g. an oligonucleotide or contiguous nucleotide sequence complementary to the target nucleic acid (region A).

In some embodiments of the invention the conjugate or oligonucleotide conjugate of the invention may optionally, comprise a linker region (second region or region B and/or region Y) which is positioned between the oligonucleotide or contiguous nucleotide sequence

complementary to the target nucleic acid (region A or first region) and the conjugate moiety (region C or third region).

Region B refers to 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).

Region Y refers to linkers that are not necessarily biocleavable but primarily serve to covalently connect a conjugate moiety (region C or third region), to an oligonucleotide (region A or first region). The region Y linkers may comprise a chain structure or an oligomer of repeating units such as ethylene glycol, amino acid units or amino alkyl groups The oligonucleotide conjugates of the present invention can be constructed of the following regional elements A-C, A-B-C, A-B-Y-C, A-Y-B-C or A-Y-C. In some embodiments the linker (region Y) is an amino alkyl, such as a C2 – C36 amino alkyl group, including, for example C6 to C12 amino alkyl groups. In a preferred embodiment the linker (region Y) is a C6 amino alkyl 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.

In some embodiments treatment is performed on a patient who has been diagnosed with a neurological disorder, such as a neurological disorder selected from the group consisting of neurodegenerative diseases including Tauopathies, Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBD), chronic traumatic encephalopathy (CTE), fronto- temporal dementia FTD) and FTD with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), tangle-

predominant senile dementia (TPSD), primary age-related Tauopathy (PART), Down syndrome and lytico-bodig disease. Upregulation of pathological Tau is associated with infantile Tauopathies including hemimegalencephaly (HME), tuberous sclerosis complex; focal cortical dysplasia type 2b; and ganglioglioma. In addition, abnormal Tau expression and/or function may also be associated with other diseases such as Hallervorden-Spatz syndrome, also known as neurodegeneration with brain iron accumulation type 1 (NBIA1), gangliocytomas, and subacute sclerosing panencephalitis. Tau may also play a role in seizure disorders (e.g., epilepsy), network dysfunction (e.g., depression), and movement disorders (e.g., Parkinson's disease).

DETAILED DESCRIPTION OF THE INVENTION

The Oligonucleotides of the Invention

The invention relates to oligonucleotides capable of modulating expression of Tau, such as inhibiting (down-regulating) Tau. The modulation is achieved by hybridizing to a target nucleic acid encoding Tau. The target nucleic acid may be a mammalian MAPT mRNA sequence, such as a sequence selected from the group consisting of SEQ ID NO: 1 and 2.

The oligonucleotide of the invention is an antisense oligonucleotide which targets MAPT resulting in reduced Tau expression.

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, more preferably at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% inhibition compared to the normal expression level of the target. In some embodiments oligonucleotides of the invention may be capable of inhibiting expression levels of Tau mRNA by at least 60% or 70% *in vitro* following application of 5 µM oligonucleotide to primary neuronal cells. In some embodiments compounds of the invention may be capable of inhibiting expression levels of Tau protein by at least 50% *in vitro* following application of 0.5 µM oligonucleotide to primary neuronal cells. Suitably, the examples provide assays which may be used to measure Tau RNA or protein inhibition (e.g. example 1 and 3). 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 Tau 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' sugar 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 sequence of at least 10 nucleotides in length with at least 90% complementarity to SEQ ID NO: 3, 4 or 5.

In some embodiments, the oligonucleotide comprises a contiguous sequence of 10 to 30 nucleotides in length, 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 or a target sequence.

It is advantageous if the oligonucleotide of the invention, or 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 comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as fully (or 100%) complementary, to contiguous nucleotides within position12051 to 12111, 39562 to 39593 or 72837 to 72940 of SEQ ID NO: 1.

In some embodiments the oligonucleotide sequence is 100% complementary to a corresponding target nucleic acid region present in SEQ ID NO: 1 and SEQ ID NO: 2.

It is advantageous if the antisense oligonucleotide is complementary to a target sequence selected from one of the regions listed in table 4. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide is at least 90% complementary to, such as fully complementary to a target sequence selected R1-R2254 (table 4) In some embodiments the oligonucleotide sequence is 100% complementary to R_223, R_738 or R_1298 (see table 4).

In some embodiment the oligonucleotide or contiguous nucleotide sequence is 90% complementary, such as fully complementary, to a region of the target nucleic acid, wherein the target nucleic acid region is selected from the group consisting of position 12051 – 12111 of SEQ ID NO: 1 such as positon 12051 – 12079, position 12085-12111 or position 12060 – 12078 of SEQ ID NO: 1.

In another embodiment the oligonucleotide or contiguous nucleotide sequence is 90% complementary, such as fully complementary, to a region of the target nucleic acid, wherein the target nucleic acid region is selected from the group consisting of position 39562-39593 of SEQ ID NO: 1 such as positon 39573-39592 of SEQ ID NO: 1.

In another embodiment of the oligonucleotide or contiguous nucleotide sequence is 90% complementary, such as fully complementary, to a region of the target nucleic acid, wherein the

target nucleic acid region is selected from the group consisting of position 72837-72940 of SEQ ID NO: 1 such as positon 72861-72891 or position 72862-72890 of SEQ ID NO: 1.

In some embodiments the oligonucleotide comprises a contiguous nucleotide sequence of 16 to 22 nucleotides, such as 16 to 20 nucleotides, in length with 100% complementary, to contiguous nucleotides within position12060 to 12078 or 39573 to 39592 or 72862-72890 of SEQ ID NO: 1.

In some embodiments, the oligonucleotide of the invention comprises or consists of 10 to 35 nucleotides in length, such as from 10 to 30, such as 11 to 25, such as from 12 to 22, such as from 14 to 20 or 14 to 18 contiguous nucleotides in length. In one embodiment, the oligonucleotide comprises or consists of 16 to 22 nucleotides in length. In a preferred embodiment, the oligonucleotide comprises or consists of 16 to 20 nucleotides in length.

In some embodiments, the oligonucleotide or contiguous nucleotide sequence thereof comprises or consists of 22 or less nucleotides, such as 20 or less nucleotides, such as 16, 17, 18, 19 or 20 nucleotides. It is to be understood that any range given herein includes the range endpoints. Accordingly, if an oligonucleotide is said to include from 10 to 30 nucleotides, both 10 and 30 nucleotides are included.

In some embodiments, the contiguous nucleotide sequence comprises or consists of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 contiguous nucleotides in length. In a preferred embodiment, the oligonucleotide comprises or consists of 16, 17, 18, 19 or 20 nucleotides in length.

In some embodiments, the oligonucleotide or contiguous nucleotide sequence comprises or consists of a sequence selected from the group consisting of sequences listed in table 5(Materials and Method section).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence selected from the group consisting of SEQ ID NO: 6 to 65 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence selected from the group consisting of SEQ ID NO: 9, 11, 49, 53, 56 and 62 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence selected from the group consisting of SEQ ID NO: 6 to 37 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence of SEQ ID NO: 9 or 11 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence selected from the group consisting of SEQ ID NO: 38 to 51 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence of SEQ ID NO: 49 or 51 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence selected from the group consisting of SEQ ID NO: 52 to 65 (see motif sequences listed in table 5).

In some embodiments, the antisense oligonucleotide or contiguous nucleotide sequence comprises or consists of 10 to 30 nucleotides in length with at least 90% identity, preferably 100% identity, to a sequence of SEQ ID NO: 56 or 62 (see motif sequences listed in table 5).

It is understood that the contiguous nucleobase sequences (motif sequence) can be modified to for example increase nuclease resistance and/or binding affinity to the target nucleic acid.

The pattern in which the modified nucleosides (such as high affinity modified nucleosides) are incorporated into the oligonucleotide sequence is generally termed oligonucleotide design.

The oligonucleotides of the invention are designed with modified nucleosides and DNA nucleosides. Advantageously, high affinity modified nucleosides are used.

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. Suitable modifications are described in the “Definitions” section under “modified nucleoside”, “high affinity modified nucleosides”, “sugar modifications”, “2’ sugar modifications” and Locked nucleic acids (LNA)”.

In an embodiment, the oligonucleotide comprises one or more sugar modified nucleosides, such as 2’ sugar modified nucleosides. Preferably the oligonucleotide of the invention comprises 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. It is advantageous if one or more of the modified nucleoside(s) is a locked nucleic acid (LNA).

In a further embodiment the oligonucleotide comprises at least one modified internucleoside linkage. Suitable internucleoside modifications are described in the "Definitions" section under "Modified internucleoside linkage". It is advantageous if at least 75%, such as 80%, such as all, 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 comprises at least one LNA nucleoside, such as 1, 2, 3, 4, 5, 6, 7, or 8 LNA nucleosides, such as from 2 to 6 LNA nucleosides, such as from 3 to 7 LNA nucleosides, 4 to 8 LNA nucleosides or 3, 4, 5, 6, 7 or 8 LNA nucleosides. In some embodiments, at least 75% of the modified nucleosides in the oligonucleotide are LNA nucleosides, such as 80%, such as 85%, such as 90% of the modified nucleosides are LNA nucleosides, in particular beta-D-oxy LNA or ScET. In a still further embodiment all the modified nucleosides in the oligonucleotide are LNA nucleosides. In a further embodiment, the oligonucleotide may comprise both beta-D-oxy-LNA, and one or more of the following LNA nucleosides: thio-LNA, amino-LNA, oxy-LNA, ScET and/or ENA in either the beta-D or alpha-L configurations or combinations thereof. In a further embodiment, all LNA cytosine units are 5-methyl-cytosine. It is advantageous for the nuclease stability of the oligonucleotide or contiguous nucleotide sequence to have at least 1 LNA nucleoside at the 5' end and at least 2 LNA nucleosides at the 3' end of the nucleotide sequence.

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

In the current invention an advantageous structural design is a gapmer design as described in the "Definitions" section under for example "Gapmer", "LNA Gapmer", "MOE gapmer" and "Mixed Wing Gapmer" "Alternating Flank Gapmer". The gapmer design includes gapmers with uniform flanks, mixed wing flanks, alternating flanks, and gapbreaker designs. In the present invention it is advantageous if the oligonucleotide of the invention is a gapmer with an F-G-F' design, particular gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise 1 - 8 nucleosides, of which 2 - 5 are 2' sugar modified and defines the 5' and 3' end of the F and F' region, and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH, such as a region comprising 6 – 16 DNA nucleosides.

In some embodiments the gapmer is an LNA gapmer.

In some embodiments of the invention the LNA gapmer is selected from the following uniform flank designs 4-10-4, 3-11-4, 4-11-4, 4-12-4 or 4-14-2.

In some embodiments of the invention the LNA gapmer is selected from the following alternating flanks designs 3-1-3-10-2, 1-3-4-6-1-3-2, 1-2-1-2-2-8-4, or 3-3-1-8-2-1-2.

Table 5 (Materials and Method section) lists preferred designs of each motif sequence.

In all instances the F-G-F' design may further include region D' and/or D'' as described in the "Definitions" section under "Region D' or D'' in an oligonucleotide". In some embodiments the oligonucleotide of the invention has 1, 2 or 3 phosphodiester linked nucleoside units, such as DNA units, at the 5' or 3' end of the gapmer region.

For some embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 6_1; 7_1; 8_1; 9_1; 9_2; 9_3; 9_4; 9_5; 9_6; 9_7; 9_8; 9_9; 9_10; 9_11; 9_12; 9_13; 9_14; 9_15; 9_16; 9_17; 9_18; 9_19; 9_20; 9_21; 9_22; 9_23; 9_24; 9_25; 9_26; 9_27; 9_28; 9_29; 9_30; 9_31; 9_32; 9_33; 9_34; 9_35; 9_36; 9_37; 9_38; 9_39; 9_40; 9_41; 9_42; 9_43; 9_44; 9_45; 9_46; 9_47; 9_48; 9_49; 9_50; 9_51; 9_52; 9_53; 9_54; 9_55; 9_56; 9_57; 9_58; 9_59; 9_60; 9_61; 9_62; 9_63; 9_64; 9_65; 9_66; 9_67; 9_68; 9_69; 9_70; 9_71; 9_72; 9_73; 9_74; 9_75; 9_76; 9_77; 9_78; 9_79; 9_80; 9_81; 9_82; 9_83; 9_84; 9_85; 9_86; 9_87; 9_88; 9_89; 9_90; 9_91; 9_92; 9_93; 9_94; 9_95; 9_96; 9_97; 9_98; 9_99; 9_100; 9_101; 9_102; 9_103; 9_104; 9_105; 9_106; 10_1; 10_2; 10_3; 10_4; 10_5; 10_6; 10_7; 10_8; 10_9; 10_10; 10_11; 10_12; 10_13; 10_14; 10_15; 10_16; 10_17; 10_18; 10_19; 10_20; 10_21; 10_22; 10_23; 10_24; 10_25; 10_26; 10_27; 10_28; 10_29; 10_30; 10_31; 10_32; 10_33; 10_34; 10_35; 10_36; 10_37; 10_38; 10_39; 10_40; 10_41; 10_42; 10_43; 10_44; 10_45; 10_46; 10_47; 10_48; 10_49; 10_50; 10_51; 10_52; 10_53; 10_54; 10_55; 10_56; 10_57; 10_58; 10_59; 10_60; 10_61; 10_62; 10_63; 10_64; 10_65; 10_66; 10_67; 10_68; 10_69; 10_70; 10_71; 10_72; 10_73; 10_74; 10_75; 10_76; 10_77; 10_78; 10_79; 10_80; 10_81; 10_82; 10_83; 10_84; 10_85; 10_86; 10_87; 10_88; 10_89; 11_1; 12_1; 13_1; 14_1; 15_1; 16_1; 17_1; 18_1; 19_1; 20_1; 21_1; 22_1; 23_1; 24_1; 24_2; 24_3; 24_4; 24_5; 24_6; 24_7; 24_8; 24_9; 24_10; 24_11; 24_12; 24_13; 24_14; 24_15; 24_16; 24_17; 24_18; 24_19; 24_20; 24_21; 24_22; 24_23; 24_24; 24_25; 24_26; 24_27; 24_28; 24_29; 24_30; 24_31; 24_32; 24_33; 24_34; 24_35; 24_36; 24_37; 24_38; 24_39; 24_40; 24_41; 24_42; 24_43; 24_44; 24_45; 24_46; 24_47; 24_48; 24_49; 24_50; 24_51; 24_52; 24_53; 24_54; 24_55; 24_56; 24_57; 24_58; 24_59; 24_60; 24_61; 24_62; 25_1; 25_2; 25_3; 25_4; 25_5; 25_6; 25_7; 25_8; 25_9; 25_10; 25_11; 25_12; 25_13; 25_14; 25_15; 25_16; 25_17; 25_18; 25_19; 25_20; 25_21; 25_22; 25_23; 25_24; 25_25; 25_26; 25_27; 25_28; 25_29; 25_30; 25_31; 25_32; 25_33; 25_34; 25_35; 25_36; 25_37; 25_38; 25_39; 25_40; 25_41; 25_42; 25_43; 26_1; 26_2; 26_3; 26_4; 26_5; 26_6; 26_7; 26_8; 26_9; 26_10; 26_11; 26_12; 26_13; 26_14; 26_15; 26_16; 26_17; 26_18; 26_19; 26_20; 26_21; 26_22; 26_23; 26_24; 26_25; 26_26; 26_27; 26_28; 26_29; 26_30; 26_31; 27_1; 28_1; 28_2; 28_3; 28_4; 28_5; 28_6; 28_7; 28_8; 28_9; 28_10; 28_11; 28_12; 28_13; 28_14; 28_15; 28_16; 28_17; 28_18; 28_19; 28_20; 28_21; 28_22; 28_23; 28_24; 28_25; 28_26; 28_27; 28_28;

28_29; 28_30; 28_31; 28_32; 28_33; 29_1; 29_2; 29_3; 29_4; 29_5; 29_6; 29_7; 29_8; 29_9; 29_10; 29_11; 29_12; 29_13; 29_14; 30_1; 30_2; 30_3; 30_4; 30_5; 30_6; 30_7; 30_8; 30_9; 30_10; 30_11; 30_12; 30_13; 30_14; 30_15; 30_16; 30_17; 30_18; 30_19; 30_20; 30_21; 30_22; 30_23; 30_24; 30_25; 31_1; 31_2; 31_3; 32_1; 32_2; 32_3; 32_4; 32_5; 32_6; 32_7; 32_8; 32_9; 32_10; 32_11; 32_12; 32_13; 32_14; 32_15; 32_16; 32_17; 32_18; 32_19; 32_20; 32_21; 32_22; 32_23; 32_24; 32_25; 32_26; 32_27; 32_28; 32_29; 32_30; 32_31; 32_32; 32_33; 32_34; 32_35; 32_36; 32_37; 32_38; 32_39; 32_40; 32_41; 32_42; 32_43; 32_44; 32_45; 32_46; 32_47; 32_48; 32_49; 32_50; 32_51; 33_1; 33_2; 33_3; 33_4; 33_5; 33_6; 33_7; 33_8; 33_9; 33_10; 33_11; 33_12; 33_13; 33_14; 33_15; 33_16; 33_17; 33_18; 33_19; 33_20; 33_21; 33_22; 33_23; 33_24; 33_25; 33_26; 33_27; 33_28; 33_29; 33_30; 33_31; 33_32; 33_33; 34_1; 35_1; 35_2; 35_3; 36_1; 37_1; 38_1; 39_1; 40_1; 41_1; 42_1; 43_1; 44_1; 45_1; 46_1; 47_1; 48_1; 49_1; 49_2; 49_3; 49_4; 49_5; 49_6; 49_7; 49_8; 49_9; 49_10; 49_11; 49_12; 49_13; 49_14; 49_15; 49_16; 49_17; 49_18; 49_19; 49_20; 49_21; 49_22; 49_23; 49_24; 49_25; 49_26; 49_27; 49_28; 49_29; 49_30; 49_31; 49_32; 49_33; 49_34; 49_35; 49_36; 49_37; 49_38; 49_39; 49_40; 49_41; 49_42; 49_43; 49_44; 49_45; 49_46; 49_47; 49_48; 49_49; 49_50; 49_51; 49_52; 49_53; 49_54; 49_55; 49_56; 49_57; 49_58; 49_59; 49_60; 49_61; 49_62; 49_63; 49_64; 49_65; 49_66; 49_67; 49_68; 49_69; 49_70; 49_71; 49_72; 49_73; 49_74; 49_75; 49_76; 49_77; 49_78; 49_79; 49_80; 49_81; 49_82; 49_83; 49_84; 49_85; 49_86; 49_87; 49_88; 49_89; 49_90; 49_91; 49_92; 49_93; 49_94; 49_95; 49_96; 49_97; 49_98; 49_99; 49_100; 49_101; 49_102; 49_103; 49_104; 49_105; 49_106; 49_107; 49_108; 49_109; 49_110; 49_111; 49_112; 49_113; 49_114; 49_115; 49_116; 49_117; 49_118; 49_119; 49_120; 49_121; 49_122; 49_123; 49_124; 49_125; 49_126; 49_127; 49_128; 49_129; 49_130; 49_131; 49_132; 49_133; 49_134; 49_135; 49_136; 49_137; 49_138; 49_139; 49_140; 49_141; 49_142; 49_143; 49_144; 49_145; 49_146; 49_147; 49_148; 49_149; 49_150; 49_151; 49_152; 49_153; 49_154; 49_155; 49_156; 49_157; 49_158; 49_159; 49_160; 49_161; 49_162; 49_163; 49_164; 49_165; 49_166; 49_167; 49_168; 49_169; 49_170; 49_171; 49_172; 49_173; 49_174; 49_175; 49_176; 49_177; 49_178; 49_179; 49_180; 49_181; 49_182; 49_183; 49_184; 49_185; 49_186; 49_187; 49_188; 49_189; 49_190; 49_191; 49_192; 50_1; 51_1; 52_1; 53_1; 54_1; 55_1; 56_1; 57_1; 58_1; 59_1; 60_1; 61_1; 62_1; 63_1; 64_1 and 65_1.

For certain embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 9_102; 9_103; 9_104; 11_1; 49_38; 49_51; 49_179; 49_189; 53_1; 56_1 and 62_1.

For certain embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 9_102; 9_103; 9_104 and 11_1.

For certain embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 49_38; 49_51; 49_179 and 49_189.

For certain embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 53_1; 56_1 and 62_1.

A particular advantageous antisense oligonucleotide in the context of the invention is an oligonucleotide compound selected from the group consisting of

CTTtAATttaatcactcAT	SEQ ID NO: 9; CMP ID NO: 9_102
CTTTaatttaatcacTCAT	SEQ ID NO: 9; CMP ID NO: 9_103
CTTTaatttaatcaCtCAT	SEQ ID NO: 9; CMP ID NO: 9_104
CTTTaatttaatcaCTCA	SEQ ID NO: 11; CMP ID NO: 11_1
TtaaCTCAaatcaaTtctCA	SEQ ID NO: 49; CMP ID NO: 49_38
TtaActCAaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_51
TTAactCaaatcaatTCtCA	SEQ ID NO: 49; CMP ID NO: 49_179
TTAActcaaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_189
CAACacctttttaattcATTA	SEQ ID NO: 53; CMP ID NO: 53_1
CTCAtcaacacctttttaaTT	SEQ ID NO: 56; CMP ID NO: 56_1
TTAactcatcaacaCCTT	SEQ ID NO: 62; CMP ID NO: 62_1

wherein capital letters are beta-D-oxy LNA nucleosides, lowercase letters are DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

In one embodiment the antisense oligonucleotide is CMP ID NO: 9_103 as shown in Fig. 2.

In one embodiment the antisense oligonucleotide is CMP ID NO: 9_104 as shown in Fig. 3.

In one embodiment the antisense oligonucleotide is CMP ID NO: 11_1 as shown in Fig. 4.

In one embodiment the antisense oligonucleotide is CMP ID NO: 49_38 as shown in Fig. 5.

In one embodiment the antisense oligonucleotide is CMP ID NO: 49_189 as shown in Fig. 6.

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) to covalently attach the conjugate moiety to the oligonucleotide. 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 salt

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to

conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin, Organic Process Research & Development 2000, 4, 427-435 or in Ansel, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457. For example, the pharmaceutically acceptable salt of the compounds provided herein may be a sodium salt.

In a further aspect the invention provides a pharmaceutically acceptable salt of the antisense oligonucleotide or a conjugate thereof. In a preferred embodiment, the pharmaceutically acceptable salt is a sodium or a potassium salt.

Pharmaceutical Composition

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof 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.

Suitable formulations for use in the present invention are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (Science 249:1527-1533, 1990). WO 2007/031091 provides further 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.

These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

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 off 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 Tau 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.

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 present invention provides an *in vivo* or *in vitro* method for modulating Tau expression in a target cell which is expressing Tau, said method comprising administering an oligonucleotide of the invention in an effective amount to said cell.

In some embodiments, the target cell, is a mammalian cell in particular a human cell. The target cell may be an *in vitro* cell culture or an *in vivo* cell forming part of a tissue in a mammal. In preferred embodiments the target cell is present in the brain or central nervous system. In particular cells in the brain stem, cerebellum, cerebal cortex, frontal cortex, medulla/pons and midbrain and spinal cord are relevant target regions. For the treatment of progressive

supranuclear palsy (PSP) target reduction in the brain regions medulla/pons and midbrain are advantageous. For the treatment of Alzheimer target reduction in the brain regions cerebal cortex, medulla/pons and midbrain are advantageous. In particular, in neurons, nerves cells, axons and basal ganglia are relevant cell types.

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

For therapeutics, the oligonucleotides may be administered to an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of Tau.

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

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

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 Tau.

In one embodiment, the invention relates to oligonucleotides, oligonucleotide conjugates or pharmaceutical compositions for use in the treatment of diseases or disorders selected from wherein the disease is selected from Tauopathies, Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBD), chronic traumatic encephalopathy (CTE), fronto- temporal dementia (FTD), FTDP-17, Pick's disease (PiD),

argyrophilic grain disease (AGD), tangle-predominant senile dementia (TPSD), primary age-related Tauopathy (PART), Down syndrome, lytico-bodig disease, infantile Tauopathies including hemimegalencephaly (HME), tuberous sclerosis complex, focal cortical dysplasia type 2b, ganglioglioma, Hallervorden-Spatz syndrome, neurodegeneration with brain iron accumulation type 1 (NBIA1), gangliocytomas, subacute sclerosing panencephalitis, seizure disorders (e.g., epilepsy), network dysfunction (e.g., depression) and movement disorders (e.g., Parkinson's disease).

In certain embodiments the disease is selected from Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

Administration

The oligonucleotides or pharmaceutical compositions of the present invention may be administered via parenteral (such as, intravenous, subcutaneous, intra-muscular, intracerebral, intracerebroventricular intraocular, or intrathecal administration).

In some embodiments, the administration is via intrathecal administration.

Advantageously, e.g. for treatment of neurological disorders, the oligonucleotide or pharmaceutical compositions of the present invention are administered intrathecally or intracranially, e.g. via intracerebral or intraventricular administration.

The invention also provides for the use of the oligonucleotide or conjugate thereof, such as pharmaceutical salts or compositions of the invention, for the manufacture of a medicament wherein the medicament is in a dosage form for subcutaneous administration.

The invention also provides for the use of the oligonucleotide of the invention, or conjugate thereof, such as pharmaceutical salts or compositions of the invention, for the manufacture of a medicament wherein the medicament is in a dosage form for intrathecal administration.

The invention also provides for the use of the oligonucleotide or oligonucleotide conjugate of the invention as described for the manufacture of a medicament wherein the medicament is in a dosage form for intrathecal administration.

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.

EMBODIMENTS

The following embodiments of the present invention may be used in combination with any other embodiments described herein.

1. An antisense oligonucleotide of 10 to 50 nucleotides in length, which comprises a contiguous nucleotide sequence of at least 10 nucleotides in length, such as 10-30 nucleotides in length, with at least 90% complementarity, such as 100% complementarity, to any target sequence in table 4 (R_1 - R_2254).

2. The oligonucleotide of embodiment 1, wherein the target sequence is selected from one of the target regions R_223, R_738 or R_1298, corresponds to SEQ ID NO: 3, 4 or 5, respectively.

3. The oligonucleotide of embodiment 1 or 2, wherein the contiguous nucleotide sequence is 100% complementary to contiguous nucleotides within position12051 to 12111, 39562 to 39593 or 72837 to 72940 of SEQ ID NO: 1.

4. The oligonucleotide of embodiment 1 to 3, wherin the contiguous nucleotide sequence is at last 16 nucleotides and 100% complementary, to contiguous nucleotides within position 12060 to 12078, position 39573 to 39592 or position 72862-72890 of SEQ ID NO: 1.

5. The oligonucleotide of embodiment 1 to 4, wherein the oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NO: 6-65.

6. The oligonucleotide of embodiment 1 to 5, wherein the oligonucleotide comprises a sequence of SEQ ID NO: 9 or 11.

7. The oligonucleotide of embodiment 1 to 5, wherein the oligonucleotide comprises a sequence of SEQ ID NO: 49.

8. The oligonucleotide of embodiment 1 to 5, wherein the oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NO: 53, 56 and 62.

9. The oligonucleotide of embodiment 1, 2 or 5 or 6, wherein the contiguous nucleotide sequence has zero to three mismatches compared to the target sequence it is complementary to.

10. The oligonucleotide of embodiment 9, wherein the contiguous nucleotide sequence has one mismatch compared to the target sequence.

11. The oligonucleotide of embodiment 9, wherein the contiguous nucleotide sequence has two mismatches compared to the target sequence.

12. The oligonucleotide of embodiment 9, wherein the contiguous nucleotide sequence is fully complementary to the target sequence.

13. The oligonucleotide of embodiment 1 to 12, wherein the oligonucleotide is capable of modulating expression of Tau.

14. The oligonucleotide of embodiment 13, wherein the oligonucleotide is capable of reducing expression of Tau.

15. The oligonucleotide of embodiment 1 to 14, wherein the oligonucleotide is capable of hybridizing to the target sequence with a ΔG° below -10 kcal.

16. The oligonucleotide of embodiment 1 to 15, wherein the target sequence is located in RNA.

17. The oligonucleotide of embodiment 16, wherein the RNA is mRNA.

18. The oligonucleotide of embodiment 17, wherein the mRNA is pre-mRNA.

19. The oligonucleotide of embodiment 1-18, wherein the contiguous nucleotide sequence comprises or consists of at least 14 contiguous nucleotides, particularly 15, 16, 17, 18, 19, 20, 21, or 22 contiguous nucleotides.

20. The oligonucleotide of embodiment 1-18, wherein the contiguous nucleotide sequence comprises or consists of from 16 to 22 nucleotides.

21. The oligonucleotide of embodiment 20, wherein the contiguous nucleotide sequence comprises or consists of from 18 to 20 nucleotides.

22. The oligonucleotide of embodiment 1-21, wherein the oligonucleotide comprises or consists of 14 to 30 nucleotides in length.

23. The oligonucleotide of embodiment 22, wherein the oligonucleotide comprises or consists of 16 to 24 nucleotides in length.

24. The oligonucleotide of embodiment 22 or 24, wherein the oligonucleotide comprises or consists of 18 to 20 nucleotides in length.

25. The oligonucleotide of embodiment 1-24, wherein the oligonucleotide or contiguous nucleotide sequence is single stranded.

26. The oligonucleotide of embodiment 1-25, wherein the oligonucleotide is not siRNA nor self-complementary.

27. The oligonucleotide of embodiment 1 -26, comprising one or more modified nucleosides.

28. The oligonucleotide of embodiment 27, wherein the one or more modified nucleoside is a high-affinity modified nucleosides.

29. The oligonucleotide of embodiment 27 or 28, wherein the one or more modified nucleoside is a 2’ sugar modified nucleoside.

30. The oligonucleotide of embodiment 29, wherein the one or more 2’ sugar modified nucleoside is 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, 2’-fluoro-ANA and LNA nucleosides.

31. The oligonucleotide of embodiment 29 or 30, wherein the one or more 2' sugar modified nucleoside is a LNA nucleoside.

32. The antisense oligonucleotide of embodiment 31, wherein the LNA nucleoside is selected from oxy-LNA, amino-LNA, thio-LNA, cET, and ENA.

33. The antisense oligonucleotide of embodiment 31or 32, wherein the modified LNA nucleoside is oxy-LNA with the following 2'-4' bridge –O-CH_2-.

34. The antisense oligonucleotide of embodiment 33, wherein the oxy-LNA is beta-D-oxy-LNA.

35. The antisense oligonucleotide of embodiment 31 or 32, wherein the modified LNA nucleoside is cET with the following 2'-4' bridge –O-CH(CH_3)-.

36. The antisense oligonucleotide of embodiment 35, wherein the cET is (S)cET, i.e. 6'(S)methyl-beta-D-oxy-LNA.

37. The antisense oligonucleotide of embodiment 31 or 32, wherein the LNA is ENA, with the following 2' – 4' bridge –O-CH_2-CH_2-.

38. The oligonucleotide of embodiment 29 or 30, wherein the one or more 2' sugar modified nucleoside is a MOE nucleoside

39. The oligonucleotide of any one of embodiments 1-38, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

40. The oligonucleotide of embodiment 39, wherein the modified internucleoside linkage is nuclease resistant.

41. The oligonucleotide of embodiment 39 or 40, wherein at least 50% of the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages or boranophosphate internucleoside linkages.

42. The oligonucleotide of embodiment 39 or 41, wherein 80% the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

43. The oligonucleotide of embodiment 39 to 42, wherein all the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

44. The oligonucleotide of embodiment 1-43, wherein the oligonucleotide is capable of recruiting RNase H.

45. The oligonucleotide of embodiment 44, wherein the oligonucleotide or the contiguous nucleotide sequence is a gapmer.

46. The oligonucleotide of embodiment 45, wherein the gapmer has the formula 5'-F-G-F'-3', where the F and F' wing regions independently comprise or consist of 1 – 8 nucleosides, of

which 2 - 5 are 2' sugar modified nucleosides in accordance with embodiment 32 to 38 and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH.

47. The antisense oligonucleotide of embodiment 46, wherein each wing region (F and F') is characterized by having at least one 2' sugar modified nucleoside at the 5' terminal and the 3' terminal of the wing and the G region has at least one DNA nucleoside adjacent to the wing regions (e.g. 5' and 3' terminal of the G region).

48. The oligonucleotide of embodiment 46 or 47, wherein all the 2' sugar modified nucleosides in region F and F' are identical LNA nucleosides.

49. The oligonucleotide of embodiment 48, wherein all the LNA nucleosides are oxy-LNA nucleosides.

50. The oligonucleotide of embodiment 46 or 47, wherein all the 2' sugar modified nucleosides in region F and F' are identical MOE nucleosides.

51. The oligonucleotide of embodiment 46 - 50, wherein

a. the F region is between 3 and 8 nucleotides in length and consists of 3-5 identical LNA nucleosides and 0-4 DNA nucleosides; and
b. the F' region is between 2 and 6 nucleotides in length and consists of 2-4 identical LNA nucleosides and 0-2 DNA nucleosides; and
c. region G is between 6 and 14 DNA nucleotides.

52. The oligonucleotide of embodiment 46 or 47, wherein at least one of region F or F' further comprises at least one 2' substituted 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 and 2'-fluoro-DNA.

53. The oligonucleotide of embodiment 46 to 50 or 52, wherein the RNaseH recruiting nucleosides in region G are independently selected from DNA, alpha-L-LNA, C4' alkylated DNA, ANA and 2'F-ANA and UNA.

54. The oligonucleotide of embodiment 53, wherein the nucleosides in region G is DNA and/or alpha-L-LNA nucleosides.

55. The oligonucleotide of embodiment 53 or 54, wherein region G consists of at least 75% DNA nucleosides.

56. The oligonucleotide of embodiment 53 to 55, wherein all the nucleotides in the G region are DNA.

57. The oligonucleotide of embodiment 1-56, wherein the oligonucleotide is selected from CMP ID NO: 9_102; 9_103; 9_104; 11_1; 49_38; 49_51; 49_179; 49_189; 53_1; 56_1 and 62_1.

58. The oligonucleotide of embodiment 57, wherein the oligonucleotide is a compound selected from the group consisting of

CTTtAATttaatcactcAT	SEQ ID NO: 9; CMP ID NO: 9_102
CTTTaatttaatcacTCAT	SEQ ID NO: 9; CMP ID NO: 9_103
CTTTaatttaatcaCtCAT	SEQ ID NO: 9; CMP ID NO: 9_104
CTTTaatttaatcaCTCA	SEQ ID NO: 11; CMP ID NO: 11_1
TtaaCTCAaatcaaTtctCA	SEQ ID NO: 49; CMP ID NO: 49_38
TtaActCAaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_51
TTAactCaaatcaatTCtCA	SEQ ID NO: 49; CMP ID NO: 49_179
TTAActcaaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_189
CAACacctttttaattcATTA	SEQ ID NO: 53; CMP ID NO: 53_1
CTCAtcaacacctttttaaTT	SEQ ID NO: 56; CMP ID NO: 56_1
TTAactcatcaacaCCTT	SEQ ID NO: 62; CMP ID NO: 62_1

wherein capital letters are beta-D-oxy LNA nucleosides, lowercase letters are DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

59. The antisense oligonucleotide according to any one of embodiments 1 – 58, wherein the antisense oligonucleotide is CMP ID NO: 9_103 as shown in Fig. 2.

60. The antisense oligonucleotide according to any one of embodiments 1 – 58, wherein the antisense oligonucleotide is CMP ID NO: 9_104 as shown in Fig. 3.

61. The antisense oligonucleotide according to any one of embodiments 1 – 58, wherein the antisense oligonucleotide is CMP ID NO: 11_1 as shown in Fig. 4.

62. The antisense oligonucleotide according to any one of embodiments 1 – 58, wherein the antisense oligonucleotide is CMP ID NO: 49_38 as shown in Fig. 5.

63. The antisense oligonucleotide according to any one of embodiments 1 – 58, wherein the antisense oligonucleotide is CMP ID NO: 49_189 as shown in Fig. 6.

64. A conjugate comprising the oligonucleotide according to any one of claims 1-58, and at least one conjugate moiety covalently attached to said oligonucleotide.

65. The oligonucleotide conjugate of embodiment 59, wherein the conjugate moiety is selected from carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins, vitamins, viral proteins or combinations thereof.

66. The oligonucleotide conjugate of embodiment 59 or 65, wherein the conjugate facilitates delivery across the blood brain barrier.

67. The oligonucleotide conjugate of embodiment 66, wherein the conjugate is an antibody or antibody fragment targeting the transferrin receptor.

68. The oligonucleotide conjugate of embodiment 59-67, comprising a linker which is positioned between the oligonucleotide and the conjugate moiety.

69. The oligonucleotide conjugate of embodiment 68, wherein the linker is a physiologically labile linker.

70. A pharmaceutical composition comprising the oligonucleotide of embodiment 1-58 or a conjugate of embodiment 59-69 and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

71. A method for manufacturing the oligonucleotide of embodiment 1-58, comprising reacting nucleotide units thereby forming covalently linked contiguous nucleotide units comprised in the oligonucleotide.

72. The method of embodiment 71, further comprising reacting the contiguous nucleotide sequence with a non-nucleotide conjugation moiety.

73. A method for manufacturing the composition of embodiment 70, comprising mixing the oligonucleotide with a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

74. An *in vivo* or *in vitro* method for modulating Tau expression in a target cell which is expressing Tau, said method comprising administering an oligonucleotide of embodiment 1-57 or a conjugate of embodiment 59-69 or the pharmaceutical composition of embodiment 70 in an effective amount to said cell.

75. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide of embodiment 1-58 or a conjugate of embodiment 59-69 or the pharmaceutical composition of embodiment 70 to a subject suffering from or susceptible to the disease.

76. The oligonucleotide of embodiment 1-57 or a conjugate of embodiment 59-69 or the pharmaceutical composition of embodiment 70, for use as a medicament for treatment or prevention of a disease in a subject.

77. Use of the oligonucleotide of oligonucleotide of embodiment 1-58 or a conjugate of embodiment 59-69 for the preparation of a medicament for treatment or prevention of a disease in a subject.

78. The method, the oligonucleotide or the use of embodiments 75 - 77, wherein the disease is associated with *in vivo* activity of Tau.

79. The method, the oligonucleotide or the use of embodiments 75 - 78, wherein the disease is associated with overexpression of Tau and/or abnormal levels of Tau.

80. The method, the oligonucleotide or the use of embodiments 79, wherein the Tau is reduced by at least 30%, or at least or at least 40%, or at least 50%, or at least 60%, or at least 70%, or

at least 80%, or at least 90%, or at least 95% compared to the expression without the oligonucleotide of embodiment 1-58 or a conjugate of embodiment 59-69 or the pharmaceutical composition of embodiment 70.

81. The method, the oligonucleotide or the use of embodiments 75 - 79, wherein the disease is selected from Tauopathies, Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBD), chronic traumatic encephalopathy (CTE), fronto-temporal dementia (FTD), FTDP-17, Pick's disease (PiD), argyrophilic grain disease (AGD), tangle-predominant senile dementia (TPSD), primary age-related Tauopathy (PART), Down syndrome, lytico-bodig disease, infantile Tauopathies including hemimegalencephaly (HME), tuberous sclerosis complex, focal cortical dysplasia type 2b, ganglioglioma, Hallervorden-Spatz syndrome, neurodegeneration with brain iron accumulation type 1 (NBIA1), gangliocytomas, subacute sclerosing panencephalitis, seizure disorders (e.g., epilepsy), network dysfunction (e.g., depression) and movement disorders (e.g., Parkinson's disease).

82. The method, the oligonucleotide or the use of embodiments 75 - 79 wherein the disease is selected from Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

83. The method, the oligonucleotide or the use of embodiments 75 - 82, wherein the subject is a mammal.

84. The method, the oligonucleotide or the use of embodiment 83, wherein the mammal is human.

EXAMPLES

Materials and methods

Oligonucleotide motif sequences and oligonucleotide compounds

Table 5: list of oligonucleotide motif sequences (indicated by SEQ ID NO), designs of these, as well as specific oligonucleotide compounds (indicated by CMP ID NO) designed based on the motif sequence.

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
6	tcactcatgccttaatc	4-11-2	TCACtcatgccttaaTC	6_1	12051	A
7	taatcactcatgcctta	4-9-4	TAATcactcatgcCTTA	7_1	12054	A
8	taatcactcatgcctt	4-8-4	TAATcactcatgCCTT	8_1	12055	A
9	ctttaatttaatcactcat	1-10-1-2-1-1-3	CtttaatttaaTcaCtCAT	9_1	12060	A
9	ctttaatttaatcactcat	1-10-1-1-2-1-3	CtttaatttaaTcACtCAT	9_2	12060	A
9	ctttaatttaatcactcat	1-10-2-3-3	CtttaatttaaTCactCAT	9_3	12060	A
9	ctttaatttaatcactcat	1-10-2-2-4	CtttaatttaaTCacTCAT	9_4	12060	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
9	ctttaatttaatcactcat	1-10-2-1-1-2-2	CtttaatttaaTCaCtcAT	9_5	12060	A
9	ctttaatttaatcactcat	1-10-2-1-1-1-3	CtttaatttaaTCaCtCAT	9_6	12060	A
9	ctttaatttaatcactcat	1-10-3-3-2	CtttaatttaaTCActcAT	9_7	12060	A
9	ctttaatttaatcactcat	1-10-3-2-3	CtttaatttaaTCActCAT	9_8	12060	A
9	ctttaatttaatcactcat	1-10-3-1-4	CtttaatttaaTCAcTCAT	9_9	12060	A
9	ctttaatttaatcactcat	1-10-4-2-2	CtttaatttaaTCACtcAT	9_10	12060	A
9	ctttaatttaatcactcat	1-5-1-8-4	CtttaaTttaatcacTCAT	9_11	12060	A
9	ctttaatttaatcactcat	1-5-1-7-1-1-3	CtttaaTttaatcaCtCAT	9_12	12060	A
9	ctttaatttaatcactcat	1-5-1-6-1-2-3	CtttaaTttaatcActCAT	9_13	12060	A
9	ctttaatttaatcactcat	1-5-1-6-1-1-4	CtttaaTttaatcAcTCAT	9_14	12060	A
9	ctttaatttaatcactcat	1-5-1-6-2-1-3	CtttaaTttaatcACtCAT	9_15	12060	A
9	ctttaatttaatcactcat	1-4-1-9-4	CtttaAtttaatcacTCAT	9_16	12060	A
9	ctttaatttaatcactcat	1-4-2-8-4	CtttaATttaatcacTCAT	9_17	12060	A
9	ctttaatttaatcactcat	1-3-1-10-4	CtttAatttaatcacTCAT	9_18	12060	A
9	ctttaatttaatcactcat	1-3-1-9-1-1-3	CtttAatttaatcaCtCAT	9_19	12060	A
9	ctttaatttaatcactcat	1-3-1-1-1-8-4	CtttAaTttaatcacTCAT	9_20	12060	A
9	ctttaatttaatcactcat	1-3-2-9-4	CtttAAtttaatcacTCAT	9_21	12060	A
9	ctttaatttaatcactcat	1-3-3-8-4	CtttAATttaatcacTCAT	9_22	12060	A
9	ctttaatttaatcactcat	1-2-1-11-4	CttTaatttaatcacTCAT	9_23	12060	A
9	ctttaatttaatcactcat	1-2-1-10-1-1-3	CttTaatttaatcaCtCAT	9_24	12060	A
9	ctttaatttaatcactcat	1-2-1-2-1-8-4	CttTaaTttaatcacTCAT	9_25	12060	A
9	ctttaatttaatcactcat	1-2-1-1-1-9-4	CttTaAtttaatcacTCAT	9_26	12060	A
9	ctttaatttaatcactcat	1-2-1-1-2-8-4	CttTaATttaatcacTCAT	9_27	12060	A
9	ctttaatttaatcactcat	1-2-2-11-3	CttTAatttaatcactCAT	9_28	12060	A
9	ctttaatttaatcactcat	1-2-2-10-4	CttTAatttaatcacTCAT	9_29	12060	A
9	ctttaatttaatcactcat	1-2-2-9-1-2-2	CttTAatttaatcaCtcAT	9_30	12060	A
9	ctttaatttaatcactcat	1-2-2-9-1-1-3	CttTAatttaatcaCtCAT	9_31	12060	A
9	ctttaatttaatcactcat	1-2-2-1-1-8-4	CttTAaTttaatcacTCAT	9_32	12060	A
9	ctttaatttaatcactcat	1-2-3-9-4	CttTAAtttaatcacTCAT	9_33	12060	A
9	ctttaatttaatcactcat	1-2-4-10-2	CttTAATttaatcactcAT	9_34	12060	A
9	ctttaatttaatcactcat	1-2-4-8-4	CttTAATttaatcacTCAT	9_35	12060	A
9	ctttaatttaatcactcat	1-1-1-3-1-8-4	CtTtaaTttaatcacTCAT	9_36	12060	A
9	ctttaatttaatcactcat	1-1-1-2-1-9-4	CtTtaAtttaatcacTCAT	9_37	12060	A
9	ctttaatttaatcactcat	1-1-1-2-2-8-4	CtTtaATttaatcacTCAT	9_38	12060	A
9	ctttaatttaatcactcat	1-1-1-1-1-10-4	CtTtAatttaatcacTCAT	9_39	12060	A
9	ctttaatttaatcactcat	1-1-1-1-1-9-1-1-3	CtTtAatttaatcaCtCAT	9_40	12060	A
9	ctttaatttaatcactcat	1-1-1-1-1-1-1-8-4	CtTtAaTttaatcacTCAT	9_41	12060	A
9	ctttaatttaatcactcat	1-1-1-1-2-9-4	CtTtAAtttaatcacTCAT	9_42	12060	A
9	ctttaatttaatcactcat	1-1-1-1-3-8-4	CtTtAATttaatcacTCAT	9_43	12060	A
9	ctttaatttaatcactcat	1-1-2-11-4	CtTTaatttaatcacTCAT	9_44	12060	A
9	ctttaatttaatcactcat	1-1-2-10-1-2-2	CtTTaatttaatcaCtcAT	9_45	12060	A
9	ctttaatttaatcactcat	1-1-2-10-1-1-3	CtTTaatttaatcaCtCAT	9_46	12060	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
9	ctttaatttaatcactcat	1-1-2-2-1-8-4	CtTTaaTttaatcacTCAT	9_47	12060	A
9	ctttaatttaatcactcat	1-1-2-1-1-9-4	CtTTaAtttaatcacTCAT	9_48	12060	A
9	ctttaatttaatcactcat	1-1-2-1-2-10-2	CtTTaATttaatcactcAT	9_49	12060	A
9	ctttaatttaatcactcat	1-1-2-1-2-8-4	CtTTaATttaatcacTCAT	9_50	12060	A
9	ctttaatttaatcactcat	1-1-3-11-3	CtTTAatttaatcactCAT	9_51	12060	A
9	ctttaatttaatcactcat	1-1-3-10-4	CtTTAatttaatcacTCAT	9_52	12060	A
9	ctttaatttaatcactcat	1-1-3-9-1-2-2	CtTTAatttaatcaCtcAT	9_53	12060	A
9	ctttaatttaatcactcat	1-1-3-9-1-1-3	CtTTAatttaatcaCtCAT	9_54	12060	A
9	ctttaatttaatcactcat	1-1-3-1-1-10-2	CtTTAaTttaatcactcAT	9_55	12060	A
9	ctttaatttaatcactcat	1-1-3-1-1-8-4	CtTTAaTttaatcacTCAT	9_56	12060	A
9	ctttaatttaatcactcat	1-1-4-11-2	CtTTAAtttaatcactcAT	9_57	12060	A
9	ctttaatttaatcactcat	1-1-4-9-4	CtTTAAtttaatcacTCAT	9_58	12060	A
9	ctttaatttaatcactcat	2-11-1-2-3	CTttaatttaatcActCAT	9_59	12060	A
9	ctttaatttaatcactcat	2-11-1-1-4	CTttaatttaatcAcTCAT	9_60	12060	A
9	ctttaatttaatcactcat	2-11-2-1-3	CTttaatttaatcACtCAT	9_61	12060	A
9	ctttaatttaatcactcat	2-9-2-4-2	CTttaatttaaTCactcAT	9_62	12060	A
9	ctttaatttaatcactcat	2-9-2-3-3	CTttaatttaaTCactCAT	9_63	12060	A
9	ctttaatttaatcactcat	2-9-2-2-4	CTttaatttaaTCacTCAT	9_64	12060	A
9	ctttaatttaatcactcat	2-9-2-1-1-2-2	CTttaatttaaTCaCtcAT	9_65	12060	A
9	ctttaatttaatcactcat	2-9-2-1-1-1-3	CTttaatttaaTCaCtCAT	9_66	12060	A
9	ctttaatttaatcactcat	2-9-3-3-2	CTttaatttaaTCActcAT	9_67	12060	A
9	ctttaatttaatcactcat	2-9-3-2-3	CTttaatttaaTCActCAT	9_68	12060	A
9	ctttaatttaatcactcat	2-9-4-2-2	CTttaatttaaTCACtcAT	9_69	12060	A
9	ctttaatttaatcactcat	2-4-1-9-3	CTttaaTttaatcactCAT	9_70	12060	A
9	ctttaatttaatcactcat	2-4-1-8-4	CTttaaTttaatcacTCAT	9_71	12060	A
9	ctttaatttaatcactcat	2-4-1-7-1-2-2	CTttaaTttaatcaCtcAT	9_72	12060	A
9	ctttaatttaatcactcat	2-4-1-7-1-1-3	CTttaaTttaatcaCtCAT	9_73	12060	A
9	ctttaatttaatcactcat	2-4-1-6-1-2-3	CTttaaTttaatcActCAT	9_74	12060	A
9	ctttaatttaatcactcat	2-4-1-6-1-1-4	CTttaaTttaatcAcTCAT	9_75	12060	A
9	ctttaatttaatcactcat	2-4-1-6-2-2-2	CTttaaTttaatcACtcAT	9_76	12060	A
9	ctttaatttaatcactcat	2-4-1-6-2-1-3	CTttaaTttaatcACtCAT	9_77	12060	A
9	ctttaatttaatcactcat	2-2-1-11-3	CTttAatttaatcactCAT	9_78	12060	A
9	ctttaatttaatcactcat	2-2-1-10-4	CTttAatttaatcacTCAT	9_79	12060	A
9	ctttaatttaatcactcat	2-2-1-9-1-1-3	CTttAatttaatcaCtCAT	9_80	12060	A
9	ctttaatttaatcactcat	2-2-1-1-1-8-4	CTttAaTttaatcacTCAT	9_81	12060	A
9	ctttaatttaatcactcat	2-2-2-9-4	CTttAAtttaatcacTCAT	9_82	12060	A
9	ctttaatttaatcactcat	2-2-3-8-4	CTttAATttaatcacTCAT	9_83	12060	A
9	ctttaatttaatcactcat	2-1-1-10-1-2-2	CTtTaatttaatcaCtcAT	9_84	12060	A
9	ctttaatttaatcactcat	2-1-1-10-1-1-3	CTtTaatttaatcaCtCAT	9_85	12060	A
9	ctttaatttaatcactcat	2-1-1-1-1-9-4	CTtTaAtttaatcacTCAT	9_86	12060	A
9	ctttaatttaatcactcat	2-1-1-1-2-10-2	CTtTaATttaatcactcAT	9_87	12060	A
9	ctttaatttaatcactcat	2-1-2-11-3	CTtTAatttaatcactCAT	9_88	12060	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
9	ctttaatttaatcactcat	2-1-2-10-4	CTtTAatttaatcacTCAT	9_89	12060	A
9	ctttaatttaatcactcat	2-1-2-9-1-2-2	CTtTAatttaatcaCtcAT	9_90	12060	A
9	ctttaatttaatcactcat	2-1-2-9-1-1-3	CTtTAatttaatcaCtCAT	9_91	12060	A
9	ctttaatttaatcactcat	2-1-2-1-1-10-2	CTtTAaTttaatcactcAT	9_92	12060	A
9	ctttaatttaatcactcat	2-1-3-11-2	CTtTAAtttaatcactcAT	9_93	12060	A
9	ctttaatttaatcactcat	2-1-3-9-4	CTtTAAtttaatcacTCAT	9_94	12060	A
9	ctttaatttaatcactcat	2-1-4-10-2	CTtTAATttaatcactcAT	9_95	12060	A
9	ctttaatttaatcactcat	3-2-2-10-2	CTTtaATttaatcactcAT	9_96	12060	A
9	ctttaatttaatcactcat	3-1-1-11-3	CTTtAatttaatcactCAT	9_97	12060	A
9	ctttaatttaatcactcat	3-1-1-10-4	CTTtAatttaatcacTCAT	9_98	12060	A
9	ctttaatttaatcactcat	3-1-1-9-1-2-2	CTTtAatttaatcaCtcAT	9_99	12060	A
9	ctttaatttaatcactcat	3-1-1-9-1-1-3	CTTtAatttaatcaCtCAT	9_100	12060	A
9	ctttaatttaatcactcat	3-1-2-9-4	CTTtAAtttaatcacTCAT	9_101	12060	A
9	ctttaatttaatcactcat	3-1-3-10-2	CTTtAATttaatcactcAT	9_102	12060	A
9	ctttaatttaatcactcat	4-11-4	CTTTaatttaatcacTCAT	9_103	12060	A
9	ctttaatttaatcactcat	4-10-1-1-3	CTTTaatttaatcaCtCAT	9_104	12060	A
9	ctttaatttaatcactcat	4-2-1-10-2	CTTTaaTttaatcactcAT	9_105	12060	A
9	ctttaatttaatcactcat	4-1-1-9-4	CTTTaAtttaatcacTCAT	9_106	12060	A
10	gctttaatttaatcactcat	1-11-1-2-1-1-3	GctttaatttaaTcaCtCAT	10_1	12060	A
10	gctttaatttaatcactcat	1-11-2-4-2	GctttaatttaaTCactcAT	10_2	12060	A
10	gctttaatttaatcactcat	1-11-2-3-3	GctttaatttaaTCactCAT	10_3	12060	A
10	gctttaatttaatcactcat	1-11-2-2-4	GctttaatttaaTCacTCAT	10_4	12060	A
10	gctttaatttaatcactcat	1-11-2-1-1-2-2	GctttaatttaaTCaCtcAT	10_5	12060	A
10	gctttaatttaatcactcat	1-11-2-1-1-1-3	GctttaatttaaTCaCtCAT	10_6	12060	A
10	gctttaatttaatcactcat	1-11-3-3-2	GctttaatttaaTCActcAT	10_7	12060	A
10	gctttaatttaatcactcat	1-11-4-2-2	GctttaatttaaTCACtcAT	10_8	12060	A
10	gctttaatttaatcactcat	1-6-1-9-3	GctttaaTttaatcactCAT	10_9	12060	A
10	gctttaatttaatcactcat	1-6-1-8-4	GctttaaTttaatcacTCAT	10_10	12060	A
10	gctttaatttaatcactcat	1-6-1-7-1-2-2	GctttaaTttaatcaCtcAT	10_11	12060	A
10	gctttaatttaatcactcat	1-6-1-7-1-1-3	GctttaaTttaatcaCtCAT	10_12	12060	A
10	gctttaatttaatcactcat	1-6-1-4-1-2-1-1-3	GctttaaTttaaTcaCtCAT	10_13	12060	A
10	gctttaatttaatcactcat	1-6-1-4-2-3-3	GctttaaTttaaTCactCAT	10_14	12060	A
10	gctttaatttaatcactcat	1-6-1-4-2-1-1-2-2	GctttaaTttaaTCaCtcAT	10_15	12060	A
10	gctttaatttaatcactcat	1-6-1-4-3-3-2	GctttaaTttaaTCActcAT	10_16	12060	A
10	gctttaatttaatcactcat	1-5-1-9-4	GctttaAtttaatcacTCAT	10_17	12060	A
10	gctttaatttaatcactcat	1-4-1-10-4	GctttAatttaatcacTCAT	10_18	12060	A
10	gctttaatttaatcactcat	1-4-1-9-1-1-3	GctttAatttaatcaCtCAT	10_19	12060	A
10	gctttaatttaatcactcat	1-4-1-1-1-8-4	GctttAaTttaatcacTCAT	10_20	12060	A
10	gctttaatttaatcactcat	1-4-2-9-4	GctttAAtttaatcacTCAT	10_21	12060	A
10	gctttaatttaatcactcat	1-4-3-8-4	GctttAATttaatcacTCAT	10_22	12060	A
10	gctttaatttaatcactcat	1-3-1-11-4	GcttTaatttaatcacTCAT	10_23	12060	A
10	gctttaatttaatcactcat	1-3-1-10-1-2-2	GcttTaatttaatcaCtcAT	10_24	12060	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
10	gctttaatttaatcactcat	1-3-1-10-1-1-3	GcttTaatttaatcaCtCAT	10_25	12060	A
10	gctttaatttaatcactcat	1-3-1-2-1-8-4	GcttTaaTttaatcacTCAT	10_26	12060	A
10	gctttaatttaatcactcat	1-3-1-1-1-9-4	GcttTaAtttaatcacTCAT	10_27	12060	A
10	gctttaatttaatcactcat	1-3-2-10-4	GcttTAatttaatcacTCAT	10_28	12060	A
10	gctttaatttaatcactcat	1-3-2-9-1-2-2	GcttTAatttaatcaCtcAT	10_29	12060	A
10	gctttaatttaatcactcat	1-3-2-9-1-1-3	GcttTAatttaatcaCtCAT	10_30	12060	A
10	gctttaatttaatcactcat	1-2-1-3-1-8-4	GctTtaaTttaatcacTCAT	10_31	12060	A
10	gctttaatttaatcactcat	1-2-1-2-1-9-4	GctTtaAtttaatcacTCAT	10_32	12060	A
10	gctttaatttaatcactcat	1-2-1-1-1-10-4	GctTtAatttaatcacTCAT	10_33	12060	A
10	gctttaatttaatcactcat	1-2-1-1-1-9-1-2-2	GctTtAatttaatcaCtcAT	10_34	12060	A
10	gctttaatttaatcactcat	1-2-1-1-1-9-1-1-3	GctTtAatttaatcaCtCAT	10_35	12060	A
10	gctttaatttaatcactcat	1-2-1-1-1-1-1-8-4	GctTtAaTttaatcacTCAT	10_36	12060	A
10	gctttaatttaatcactcat	1-2-1-1-2-9-4	GctTtAAtttaatcacTCAT	10_37	12060	A
10	gctttaatttaatcactcat	1-2-2-11-4	GctTTaatttaatcacTCAT	10_38	12060	A
10	gctttaatttaatcactcat	1-2-2-10-1-2-2	GctTTaatttaatcaCtcAT	10_39	12060	A
10	gctttaatttaatcactcat	1-2-2-10-1-1-3	GctTTaatttaatcaCtCAT	10_40	12060	A
10	gctttaatttaatcactcat	1-2-2-1-1-9-4	GctTTaAtttaatcacTCAT	10_41	12060	A
10	gctttaatttaatcactcat	1-2-3-9-1-2-2	GctTTAatttaatcaCtcAT	10_42	12060	A
10	gctttaatttaatcactcat	1-1-1-9-2-4-2	GcTttaatttaaTCactcAT	10_43	12060	A
10	gctttaatttaatcactcat	1-1-1-9-2-3-3	GcTttaatttaaTCactCAT	10_44	12060	A
10	gctttaatttaatcactcat	1-1-1-9-2-1-1-2-2	GcTttaatttaaTCaCtcAT	10_45	12060	A
10	gctttaatttaatcactcat	1-1-1-9-3-3-2	GcTttaatttaaTCActcAT	10_46	12060	A
10	gctttaatttaatcactcat	1-1-1-4-1-9-3	GcTttaaTttaatcactCAT	10_47	12060	A
10	gctttaatttaatcactcat	1-1-1-4-1-8-4	GcTttaaTttaatcacTCAT	10_48	12060	A
10	gctttaatttaatcactcat	1-1-1-4-1-7-1-2-2	GcTttaaTttaatcaCtcAT	10_49	12060	A
10	gctttaatttaatcactcat	1-1-1-4-1-7-1-1-3	GcTttaaTttaatcaCtCAT	10_50	12060	A
10	gctttaatttaatcactcat	1-1-1-3-1-9-4	GcTttaAtttaatcacTCAT	10_51	12060	A
10	gctttaatttaatcactcat	1-1-1-2-1-10-4	GcTttAatttaatcacTCAT	10_52	12060	A
10	gctttaatttaatcactcat	1-1-1-2-1-9-1-2-2	GcTttAatttaatcaCtcAT	10_53	12060	A
10	gctttaatttaatcactcat	1-1-1-2-1-9-1-1-3	GcTttAatttaatcaCtCAT	10_54	12060	A
10	gctttaatttaatcactcat	1-1-1-2-1-1-1-8-4	GcTttAaTttaatcacTCAT	10_55	12060	A
10	gctttaatttaatcactcat	1-1-1-2-2-9-4	GcTttAAtttaatcacTCAT	10_56	12060	A
10	gctttaatttaatcactcat	1-1-1-1-1-11-4	GcTtTaatttaatcacTCAT	10_57	12060	A
10	gctttaatttaatcactcat	1-1-1-1-1-10-1-1-3	GcTtTaatttaatcaCtCAT	10_58	12060	A
10	gctttaatttaatcactcat	1-1-1-1-1-2-1-8-4	GcTtTaaTttaatcacTCAT	10_59	12060	A
10	gctttaatttaatcactcat	1-1-1-1-1-1-1-9-4	GcTtTaAtttaatcacTCAT	10_60	12060	A
10	gctttaatttaatcactcat	1-1-1-1-2-9-1-2-2	GcTtTAatttaatcaCtcAT	10_61	12060	A
10	gctttaatttaatcactcat	1-1-1-1-3-11-2	GcTtTAAtttaatcactcAT	10_62	12060	A
10	gctttaatttaatcactcat	1-1-2-3-1-8-4	GcTTtaaTttaatcacTCAT	10_63	12060	A
10	gctttaatttaatcactcat	1-1-2-2-1-11-2	GcTTtaAtttaatcactcAT	10_64	12060	A
10	gctttaatttaatcactcat	1-1-2-2-1-9-4	GcTTtaAtttaatcacTCAT	10_65	12060	A
10	gctttaatttaatcactcat	1-1-2-1-1-10-4	GcTTtAatttaatcacTCAT	10_66	12060	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
10	gctttaatttaatcactcat	1-1-2-1-1-9-1-1-3	GcTTtAatttaatcaCtCAT	10_67	12060	A
10	gctttaatttaatcactcat	1-1-2-1-2-11-2	GcTTtAAtttaatcactcAT	10_68	12060	A
10	gctttaatttaatcactcat	1-1-3-10-2-1-2	GcTTTaatttaatcaCTcAT	10_69	12060	A
10	gctttaatttaatcactcat	1-1-4-9-1-2-2	GcTTTAatttaatcaCtcAT	10_70	12060	A
10	gctttaatttaatcactcat	2-11-1-4-2	GCtttaatttaatCactcAT	10_71	12060	A
10	gctttaatttaatcactcat	2-10-2-4-2	GCtttaatttaaTCactcAT	10_72	12060	A
10	gctttaatttaatcactcat	2-5-1-10-2	GCtttaaTttaatcactcAT	10_73	12060	A
10	gctttaatttaatcactcat	2-5-1-9-3	GCtttaaTttaatcactCAT	10_74	12060	A
10	gctttaatttaatcactcat	2-5-1-7-1-2-2	GCtttaaTttaatcaCtcAT	10_75	12060	A
10	gctttaatttaatcactcat	2-4-2-10-2	GCtttaATttaatcactcAT	10_76	12060	A
10	gctttaatttaatcactcat	2-3-1-9-1-2-2	GCtttAatttaatcaCtcAT	10_77	12060	A
10	gctttaatttaatcactcat	2-3-2-11-2	GCtttAAtttaatcactcAT	10_78	12060	A
10	gctttaatttaatcactcat	2-2-1-10-1-2-2	GCttTaatttaatcaCtcAT	10_79	12060	A
10	gctttaatttaatcactcat	2-2-1-1-1-11-2	GCttTaAtttaatcactcAT	10_80	12060	A
10	gctttaatttaatcactcat	2-2-3-11-2	GCttTAAtttaatcactcAT	10_81	12060	A
10	gctttaatttaatcactcat	2-1-1-2-1-11-2	GCtTtaAtttaatcactcAT	10_82	12060	A
10	gctttaatttaatcactcat	2-1-1-1-1-9-1-2-2	GCtTtAatttaatcaCtcAT	10_83	12060	A
10	gctttaatttaatcactcat	2-1-1-1-2-11-2	GCtTtAAtttaatcactcAT	10_84	12060	A
10	gctttaatttaatcactcat	3-10-1-4-2	GCTttaatttaatCactcAT	10_85	12060	A
10	gctttaatttaatcactcat	3-4-1-10-2	GCTttaaTttaatcactcAT	10_86	12060	A
10	gctttaatttaatcactcat	3-3-1-11-2	GCTttaAtttaatcactcAT	10_87	12060	A
10	gctttaatttaatcactcat	3-2-2-11-2	GCTttAAtttaatcactcAT	10_88	12060	A
10	gctttaatttaatcactcat	3-1-1-9-1-1-1-1-2	GCTtTaatttaatcAcTcAT	10_89	12060	A
11	ctttaatttaatcactca	4-10-4	CTTTaatttaatcaCTCA	11_1	12061	A
12	ctttaatttaatcactc	4-9-4	CTTTaatttaatcACTC	12_1	12062	A
13	tccaagtcaatgcctggctt	3-14-3	TCCaagtcaatgcctggCTT	13_1	12076	A
14	atccaagtcaatgcctggct	3-14-3	ATCcaagtcaatgcctgGCT	14_1	12077	A
15	accatccaagtcaatgcctg	3-14-3	ACCatccaagtcaatgcCTG	15_1	12080	A
16	caccatccaagtcaatgcct	3-14-3	CACcatccaagtcaatgCCT	16_1	12081	A
17	tacaccatccaagtcaatgc	3-14-3	TACaccatccaagtcaaTGC	17_1	12083	A
18	ttacaccatccaagtcaatg	3-14-3	TTAcaccatccaagtcaATG	18_1	12084	A
19	acaccatccaagtcaat	3-10-4	ACAccatccaagtCAAT	19_1	12085	A
20	tacaccatccaagtcaa	3-10-4	TACaccatccaagTCAA	20_1	12086	A
21	ttacaccatccaagtca	4-11-2	TTACaccatccaagtCA	21_1	12087	A
22	ttacaccatccaagtc	4-9-3	TTACaccatccaaGTC	22_1	12088	A
23	aatattacaccatccaa	4-9-4	AATAttacaccatCCAA	23_1	12091	A
24	agaatattacaccatccaa	1-3-1-10-4	AgaaTattacaccatCCAA	24_1	12091	A
24	agaatattacaccatccaa	1-3-1-9-1-1-3	AgaaTattacaccaTcCAA	24_2	12091	A
24	agaatattacaccatccaa	1-3-1-9-2-1-2	AgaaTattacaccaTCcAA	24_3	12091	A
24	agaatattacaccatccaa	1-3-1-8-1-2-3	AgaaTattacaccAtcCAA	24_4	12091	A
24	agaatattacaccatccaa	1-3-1-8-1-1-4	AgaaTattacaccAtCCAA	24_5	12091	A
24	agaatattacaccatccaa	1-3-1-8-2-1-3	AgaaTattacaccATcCAA	24_6	12091	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
24	agaatattacaccatccaa	1-3-1-8-3-1-2	AgaaTattacaccATCcAA	24_7	12091	A
24	agaatattacaccatccaa	1-3-1-7-1-1-2-1-2	AgaaTattacacCaTCcAA	24_8	12091	A
24	agaatattacaccatccaa	1-3-1-6-1-1-1-1-1-1-2	AgaaTattacaCcAtCcAA	24_9	12091	A
24	agaatattacaccatccaa	1-3-1-6-1-1-2-1-3	AgaaTattacaCcATcCAA	24_10	12091	A
24	agaatattacaccatccaa	1-2-1-11-4	AgaAtattacaccatCCAA	24_11	12091	A
24	agaatattacaccatccaa	1-2-1-10-1-1-3	AgaAtattacaccaTcCAA	24_12	12091	A
24	agaatattacaccatccaa	1-2-2-11-3	AgaATattacaccatcCAA	24_13	12091	A
24	agaatattacaccatccaa	1-2-2-9-2-1-2	AgaATattacaccaTCcAA	24_14	12091	A
24	agaatattacaccatccaa	1-2-2-8-1-2-3	AgaATattacaccAtcCAA	24_15	12091	A
24	agaatattacaccatccaa	1-2-2-8-1-1-1-1-2	AgaATattacaccAtCcAA	24_16	12091	A
24	agaatattacaccatccaa	1-2-2-8-3-1-2	AgaATattacaccATCcAA	24_17	12091	A
24	agaatattacaccatccaa	1-2-2-7-2-1-1-1-2	AgaATattacaCAtCcAA	24_18	12091	A
24	agaatattacaccatccaa	1-1-1-10-1-1-4	AgAatattacaccAtCCAA	24_19	12091	A
24	agaatattacaccatccaa	1-1-1-10-3-1-2	AgAatattacaccATCcAA	24_20	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-11-3	AgAaTattacaccatcCAA	24_21	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-9-2-1-2	AgAaTattacaccaTCcAA	24_22	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-8-1-2-3	AgAaTattacaccAtcCAA	24_23	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-8-1-1-1-1-2	AgAaTattacaccAtCcAA	24_24	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-8-3-1-2	AgAaTattacaccATCcAA	24_25	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-7-1-3-3	AgAaTattacaCatcCAA	24_26	12091	A
24	agaatattacaccatccaa	1-1-1-1-1-6-1-4-3	AgAaTattacaCcatcCAA	24_27	12091	A
24	agaatattacaccatccaa	1-1-1-1-2-6-2-3-2	AgAaTAttacaCAtccAA	24_28	12091	A
24	agaatattacaccatccaa	1-1-2-10-2-1-2	AgAAtattacaccaTCcAA	24_29	12091	A
24	agaatattacaccatccaa	1-1-3-11-3	AgAATattacaccatcCAA	24_30	12091	A
24	agaatattacaccatccaa	1-1-3-10-1-1-2	AgAATattacaccatCcAA	24_31	12091	A
24	agaatattacaccatccaa	1-1-3-9-2-1-2	AgAATattacaccaTCcAA	24_32	12091	A
24	agaatattacaccatccaa	1-1-3-8-1-2-3	AgAATattacaccAtcCAA	24_33	12091	A
24	agaatattacaccatccaa	1-1-3-8-1-1-1-1-2	AgAATattacaccAtCcAA	24_34	12091	A
24	agaatattacaccatccaa	1-1-3-7-1-1-2-1-2	AgAATattacaCaTCcAA	24_35	12091	A
24	agaatattacaccatccaa	2-3-1-8-2-1-2	AGaatAttacaccaTCcAA	24_36	12091	A
24	agaatattacaccatccaa	2-3-1-6-1-3-3	AGaatAttacaCatcCAA	24_37	12091	A
24	agaatattacaccatccaa	2-2-1-11-3	AGaaTattacaccatcCAA	24_38	12091	A
24	agaatattacaccatccaa	2-2-1-10-1-1-2	AGaaTattacaccatCcAA	24_39	12091	A
24	agaatattacaccatccaa	2-2-1-9-2-1-2	AGaaTattacaccaTCcAA	24_40	12091	A
24	agaatattacaccatccaa	2-2-1-8-1-2-3	AGaaTattacaccAtcCAA	24_41	12091	A
24	agaatattacaccatccaa	2-2-1-8-1-1-1-1-2	AGaaTattacaccAtCcAA	24_42	12091	A
24	agaatattacaccatccaa	2-2-1-8-3-1-2	AGaaTattacaccATCcAA	24_43	12091	A
24	agaatattacaccatccaa	2-2-1-6-1-1-1-1-1-1-2	AGaaTattacaCcAtCcAA	24_44	12091	A
24	agaatattacaccatccaa	2-2-2-6-1-2-1-1-2	AGaaTAttacacCatCcAA	24_45	12091	A
24	agaatattacaccatccaa	2-1-1-10-2-1-2	AGaAtattacaccaTCcAA	24_46	12091	A
24	agaatattacaccatccaa	2-1-1-1-1-6-1-1-2-1-2	AGaAtAttacacCaTCcAA	24_47	12091	A
24	agaatattacaccatccaa	2-1-2-11-3	AGaATattacaccatcCAA	24_48	12091	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
24	agaatattacaccatccaa	2-1-2-10-1-1-2	AGaATattacaccatCcAA	24_49	12091	A
24	agaatattacaccatccaa	2-1-2-9-2-1-2	AGaATattacaccaTCcAA	24_50	12091	A
24	agaatattacaccatccaa	2-1-2-8-1-2-3	AGaATattacaccAtcCAA	24_51	12091	A
24	agaatattacaccatccaa	2-1-2-8-1-1-1-1-2	AGaATattacaccAtCcAA	24_52	12091	A
24	agaatattacaccatccaa	2-1-3-9-1-1-2	AGaATAttacaccatCcAA	24_53	12091	A
24	agaatattacaccatccaa	3-11-2-1-2	AGAatattacaccaTCcAA	24_54	12091	A
24	agaatattacaccatccaa	3-10-1-2-3	AGAatattacaccAtcCAA	24_55	12091	A
24	agaatattacaccatccaa	3-10-1-1-1-1-2	AGAatattacaccAtCcAA	24_56	12091	A
24	agaatattacaccatccaa	3-1-1-10-1-1-2	AGAaTattacaccatCcAA	24_57	12091	A
24	agaatattacaccatccaa	3-1-1-8-1-3-2	AGAaTattacaccAtccAA	24_58	12091	A
24	agaatattacaccatccaa	3-1-1-8-1-1-1-1-2	AGAaTattacaccAtCcAA	24_59	12091	A
24	agaatattacaccatccaa	4-11-1-1-2	AGAAtattacaccatCcAA	24_60	12091	A
24	agaatattacaccatccaa	4-8-1-4-2	AGAAtattacacCatccAA	24_61	12091	A
24	agaatattacaccatccaa	4-1-1-9-1-1-2	AGAAtAttacaccatCcAA	24_62	12091	A
25	cagaatattacaccatccaa	1-4-1-9-1-1-3	CagaaTattacaccaTcCAA	25_1	12091	A
25	cagaatattacaccatccaa	1-4-1-9-2-1-2	CagaaTattacaccaTCcAA	25_2	12091	A
25	cagaatattacaccatccaa	1-4-1-7-1-2-1-1-2	CagaaTattacacCatCcAA	25_3	12091	A
25	cagaatattacaccatccaa	1-4-1-6-1-1-1-1-1-1-2	CagaaTattacaCcAtCcAA	25_4	12091	A
25	cagaatattacaccatccaa	1-3-1-10-2-1-2	CagaAtattacaccaTCcAA	25_5	12091	A
25	cagaatattacaccatccaa	1-3-1-7-2-4-2	CagaAtattacaCCatccAA	25_6	12091	A
25	cagaatattacaccatccaa	1-3-1-1-1-6-2-3-2	CagaAtAttacacCAtccAA	25_7	12091	A
25	cagaatattacaccatccaa	1-3-2-11-3	CagaATattacaccatcCAA	25_8	12091	A
25	cagaatattacaccatccaa	1-3-2-10-1-1-2	CagaATattacaccatCcAA	25_9	12091	A
25	cagaatattacaccatccaa	1-3-2-9-2-1-2	CagaATattacaccaTCcAA	25_10	12091	A
25	cagaatattacaccatccaa	1-3-2-8-1-1-1-1-2	CagaATattacaccAtCcAA	25_11	12091	A
25	cagaatattacaccatccaa	1-2-1-11-2-1-2	CagAatattacaccaTCcAA	25_12	12091	A
25	cagaatattacaccatccaa	1-2-1-10-1-2-3	CagAatattacaccAtcCAA	25_13	12091	A
25	cagaatattacaccatccaa	1-2-1-2-1-6-1-1-2-1-2	CagAatAttacacCaTCcAA	25_14	12091	A
25	cagaatattacaccatccaa	1-2-1-1-1-11-3	CagAaTattacaccatcCAA	25_15	12091	A
25	cagaatattacaccatccaa	1-2-1-1-1-9-2-1-2	CagAaTattacaccaTCcAA	25_16	12091	A
25	cagaatattacaccatccaa	1-2-1-1-1-8-1-2-3	CagAaTattacaccAtcCAA	25_17	12091	A
25	cagaatattacaccatccaa	1-2-1-1-1-8-1-1-1-1-2	CagAaTattacaccAtCcAA	25_18	12091	A
25	cagaatattacaccatccaa	1-2-1-1-1-7-1-1-2-1-2	CagAaTattacacCaTCcAA	25_19	12091	A
25	cagaatattacaccatccaa	1-2-1-1-2-6-1-2-1-1-2	CagAaTAttacacCatCcAA	25_20	12091	A
25	cagaatattacaccatccaa	1-2-2-8-2-3-2	CagAAtattacacCAtccAA	25_21	12091	A
25	cagaatattacaccatccaa	1-2-2-8-2-1-1-1-2	CagAAtattacacCAtCcAA	25_22	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-11-3	CaGaaTattacaccatcCAA	25_23	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-10-1-1-2	CaGaaTattacaccatCcAA	25_24	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-9-2-1-2	CaGaaTattacaccaTCcAA	25_25	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-8-1-2-3	CaGaaTattacaccAtcCAA	25_26	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-8-1-1-1-1-2	CaGaaTattacaccAtCcAA	25_27	12091	A
25	cagaatattacaccatccaa	1-1-1-2-1-6-1-5-2	CaGaaTattacaCcatccAA	25_28	12091	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
25	cagaatattacaccatccaa	1-1-1-1-1-11-1-1-2	CaGaAtattacaccatCcAA	25_29	12091	A
25	cagaatattacaccatccaa	1-1-1-1-1-10-2-1-2	CaGaAtattacaccaTCcAA	25_30	12091	A
25	cagaatattacaccatccaa	1-1-1-1-1-1-1-9-1-1-2	CaGaAtAttacaccatCcAA	25_31	12091	A
25	cagaatattacaccatccaa	1-1-1-1-1-1-1-6-2-3-2	CaGaAtAttacacCAtccAA	25_32	12091	A
25	cagaatattacaccatccaa	1-1-2-10-1-1-1-1-2	CaGAatattacaccAtCcAA	25_33	12091	A
25	cagaatattacaccatccaa	1-1-2-8-1-1-1-3-2	CaGAatattacaCcAtccAA	25_34	12091	A
25	cagaatattacaccatccaa	2-3-1-10-1-1-2	CAgaaTattacaccatCcAA	25_35	12091	A
25	cagaatattacaccatccaa	2-3-1-8-1-3-2	CAgaaTattacaccAtccAA	25_36	12091	A
25	cagaatattacaccatccaa	2-3-1-8-1-1-1-1-2	CAgaaTattacaccAtCcAA	25_37	12091	A
25	cagaatattacaccatccaa	2-2-1-11-1-1-2	CAgaAtattacaccatCcAA	25_38	12091	A
25	cagaatattacaccatccaa	2-1-1-10-1-3-2	CAgAatattacaccAtccAA	25_39	12091	A
25	cagaatattacaccatccaa	2-1-1-10-1-1-1-1-2	CAgAatattacaccAtCcAA	25_40	12091	A
25	cagaatattacaccatccaa	2-1-1-1-1-8-1-3-2	CAgAaTattacaccAtccAA	25_41	12091	A
25	cagaatattacaccatccaa	2-1-1-1-1-7-1-4-2	CAgAaTattacacCatccAA	25_42	12091	A
25	cagaatattacaccatccaa	2-1-2-11-1-1-2	CAgAAtattacaccatCcAA	25_43	12091	A
26	gaatattacaccatccaa	1-10-2-1-4	GaatattacacCAtCCAA	26_1	12091	A
26	gaatattacaccatccaa	1-10-3-1-3	GaatattacacCATcCAA	26_2	12091	A
26	gaatattacaccatccaa	1-10-4-1-2	GaatattacacCATCcAA	26_3	12091	A
26	gaatattacaccatccaa	1-3-1-9-4	GaatAttacaccatCCAA	26_4	12091	A
26	gaatattacaccatccaa	1-2-1-10-4	GaaTattacaccatCCAA	26_5	12091	A
26	gaatattacaccatccaa	1-2-1-8-1-1-4	GaaTattacaccAtCCAA	26_6	12091	A
26	gaatattacaccatccaa	1-2-2-6-2-1-1-1-2	GaaTAttacacCAtCcAA	26_7	12091	A
26	gaatattacaccatccaa	1-1-1-11-4	GaAtattacaccatCCAA	26_8	12091	A
26	gaatattacaccatccaa	1-1-1-1-1-9-4	GaAtAttacaccatCCAA	26_9	12091	A
26	gaatattacaccatccaa	1-1-1-1-1-6-4-1-2	GaAtAttacacCATCcAA	26_10	12091	A
26	gaatattacaccatccaa	1-1-2-10-4	GaATattacaccatCCAA	26_11	12091	A
26	gaatattacaccatccaa	1-1-2-9-2-1-2	GaATattacaccaTCcAA	26_12	12091	A
26	gaatattacaccatccaa	1-1-2-8-1-1-4	GaATattacaccAtCCAA	26_13	12091	A
26	gaatattacaccatccaa	1-1-2-8-3-1-2	GaATattacaccATCcAA	26_14	12091	A
26	gaatattacaccatccaa	1-1-2-7-2-2-3	GaATattacacCAtcCAA	26_15	12091	A
26	gaatattacaccatccaa	2-10-1-1-4	GAatattacaccAtCCAA	26_16	12091	A
26	gaatattacaccatccaa	2-10-3-1-2	GAatattacaccATCcAA	26_17	12091	A
26	gaatattacaccatccaa	2-9-4-1-2	GAatattacacCATCcAA	26_18	12091	A
26	gaatattacaccatccaa	2-2-1-6-4-1-2	GAatAttacacCATCcAA	26_19	12091	A
26	gaatattacaccatccaa	2-1-1-11-3	GAaTattacaccatcCAA	26_20	12091	A
26	gaatattacaccatccaa	2-1-1-9-2-1-2	GAaTattacaccaTCcAA	26_21	12091	A
26	gaatattacaccatccaa	2-1-1-8-1-2-3	GAaTattacaccAtcCAA	26_22	12091	A
26	gaatattacaccatccaa	2-1-1-8-3-1-2	GAaTattacaccATCcAA	26_23	12091	A
26	gaatattacaccatccaa	2-1-1-7-1-3-3	GAaTattacacCatcCAA	26_24	12091	A
26	gaatattacaccatccaa	2-1-1-7-2-3-2	GAaTattacacCAtccAA	26_25	12091	A
26	gaatattacaccatccaa	3-11-4	GAAtattacaccatCCAA	26_26	12091	A
26	gaatattacaccatccaa	3-10-2-1-2	GAAtattacaccaTCcAA	26_27	12091	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
26	gaatattacaccatccaa	3-8-2-1-1-1-2	GAAtattacacCAtCcAA	26_28	12091	A
26	gaatattacaccatccaa	4-11-3	GAATattacaccatcCAA	26_29	12091	A
26	gaatattacaccatccaa	4-8-1-2-3	GAATattacaccAtcCAA	26_30	12091	A
26	gaatattacaccatccaa	4-7-1-1-2-1-2	GAATattacacCaTCcAA	26_31	12091	A
27	aatattacaccatcca	4-8-4	AATAttacaccaTCCA	27_1	12092	A
28	agaatattacaccatcca	1-3-1-10-3	AgaaTattacaccatCCA	28_1	12092	A
28	agaatattacaccatcca	1-3-1-9-1-1-2	AgaaTattacaccaTcCA	28_2	12092	A
28	agaatattacaccatcca	1-3-1-8-1-1-3	AgaaTattacaccAtCCA	28_3	12092	A
28	agaatattacaccatcca	1-3-1-8-2-1-2	AgaaTattacaccATcCA	28_4	12092	A
28	agaatattacaccatcca	1-2-1-11-3	AgaAtattacaccatCCA	28_5	12092	A
28	agaatattacaccatcca	1-2-1-10-4	AgaAtattacaccaTCCA	28_6	12092	A
28	agaatattacaccatcca	1-2-1-1-1-8-1-1-2	AgaAtAttacaccaTcCA	28_7	12092	A
28	agaatattacaccatcca	1-2-1-1-1-6-1-3-2	AgaAtAttacacCatcCA	28_8	12092	A
28	agaatattacaccatcca	1-2-2-11-2	AgaATattacaccatcCA	28_9	12092	A
28	agaatattacaccatcca	1-2-2-8-1-2-2	AgaATattacaccAtcCA	28_10	12092	A
28	agaatattacaccatcca	1-1-1-11-4	AgAatattacaccaTCCA	28_11	12092	A
28	agaatattacaccatcca	1-1-1-10-1-1-3	AgAatattacaccAtCCA	28_12	12092	A
28	agaatattacaccatcca	1-1-1-9-2-2-2	AgAatattacacCAtcCA	28_13	12092	A
28	agaatattacaccatcca	1-1-1-2-1-6-1-3-2	AgAatAttacacCatcCA	28_14	12092	A
28	agaatattacaccatcca	1-1-1-2-1-6-1-2-3	AgAatAttacacCatCCA	28_15	12092	A
28	agaatattacaccatcca	1-1-1-1-1-11-2	AgAaTattacaccatcCA	28_16	12092	A
28	agaatattacaccatcca	1-1-1-1-1-10-3	AgAaTattacaccatCCA	28_17	12092	A
28	agaatattacaccatcca	1-1-1-1-1-8-1-2-2	AgAaTattacaccAtcCA	28_18	12092	A
28	agaatattacaccatcca	1-1-1-1-1-8-1-1-3	AgAaTattacaccAtCCA	28_19	12092	A
28	agaatattacaccatcca	1-1-1-1-1-7-1-3-2	AgAaTattacacCatcCA	28_20	12092	A
28	agaatattacaccatcca	1-1-1-1-1-6-1-4-2	AgAaTattacaCcatcCA	28_21	12092	A
28	agaatattacaccatcca	1-1-1-1-2-6-1-3-2	AgAaTAttacacCatcCA	28_22	12092	A
28	agaatattacaccatcca	1-1-2-11-3	AgAAtattacaccatCCA	28_23	12092	A
28	agaatattacaccatcca	1-1-3-11-2	AgAATattacaccatcCA	28_24	12092	A
28	agaatattacaccatcca	1-1-3-8-1-2-2	AgAATattacaccAtcCA	28_25	12092	A
28	agaatattacaccatcca	2-2-1-11-2	AGaaTattacaccatcCA	28_26	12092	A
28	agaatattacaccatcca	2-2-1-8-1-2-2	AGaaTattacaccAtcCA	28_27	12092	A
28	agaatattacaccatcca	2-1-1-11-3	AGaAtattacaccatCCA	28_28	12092	A
28	agaatattacaccatcca	2-1-2-11-2	AGaATattacaccatcCA	28_29	12092	A
28	agaatattacaccatcca	2-1-2-8-1-2-2	AGaATattacaccAtcCA	28_30	12092	A
28	agaatattacaccatcca	3-10-1-2-2	AGAatattacaccAtcCA	28_31	12092	A
28	agaatattacaccatcca	3-1-1-11-2	AGAaTattacaccatcCA	28_32	12092	A
28	agaatattacaccatcca	3-1-1-8-1-2-2	AGAaTattacaccAtcCA	28_33	12092	A
29	cagaatattacaccatcca	1-4-1-9-1-1-2	CagaaTattacaccaTcCA	29_1	12092	A
29	cagaatattacaccatcca	1-3-1-11-3	CagaAtattacaccatCCA	29_2	12092	A
29	cagaatattacaccatcca	1-3-1-7-1-4-2	CagaAtattacaCcatcCA	29_3	12092	A
29	cagaatattacaccatcca	1-3-2-11-2	CagaATattacaccatcCA	29_4	12092	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
29	cagaatattacaccatcca	1-3-2-8-1-2-2	CagaATattacaccAtcCA	29_5	12092	A
29	cagaatattacaccatcca	1-3-2-7-1-3-2	CagaATattacacCatcCA	29_6	12092	A
29	cagaatattacaccatcca	1-2-1-1-1-11-2	CagAaTattacaccatcCA	29_7	12092	A
29	cagaatattacaccatcca	1-2-1-1-1-8-1-2-2	CagAaTattacaccAtcCA	29_8	12092	A
29	cagaatattacaccatcca	1-2-3-11-2	CagAATattacaccatcCA	29_9	12092	A
29	cagaatattacaccatcca	1-1-1-2-1-11-2	CaGaaTattacaccatcCA	29_10	12092	A
29	cagaatattacaccatcca	1-1-1-2-1-8-1-2-2	CaGaaTattacaccAtcCA	29_11	12092	A
29	cagaatattacaccatcca	1-1-2-10-1-2-2	CaGAatattacaccAtcCA	29_12	12092	A
29	cagaatattacaccatcca	2-1-1-10-1-2-2	CAgAatattacaccAtcCA	29_13	12092	A
29	cagaatattacaccatcca	2-1-1-7-1-2-1-2-2	CAgAatattacAccAtcCA	29_14	12092	A
30	gaatattacaccatcca	1-10-2-1-3	GaatattacaCAtCCA	30_1	12092	A
30	gaatattacaccatcca	1-3-1-8-4	GaatAttacaccaTCCA	30_2	12092	A
30	gaatattacaccatcca	1-2-1-10-3	GaaTattacaccatCCA	30_3	12092	A
30	gaatattacaccatcca	1-2-1-8-1-1-3	GaaTattacaccAtCCA	30_4	12092	A
30	gaatattacaccatcca	1-1-1-11-3	GaAtattacaccatCCA	30_5	12092	A
30	gaatattacaccatcca	1-1-1-10-4	GaAtattacaccaTCCA	30_6	12092	A
30	gaatattacaccatcca	1-1-1-8-2-1-3	GaAtattacacCAtCCA	30_7	12092	A
30	gaatattacaccatcca	1-1-1-7-2-3-2	GaAtattacaCCatcCA	30_8	12092	A
30	gaatattacaccatcca	1-1-1-1-1-6-3-1-2	GaAtAttacacCATcCA	30_9	12092	A
30	gaatattacaccatcca	1-1-2-10-3	GaATattacaccatCCA	30_10	12092	A
30	gaatattacaccatcca	1-1-2-8-1-1-3	GaATattacaccAtCCA	30_11	12092	A
30	gaatattacaccatcca	2-11-4	GAatattacaccaTCCA	30_12	12092	A
30	gaatattacaccatcca	2-10-1-1-3	GAatattacaccAtCCA	30_13	12092	A
30	gaatattacaccatcca	2-2-1-9-3	GAatAttacaccatCCA	30_14	12092	A
30	gaatattacaccatcca	2-2-1-6-1-3-2	GAatAttacacCatcCA	30_15	12092	A
30	gaatattacaccatcca	2-1-1-11-2	GAaTattacaccatcCA	30_16	12092	A
30	gaatattacaccatcca	2-1-1-10-3	GAaTattacaccatCCA	30_17	12092	A
30	gaatattacaccatcca	2-1-1-8-1-2-2	GAaTattacaccAtcCA	30_18	12092	A
30	gaatattacaccatcca	2-1-1-8-1-1-3	GAaTattacaccAtCCA	30_19	12092	A
30	gaatattacaccatcca	2-1-1-7-2-2-2	GAaTattacacCAtcCA	30_20	12092	A
30	gaatattacaccatcca	2-1-1-6-1-4-2	GAaTattacaCcatcCA	30_21	12092	A
30	gaatattacaccatcca	3-11-3	GAAtattacaccatCCA	30_22	12092	A
30	gaatattacaccatcca	3-8-1-3-2	GAAtattacacCatcCA	30_23	12092	A
30	gaatattacaccatcca	4-11-2	GAATattacaccatcCA	30_24	12092	A
30	gaatattacaccatcca	4-8-1-2-2	GAATattacaccAtcCA	30_25	12092	A
31	tcagaatattacaccatcca	1-1-1-3-1-11-2	TcAgaaTattacaccatcCA	31_1	12092	A
31	tcagaatattacaccatcca	1-1-1-3-1-8-1-2-2	TcAgaaTattacaccAtcCA	31_2	12092	A
31	tcagaatattacaccatcca	1-1-1-2-1-10-1-1-2	TcAgaAtattacaccaTcCA	31_3	12092	A
32	agaatattacaccatcc	1-3-1-9-3	AgaaTattacaccaTCC	32_1	12093	A
32	agaatattacaccatcc	1-3-1-8-4	AgaaTattacaccATCC	32_2	12093	A
32	agaatattacaccatcc	1-3-2-6-1-2-2	AgaaTAttacacCatCC	32_3	12093	A
32	agaatattacaccatcc	1-2-1-10-3	AgaAtattacaccaTCC	32_4	12093	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
32	agaatattacaccatcc	1-2-1-6-2-1-1-1-2	AgaAtattacACcAtCC	32_5	12093	A
32	agaatattacaccatcc	1-2-1-1-1-6-1-2-2	AgaAtAttacacCatCC	32_6	12093	A
32	agaatattacaccatcc	1-2-2-9-3	AgaATattacaccaTCC	32_7	12093	A
32	agaatattacaccatcc	1-2-2-8-1-1-2	AgaATattacaccAtCC	32_8	12093	A
32	agaatattacaccatcc	1-2-2-8-4	AgaATattacaccATCC	32_9	12093	A
32	agaatattacaccatcc	1-1-1-11-3	AgAatattacaccaTCC	32_10	12093	A
32	agaatattacaccatcc	1-1-1-10-4	AgAatattacaccATCC	32_11	12093	A
32	agaatattacaccatcc	1-1-1-8-1-1-1-1-2	AgAatattacaCcAtCC	32_12	12093	A
32	agaatattacaccatcc	1-1-1-8-1-1-4	AgAatattacaCcATCC	32_13	12093	A
32	agaatattacaccatcc	1-1-1-7-1-3-3	AgAatattacAccaTCC	32_14	12093	A
32	agaatattacaccatcc	1-1-1-7-2-3-2	AgAatattacACcatCC	32_15	12093	A
32	agaatattacaccatcc	1-1-1-7-3-2-2	AgAatattacACCatCC	32_16	12093	A
32	agaatattacaccatcc	1-1-1-1-1-9-3	AgAaTattacaccaTCC	32_17	12093	A
32	agaatattacaccatcc	1-1-1-1-1-8-1-1-2	AgAaTattacaccAtCC	32_18	12093	A
32	agaatattacaccatcc	1-1-1-1-1-8-4	AgAaTattacaccATCC	32_19	12093	A
32	agaatattacaccatcc	1-1-1-1-1-7-1-2-2	AgAaTattacacCatCC	32_20	12093	A
32	agaatattacaccatcc	1-1-1-1-1-6-1-1-1-1-2	AgAaTattacaCcAtCC	32_21	12093	A
32	agaatattacaccatcc	1-1-2-10-3	AgAAtattacaccaTCC	32_22	12093	A
32	agaatattacaccatcc	1-1-2-7-2-2-2	AgAAtattacaCCatCC	32_23	12093	A
32	agaatattacaccatcc	1-1-2-6-1-1-2-1-2	AgAAtattacAcCAtCC	32_24	12093	A
32	agaatattacaccatcc	1-1-3-10-2	AgAATattacaccatCC	32_25	12093	A
32	agaatattacaccatcc	1-1-3-9-3	AgAATattacaccaTCC	32_26	12093	A
32	agaatattacaccatcc	1-1-3-8-1-1-2	AgAATattacaccAtCC	32_27	12093	A
32	agaatattacaccatcc	1-1-3-8-4	AgAATattacaccATCC	32_28	12093	A
32	agaatattacaccatcc	1-1-3-6-1-1-1-1-2	AgAATattacaCcAtCC	32_29	12093	A
32	agaatattacaccatcc	2-2-1-10-2	AGaaTattacaccatCC	32_30	12093	A
32	agaatattacaccatcc	2-2-1-9-3	AGaaTattacaccaTCC	32_31	12093	A
32	agaatattacaccatcc	2-2-1-8-1-1-2	AGaaTattacaccAtCC	32_32	12093	A
32	agaatattacaccatcc	2-2-1-8-4	AGaaTattacaccATCC	32_33	12093	A
32	agaatattacaccatcc	2-1-1-11-2	AGaAtattacaccatCC	32_34	12093	A
32	agaatattacaccatcc	2-1-1-10-3	AGaAtattacaccaTCC	32_35	12093	A
32	agaatattacaccatcc	2-1-1-8-1-1-3	AGaAtattacacCaTCC	32_36	12093	A
32	agaatattacaccatcc	2-1-1-6-1-2-4	AGaAtattacAccATCC	32_37	12093	A
32	agaatattacaccatcc	2-1-2-10-2	AGaATattacaccatCC	32_38	12093	A
32	agaatattacaccatcc	2-1-2-8-1-1-2	AGaATattacaccAtCC	32_39	12093	A
32	agaatattacaccatcc	3-11-3	AGAatattacaccaTCC	32_40	12093	A
32	agaatattacaccatcc	3-10-1-1-2	AGAatattacaccAtCC	32_41	12093	A
32	agaatattacaccatcc	3-7-1-3-3	AGAatattacAccaTCC	32_42	12093	A
32	agaatattacaccatcc	3-7-1-2-1-1-2	AGAatattacAccAtCC	32_43	12093	A
32	agaatattacaccatcc	3-7-1-1-1-2-2	AGAatattacAcCatCC	32_44	12093	A
32	agaatattacaccatcc	3-2-1-9-2	AGAatAttacaccatCC	32_45	12093	A
32	agaatattacaccatcc	3-1-1-10-2	AGAaTattacaccatCC	32_46	12093	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
32	agaatattacaccatcc	3-1-1-8-1-1-2	AGAaTattacaccAtCC	32_47	12093	A
32	agaatattacaccatcc	4-11-2	AGAAtattacaccatCC	32_48	12093	A
32	agaatattacaccatcc	4-10-3	AGAAtattacaccaTCC	32_49	12093	A
32	agaatattacaccatcc	4-8-1-2-2	AGAAtattacacCatCC	32_50	12093	A
32	agaatattacaccatcc	4-6-1-1-1-2-2	AGAAtattacAcCatCC	32_51	12093	A
33	cagaatattacaccatcc	1-4-1-9-3	CagaaTattacaccaTCC	33_1	12093	A
33	cagaatattacaccatcc	1-3-1-10-3	CagaAtattacaccaTCC	33_2	12093	A
33	cagaatattacaccatcc	1-3-1-7-1-2-3	CagaAtattacaCcaTCC	33_3	12093	A
33	cagaatattacaccatcc	1-3-1-6-1-3-3	CagaAtattacAccaTCC	33_4	12093	A
33	cagaatattacaccatcc	1-3-1-6-2-3-2	CagaAtattacACcatCC	33_5	12093	A
33	cagaatattacaccatcc	1-3-2-10-2	CagaATattacaccatCC	33_6	12093	A
33	cagaatattacaccatcc	1-3-2-9-3	CagaATattacaccaTCC	33_7	12093	A
33	cagaatattacaccatcc	1-3-2-8-1-1-2	CagaATattacaccAtCC	33_8	12093	A
33	cagaatattacaccatcc	1-2-1-11-3	CagAatattacaccaTCC	33_9	12093	A
33	cagaatattacaccatcc	1-2-1-2-1-8-3	CagAatAttacaccaTCC	33_10	12093	A
33	cagaatattacaccatcc	1-2-1-1-1-9-3	CagAaTattacaccaTCC	33_11	12093	A
33	cagaatattacaccatcc	1-2-2-10-3	CagAAtattacaccaTCC	33_12	12093	A
33	cagaatattacaccatcc	1-2-2-8-1-1-3	CagAAtattacacCaTCC	33_13	12093	A
33	cagaatattacaccatcc	1-2-3-6-1-3-2	CagAATattacaCcatCC	33_14	12093	A
33	cagaatattacaccatcc	1-1-1-3-1-6-2-1-2	CaGaatAttacacCAtCC	33_15	12093	A
33	cagaatattacaccatcc	1-1-1-2-1-8-1-1-2	CaGaaTattacaccAtCC	33_16	12093	A
33	cagaatattacaccatcc	1-1-1-1-1-11-2	CaGaAtattacaccatCC	33_17	12093	A
33	cagaatattacaccatcc	1-1-1-1-1-10-3	CaGaAtattacaccaTCC	33_18	12093	A
33	cagaatattacaccatcc	1-1-1-1-1-7-1-3-2	CaGaAtattacaCcatCC	33_19	12093	A
33	cagaatattacaccatcc	1-1-1-1-1-6-2-1-1-1-2	CaGaAtattacACcAtCC	33_20	12093	A
33	cagaatattacaccatcc	1-1-2-10-1-1-2	CaGAatattacaccAtCC	33_21	12093	A
33	cagaatattacaccatcc	2-3-1-10-2	CAgaaTattacaccatCC	33_22	12093	A
33	cagaatattacaccatcc	2-3-1-8-1-1-2	CAgaaTattacaccAtCC	33_23	12093	A
33	cagaatattacaccatcc	2-2-1-11-2	CAgaAtattacaccatCC	33_24	12093	A
33	cagaatattacaccatcc	2-2-1-10-3	CAgaAtattacaccaTCC	33_25	12093	A
33	cagaatattacaccatcc	2-2-1-1-1-6-1-2-2	CAgaAtAttacacCatCC	33_26	12093	A
33	cagaatattacaccatcc	2-1-1-11-3	CAgAatattacaccaTCC	33_27	12093	A
33	cagaatattacaccatcc	2-1-1-10-1-1-2	CAgAatattacaccAtCC	33_28	12093	A
33	cagaatattacaccatcc	2-1-1-1-1-10-2	CAgAaTattacaccatCC	33_29	12093	A
33	cagaatattacaccatcc	2-1-1-1-1-8-1-1-2	CAgAaTattacaccAtCC	33_30	12093	A
33	cagaatattacaccatcc	2-1-2-11-2	CAgAAtattacaccatCC	33_31	12093	A
33	cagaatattacaccatcc	2-1-2-6-1-4-2	CAgAAtattacAccatCC	33_32	12093	A
33	cagaatattacaccatcc	3-1-1-11-2	CAGaAtattacaccatCC	33_33	12093	A
34	gaatattacaccatcc	4-8-4	GAATattacaccATCC	34_1	12093	A
35	tcagaatattacaccatcc	2-4-1-10-2	TCagaaTattacaccatCC	35_1	12093	A
35	tcagaatattacaccatcc	2-3-1-11-2	TCagaAtattacaccatCC	35_2	12093	A
35	tcagaatattacaccatcc	2-3-1-6-1-4-2	TCagaAtattacAccatCC	35_3	12093	A

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
36	agaatattacaccatc	4-8-4	AGAAtattacacCATC	36_1	12094	A
37	cagaatattacaccat	4-8-4	CAGAatattacaCCAT	37_1	12095	A
38	caattctcatttcaaccttc	2-14-4	CAattctcatttcaacCTTC	38_1	39562	B
39	tcaattctcatttcaacctt	2-15-3	TCaattctcatttcaacCTT	39_1	39563	B
40	atcaattctcatttcaacct	3-15-2	ATCaattctcatttcaacCT	40_1	39564	B
41	aatcaattctcatttcaacc	4-13-3	AATCaattctcatttcaACC	41_1	39565	B
42	aaatcaattctcatttcaac	4-12-4	AAATcaattctcatttCAAC	42_1	39566	B
43	caaatcaattctcatttcaa	4-12-4	CAAAtcaattctcattTCAA	43_1	39567	B
44	tcaaatcaattctcatttca	3-13-4	TCAaatcaattctcatTTCA	44_1	39568	B
45	ctcaaatcaattctcatttc	4-13-3	CTCAaatcaattctcatTTC	45_1	39569	B
46	actcaaatcaattctcattt	4-12-4	ACTCaaatcaattctcATTT	46_1	39570	B
47	aactcaaatcaattctcatt	4-12-4	AACTcaaatcaattctCATT	47_1	39571	B
48	taactcaaatcaattctcat	4-12-4	TAACtcaaatcaattcTCAT	48_1	39572	B
49	ttaactcaaatcaattctca	1-5-1-10-3	TtaactCaaatcaattcTCA	49_1	39573	B
49	ttaactcaaatcaattctca	1-5-2-10-2	TtaactCAaatcaattctCA	49_2	39573	B
49	ttaactcaaatcaattctca	1-5-2-9-3	TtaactCAaatcaattcTCA	49_3	39573	B
49	ttaactcaaatcaattctca	1-4-2-11-2	TtaacTCaaatcaattctCA	49_4	39573	B
49	ttaactcaaatcaattctca	1-4-3-10-2	TtaacTCAaatcaattctCA	49_5	39573	B
49	ttaactcaaatcaattctca	1-3-1-11-1-1-2	TtaaCtcaaatcaattCtCA	49_6	39573	B
49	ttaactcaaatcaattctca	1-3-1-11-4	TtaaCtcaaatcaattCTCA	49_7	39573	B
49	ttaactcaaatcaattctca	1-3-1-10-2-1-2	TtaaCtcaaatcaatTCtCA	49_8	39573	B
49	ttaactcaaatcaattctca	1-3-1-9-1-3-2	TtaaCtcaaatcaaTtctCA	49_9	39573	B
49	ttaactcaaatcaattctca	1-3-1-9-1-2-3	TtaaCtcaaatcaaTtcTCA	49_10	39573	B
49	ttaactcaaatcaattctca	1-3-1-9-1-1-1-1-2	TtaaCtcaaatcaaTtCtCA	49_11	39573	B
49	ttaactcaaatcaattctca	1-3-1-9-1-1-4	TtaaCtcaaatcaaTtCTCA	49_12	39573	B
49	ttaactcaaatcaattctca	1-3-1-9-3-1-2	TtaaCtcaaatcaaTTCtCA	49_13	39573	B
49	ttaactcaaatcaattctca	1-3-1-7-1-4-3	TtaaCtcaaatcAattcTCA	49_14	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-9-3	TtaaCtcAaatcaattcTCA	49_15	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-8-1-1-2	TtaaCtcAaatcaattCtCA	49_16	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-8-4	TtaaCtcAaatcaattCTCA	49_17	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-7-1-2-2	TtaaCtcAaatcaatTctCA	49_18	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-7-2-1-2	TtaaCtcAaatcaatTCtCA	49_19	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-6-1-3-2	TtaaCtcAaatcaaTtctCA	49_20	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-6-1-2-3	TtaaCtcAaatcaaTtcTCA	49_21	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-6-1-1-1-1-2	TtaaCtcAaatcaaTtCtCA	49_22	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-6-1-1-4	TtaaCtcAaatcaaTtCTCA	49_23	39573	B
49	ttaactcaaatcaattctca	1-3-1-2-1-6-3-1-2	TtaaCtcAaatcaaTTCtCA	49_24	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-1-11-2	TtaaCtCaaatcaattctCA	49_25	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-1-10-3	TtaaCtCaaatcaattcTCA	49_26	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-1-9-1-1-2	TtaaCtCaaatcaattCtCA	49_27	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-1-9-4	TtaaCtCaaatcaattCTCA	49_28	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-1-8-2-1-2	TtaaCtCaaatcaatTCtCA	49_29	39573	B

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
49	ttaactcaaatcaattctca	1-3-1-1-2-10-2	TtaaCtCAaatcaattctCA	49_30	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-2-9-3	TtaaCtCAaatcaattcTCA	49_31	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-2-8-1-1-2	TtaaCtCAaatcaattCtCA	49_32	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-2-6-1-3-2	TtaaCtCAaatcaaTtctCA	49_33	39573	B
49	ttaactcaaatcaattctca	1-3-1-1-2-6-1-1-1-1-2	TtaaCtCAaatcaaTtCtCA	49_34	39573	B
49	ttaactcaaatcaattctca	1-3-3-11-2	TtaaCTCaaatcaattctCA	49_35	39573	B
49	ttaactcaaatcaattctca	1-3-3-9-1-1-2	TtaaCTCaaatcaattCtCA	49_36	39573	B
49	ttaactcaaatcaattctca	1-3-4-10-2	TtaaCTCAaatcaattctCA	49_37	39573	B
49	ttaactcaaatcaattctca	1-3-4-6-1-3-2	TtaaCTCAaatcaaTtctCA	49_38	39573	B
49	ttaactcaaatcaattctca	1-2-1-11-2-1-2	TtaActcaaatcaatTCtCA	49_39	39573	B
49	ttaactcaaatcaattctca	1-2-1-10-1-1-1-1-2	TtaActcaaatcaaTtCtCA	49_40	39573	B
49	ttaactcaaatcaattctca	1-2-1-10-1-1-4	TtaActcaaatcaaTtCTCA	49_41	39573	B
49	ttaactcaaatcaattctca	1-2-1-3-1-8-1-1-2	TtaActcAaatcaattCtCA	49_42	39573	B
49	ttaactcaaatcaattctca	1-2-1-3-1-7-2-1-2	TtaActcAaatcaatTCtCA	49_43	39573	B
49	ttaactcaaatcaattctca	1-2-1-3-1-6-1-2-3	TtaActcAaatcaaTtcTCA	49_44	39573	B
49	ttaactcaaatcaattctca	1-2-1-3-1-6-1-1-1-1-2	TtaActcAaatcaaTtCtCA	49_45	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-1-9-1-1-2	TtaActCaaatcaattCtCA	49_46	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-1-9-4	TtaActCaaatcaattCTCA	49_47	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-1-8-2-1-2	TtaActCaaatcaatTCtCA	49_48	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-10-2	TtaActCAaatcaattctCA	49_49	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-8-1-1-2	TtaActCAaatcaattCtCA	49_50	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-8-4	TtaActCAaatcaattCTCA	49_51	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-7-2-1-2	TtaActCAaatcaatTCtCA	49_52	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-6-1-3-2	TtaActCAaatcaaTtctCA	49_53	39573	B
49	ttaactcaaatcaattctca	1-2-1-2-2-6-1-1-1-1-2	TtaActCAaatcaaTtCtCA	49_54	39573	B
49	ttaactcaaatcaattctca	1-2-1-1-2-9-1-1-2	TtaAcTCaaatcaattCtCA	49_55	39573	B
49	ttaactcaaatcaattctca	1-2-2-11-1-1-2	TtaACtcaaatcaattCtCA	49_56	39573	B
49	ttaactcaaatcaattctca	1-2-2-11-4	TtaACtcaaatcaattCTCA	49_57	39573	B
49	ttaactcaaatcaattctca	1-2-2-10-2-1-2	TtaACtcaaatcaatTCtCA	49_58	39573	B
49	ttaactcaaatcaattctca	1-2-2-9-1-3-2	TtaACtcaaatcaaTtctCA	49_59	39573	B
49	ttaactcaaatcaattctca	1-2-2-9-1-1-1-1-2	TtaACtcaaatcaaTtCtCA	49_60	39573	B
49	ttaactcaaatcaattctca	1-2-2-9-1-1-4	TtaACtcaaatcaaTtCTCA	49_61	39573	B
49	ttaactcaaatcaattctca	1-2-2-9-3-1-2	TtaACtcaaatcaaTTCtCA	49_62	39573	B
49	ttaactcaaatcaattctca	1-2-2-7-1-5-2	TtaACtcaaatcAattctCA	49_63	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-10-2	TtaACtcAaatcaattctCA	49_64	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-8-1-1-2	TtaACtcAaatcaattCtCA	49_65	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-8-4	TtaACtcAaatcaattCTCA	49_66	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-7-2-1-2	TtaACtcAaatcaatTCtCA	49_67	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-6-1-3-2	TtaACtcAaatcaaTtctCA	49_68	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-6-1-1-1-1-2	TtaACtcAaatcaaTtCtCA	49_69	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-6-1-1-4	TtaACtcAaatcaaTtCTCA	49_70	39573	B
49	ttaactcaaatcaattctca	1-2-2-2-1-6-3-1-2	TtaACtcAaatcaaTTCtCA	49_71	39573	B

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
49	ttaactcaaatcaattctca	1-2-2-1-1-11-2	TtaACtCaaatcaattctCA	49_72	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-1-9-1-1-2	TtaACtCaaatcaattCtCA	49_73	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-1-9-4	TtaACtCaaatcaattCTCA	49_74	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-1-8-2-1-2	TtaACtCaaatcaatTCtCA	49_75	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-2-10-2	TtaACtCAaatcaattctCA	49_76	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-2-8-1-1-2	TtaACtCAaatcaattCtCA	49_77	39573	B
49	ttaactcaaatcaattctca	1-2-2-1-2-6-1-3-2	TtaACtCAaatcaaTtctCA	49_78	39573	B
49	ttaactcaaatcaattctca	1-2-4-9-1-1-2	TtaACTCaaatcaattCtCA	49_79	39573	B
49	ttaactcaaatcaattctca	1-1-1-11-1-1-1-1-2	TtAactcaaatcaaTtCtCA	49_80	39573	B
49	ttaactcaaatcaattctca	1-1-1-10-1-2-1-1-2	TtAactcaaatcaAttCtCA	49_81	39573	B
49	ttaactcaaatcaattctca	1-1-1-10-1-1-2-1-2	TtAactcaaatcaAtTCtCA	49_82	39573	B
49	ttaactcaaatcaattctca	1-1-1-10-2-1-1-1-2	TtAactcaaatcaATtCtCA	49_83	39573	B
49	ttaactcaaatcaattctca	1-1-1-10-4-1-2	TtAactcaaatcaATTCtCA	49_84	39573	B
49	ttaactcaaatcaattctca	1-1-1-4-1-7-2-1-2	TtAactcAaatcaatTCtCA	49_85	39573	B
49	ttaactcaaatcaattctca	1-1-1-4-1-6-1-1-1-1-2	TtAactcAaatcaaTtCtCA	49_86	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-1-9-1-1-2	TtAactCaaatcaattCtCA	49_87	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-1-9-4	TtAactCaaatcaattCTCA	49_88	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-1-8-2-1-2	TtAactCaaatcaatTCtCA	49_89	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-2-8-1-1-2	TtAactCAaatcaattCtCA	49_90	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-2-7-2-1-2	TtAactCAaatcaatTCtCA	49_91	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-2-6-1-1-1-1-2	TtAactCAaatcaaTtCtCA	49_92	39573	B
49	ttaactcaaatcaattctca	1-1-1-3-2-6-3-1-2	TtAactCAaatcaaTTCtCA	49_93	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-11-1-1-2	TtAaCtcaaatcaattCtCA	49_94	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-10-2-1-2	TtAaCtcaaatcaatTCtCA	49_95	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-9-1-3-2	TtAaCtcaaatcaaTtctCA	49_96	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-9-1-1-1-1-2	TtAaCtcaaatcaaTtCtCA	49_97	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-9-1-1-4	TtAaCtcaaatcaaTtCTCA	49_98	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-9-3-1-2	TtAaCtcaaatcaaTTCtCA	49_99	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-7-1-5-2	TtAaCtcaaatcAattctCA	49_100	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-10-2	TtAaCtcAaatcaattctCA	49_101	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-8-1-1-2	TtAaCtcAaatcaattCtCA	49_102	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-8-4	TtAaCtcAaatcaattCTCA	49_103	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-7-2-1-2	TtAaCtcAaatcaatTCtCA	49_104	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-6-1-3-2	TtAaCtcAaatcaaTtctCA	49_105	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-6-1-1-1-1-2	TtAaCtcAaatcaaTtCtCA	49_106	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-6-1-1-4	TtAaCtcAaatcaaTtCTCA	49_107	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-2-1-6-3-1-2	TtAaCtcAaatcaaTTCtCA	49_108	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-1-1-11-2	TtAaCtCaaatcaattctCA	49_109	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-1-1-9-1-1-2	TtAaCtCaaatcaattCtCA	49_110	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-1-1-8-2-1-2	TtAaCtCaaatcaatTCtCA	49_111	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-1-2-10-2	TtAaCtCAaatcaattctCA	49_112	39573	B

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
49	ttaactcaaatcaattctca	1-1-1-1-1-1-2-8-1-1-2	TtAaCtCAaatcaattCtCA	49_113	39573	B
49	ttaactcaaatcaattctca	1-1-1-1-1-1-2-6-1-3-2	TtAaCtCAaatcaaTtctCA	49_114	39573	B
49	ttaactcaaatcaattctca	1-1-2-11-2-1-2	TtAActcaaatcaatTCtCA	49_115	39573	B
49	ttaactcaaatcaattctca	1-1-2-10-1-1-1-1-2	TtAActcaaatcaaTtCtCA	49_116	39573	B
49	ttaactcaaatcaattctca	1-1-2-3-1-8-1-1-2	TtAActcAaatcaattCtCA	49_117	39573	B
49	ttaactcaaatcaattctca	1-1-2-3-1-7-2-1-2	TtAActcAaatcaatTCtCA	49_118	39573	B
49	ttaactcaaatcaattctca	1-1-2-3-1-6-1-1-1-1-2	TtAActcAaatcaaTtCtCA	49_119	39573	B
49	ttaactcaaatcaattctca	1-1-2-2-1-9-1-1-2	TtAActCaaatcaattCtCA	49_120	39573	B
49	ttaactcaaatcaattctca	1-1-2-2-1-8-2-1-2	TtAActCaaatcaatTCtCA	49_121	39573	B
49	ttaactcaaatcaattctca	1-1-2-2-2-8-1-1-2	TtAActCAaatcaattCtCA	49_122	39573	B
49	ttaactcaaatcaattctca	1-1-2-2-2-7-2-1-2	TtAActCAaatcaatTCtCA	49_123	39573	B
49	ttaactcaaatcaattctca	1-1-2-2-2-6-1-1-1-1-2	TtAActCAaatcaaTtCtCA	49_124	39573	B
49	ttaactcaaatcaattctca	1-1-3-11-1-1-2	TtAACtcaaatcaattCtCA	49_125	39573	B
49	ttaactcaaatcaattctca	1-1-3-11-4	TtAACtcaaatcaattCTCA	49_126	39573	B
49	ttaactcaaatcaattctca	1-1-3-10-2-1-2	TtAACtcaaatcaatTCtCA	49_127	39573	B
49	ttaactcaaatcaattctca	1-1-3-9-1-3-2	TtAACtcaaatcaaTtctCA	49_128	39573	B
49	ttaactcaaatcaattctca	1-1-3-9-1-1-1-1-2	TtAACtcaaatcaaTtCtCA	49_129	39573	B
49	ttaactcaaatcaattctca	1-1-3-9-3-1-2	TtAACtcaaatcaaTTCtCA	49_130	39573	B
49	ttaactcaaatcaattctca	1-1-3-7-1-5-2	TtAACtcaaatcAattctCA	49_131	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-10-2	TtAACtcAaatcaattctCA	49_132	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-8-1-1-2	TtAACtcAaatcaattCtCA	49_133	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-7-2-1-2	TtAACtcAaatcaatTCtCA	49_134	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-6-1-3-2	TtAACtcAaatcaaTtctCA	49_135	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-6-1-1-1-1-2	TtAACtcAaatcaaTtCtCA	49_136	39573	B
49	ttaactcaaatcaattctca	1-1-3-2-1-6-3-1-2	TtAACtcAaatcaaTTCtCA	49_137	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-1-11-2	TtAACtCaaatcaattctCA	49_138	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-1-9-1-1-2	TtAACtCaaatcaattCtCA	49_139	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-1-9-4	TtAACtCaaatcaattCTCA	49_140	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-1-8-2-1-2	TtAACtCaaatcaatTCtCA	49_141	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-2-8-1-1-2	TtAACtCAaatcaattCtCA	49_142	39573	B
49	ttaactcaaatcaattctca	1-1-3-1-2-6-1-3-2	TtAACtCAaatcaaTtctCA	49_143	39573	B
49	ttaactcaaatcaattctca	2-5-1-8-1-1-2	TTaactcAaatcaattCtCA	49_144	39573	B
49	ttaactcaaatcaattctca	2-5-1-7-2-1-2	TTaactcAaatcaatTCtCA	49_145	39573	B
49	ttaactcaaatcaattctca	2-5-1-6-1-1-1-1-2	TTaactcAaatcaaTtCtCA	49_146	39573	B
49	ttaactcaaatcaattctca	2-5-1-6-3-1-2	TTaactcAaatcaaTTCtCA	49_147	39573	B
49	ttaactcaaatcaattctca	2-4-2-8-1-1-2	TTaactCAaatcaattCtCA	49_148	39573	B
49	ttaactcaaatcaattctca	2-4-2-7-2-1-2	TTaactCAaatcaatTCtCA	49_149	39573	B
49	ttaactcaaatcaattctca	2-2-1-11-1-1-2	TTaaCtcaaatcaattCtCA	49_150	39573	B
49	ttaactcaaatcaattctca	2-2-1-11-4	TTaaCtcaaatcaattCTCA	49_151	39573	B
49	ttaactcaaatcaattctca	2-2-1-10-2-1-2	TTaaCtcaaatcaatTCtCA	49_152	39573	B
49	ttaactcaaatcaattctca	2-2-1-9-1-3-2	TTaaCtcaaatcaaTtctCA	49_153	39573	B
49	ttaactcaaatcaattctca	2-2-1-9-1-1-1-1-2	TTaaCtcaaatcaaTtCtCA	49_154	39573	B

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
49	ttaactcaaatcaattctca	2-2-1-7-1-5-2	TTaaCtcaaatcAattctCA	49_155	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-10-2	TTaaCtcAaatcaattctCA	49_156	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-8-1-1-2	TTaaCtcAaatcaattCtCA	49_157	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-8-4	TTaaCtcAaatcaattCTCA	49_158	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-7-2-1-2	TTaaCtcAaatcaatTCtCA	49_159	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-6-1-3-2	TTaaCtcAaatcaaTtctCA	49_160	39573	B
49	ttaactcaaatcaattctca	2-2-1-2-1-6-1-1-1-1-2	TTaaCtcAaatcaaTtCtCA	49_161	39573	B
49	ttaactcaaatcaattctca	2-2-1-1-1-11-2	TTaaCtCaaatcaattctCA	49_162	39573	B
49	ttaactcaaatcaattctca	2-2-1-1-1-9-1-1-2	TTaaCtCaaatcaattCtCA	49_163	39573	B
49	ttaactcaaatcaattctca	2-2-1-1-2-10-2	TTaaCtCAaatcaattctCA	49_164	39573	B
49	ttaactcaaatcaattctca	2-2-1-1-2-6-1-3-2	TTaaCtCAaatcaaTtctCA	49_165	39573	B
49	ttaactcaaatcaattctca	2-1-1-10-1-1-1-1-2	TTaActcaaatcaaTtCtCA	49_166	39573	B
49	ttaactcaaatcaattctca	2-1-1-2-1-9-1-1-2	TTaActCaaatcaattCtCA	49_167	39573	B
49	ttaactcaaatcaattctca	2-1-1-2-2-8-1-1-2	TTaActCAaatcaattCtCA	49_168	39573	B
49	ttaactcaaatcaattctca	2-1-2-9-1-1-1-1-2	TTaACtcaaatcaaTtCtCA	49_169	39573	B
49	ttaactcaaatcaattctca	2-1-2-2-1-7-2-1-2	TTaACtcAaatcaatTCtCA	49_170	39573	B
49	ttaactcaaatcaattctca	2-1-2-2-1-6-1-1-1-1-2	TTaACtcAaatcaaTtCtCA	49_171	39573	B
49	ttaactcaaatcaattctca	3-11-1-1-1-1-2	TTAactcaaatcaaTtCtCA	49_172	39573	B
49	ttaactcaaatcaattctca	3-10-1-2-1-1-2	TTAactcaaatcaAttCtCA	49_173	39573	B
49	ttaactcaaatcaattctca	3-10-1-1-2-1-2	TTAactcaaatcaAtTCtCA	49_174	39573	B
49	ttaactcaaatcaattctca	3-4-1-7-2-1-2	TTAactcAaatcaatTCtCA	49_175	39573	B
49	ttaactcaaatcaattctca	3-4-1-6-1-1-1-1-2	TTAactcAaatcaaTtCtCA	49_176	39573	B
49	ttaactcaaatcaattctca	3-3-1-9-1-1-2	TTAactCaaatcaattCtCA	49_177	39573	B
49	ttaactcaaatcaattctca	3-3-1-9-4	TTAactCaaatcaattCTCA	49_178	39573	B
49	ttaactcaaatcaattctca	3-3-1-8-2-1-2	TTAactCaaatcaatTCtCA	49_179	39573	B
49	ttaactcaaatcaattctca	3-3-2-8-1-1-2	TTAactCAaatcaattCtCA	49_180	39573	B
49	ttaactcaaatcaattctca	3-1-1-11-1-1-2	TTAaCtcaaatcaattCtCA	49_181	39573	B
49	ttaactcaaatcaattctca	3-1-1-9-1-3-2	TTAaCtcaaatcaaTtctCA	49_182	39573	B
49	ttaactcaaatcaattctca	3-1-1-9-1-1-1-1-2	TTAaCtcaaatcaaTtCtCA	49_183	39573	B
49	ttaactcaaatcaattctca	3-1-1-7-1-5-2	TTAaCtcaaatcAattctCA	49_184	39573	B
49	ttaactcaaatcaattctca	3-1-1-2-1-10-2	TTAaCtcAaatcaattctCA	49_185	39573	B
49	ttaactcaaatcaattctca	3-1-1-2-1-8-1-1-2	TTAaCtcAaatcaattCtCA	49_186	39573	B
49	ttaactcaaatcaattctca	3-1-1-2-1-6-1-3-2	TTAaCtcAaatcaaTtctCA	49_187	39573	B
49	ttaactcaaatcaattctca	3-1-1-1-1-11-2	TTAaCtCaaatcaattctCA	49_188	39573	B
49	ttaactcaaatcaattctca	4-12-4	TTAActcaaatcaattCTCA	49_189	39573	B
49	ttaactcaaatcaattctca	4-11-2-1-2	TTAActcaaatcaatTCtCA	49_190	39573	B
49	ttaactcaaatcaattctca	4-3-1-7-2-1-2	TTAActcAaatcaatTCtCA	49_191	39573	B
49	ttaactcaaatcaattctca	4-2-1-9-1-1-2	TTAActCaaatcaattCtCA	49_192	39573	B
50	tttaactcaaatcaattctc	4-12-4	TTTAactcaaatcaatTCTC	50_1	39574	B
51	tttaactcaaatcaattct	4-11-4	TTTAactcaaatcaaTTCT	51_1	39575	B
52	ccttttaattcattag	4-8-4	CCTTttaattcaTTAG	52_1	72861	C
53	caacacctttaattcatta	4-12-4	CAACacctttaattcATTA	53_1	72862	C

SEQ ID NO	motif sequence	Design	Oligonucleotide Compound	CMP ID NO	Start on SEQ ID NO: 1	Region
54	aacacctttaattcatt	4-10-4	AACAcctttaattCATT	54_1	72863	C
55	catcaacacctttaattca	2-14-4	CAtcaacacctttaaTTCA	55_1	72865	C
56	ctcatcaacacctttaatt	4-14-2	CTCAtcaacacctttaaTT	56_1	72867	C
57	actcatcaacacctttaat	2-14-4	ACtcatcaacaccttTAAT	57_1	72868	C
58	aactcatcaacacctttaa	3-13-4	AACtcatcaacaccttTTAA	58_1	72869	C
59	taactcatcaacacctttta	4-14-2	TAACtcatcaacaccttTA	59_1	72870	C
60	ttaactcatcaacacctttt	4-13-3	TTAActcatcaacacctTTT	60_1	72871	C
61	ttaactcatcaacaccttt	3-12-4	TTAactcatcaacacCTTT	61_1	72872	C
62	ttaactcatcaacacctt	3-11-4	TTAactcatcaacaCCTT	62_1	72873	C
63	ttaactcatcaacacct	4-9-4	TTAActcatcaacACCT	63_1	72874	C
64	gttaactcatcaacacc	4-10-3	GTTAactcatcaacACC	64_1	72875	C
65	gttaactcatcaacac	4-9-3	GTTAactcatcaaCAC	65_1	72876	C
66	atttccaaattcactttac	1-1-3-10-2-1-2	AtTTCcaaattcactTTtAC	66_1	133964	-
67	ccgttttcttaccaccct	5-10-5	CC$_o$GTTttettaeeAC$_o$CCT	67_1	114184	-

Motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide.

Designs refer to the gapmer design, F-G-F'. In classic gapmer design e.g. 3-10-3 all the nucleotides in the flanks (F and F') are constituted of the same 2'-sugar modified nucleoside, e.g. LNA, cET, or MOE, and a stretch of DNA in the middle forming the gap (G). In gapmers with alternating flank designs the flanks of oligonucleotide is annotated as a series of integers, representing a number of 2' sugar modified nucleosides (M) followed by a number of DNA nucleosides (D). For example a flank with a 2-2-1 motif represents 5' $[M]_2$-$[D]_2$-[M] 3' and a 1-1-1-1-1 motif represents 5' [M]-[D]-[M]-[D]-[M] 3'. Both flanks have a 2' sugar modified nucleoside at the 5' and 3' terminal. The gap region (G), which is constituted of a number of DNA nucleosides (typically between 6 and 16), is located between the flanks.

The heading "Oligonucleotide compound" in the table represents a specific design of the motif sequence. Capital letters represent beta-D-oxy LNA nucleosides, Underlined capital letter represent MOE nucleosides, lowercase letters represent DNA nucleosides, all LNA C are 5-methyl cytosine, e represents a 5-methyl cytosine DNA, all internucleoside linkages are phosphorothioate internucleoside linkages unless marked by a subscript letter between the nucleotides, subscript o represents a phosphodiester linkage.

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), or 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). Phosphodiester 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 amino linker 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 95°C 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 20°C to 95°C and then down to 25°C, 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.

Primary neuronal cell cultures

Primary neuronal cultures were established from the forebrain of E18 transgenic mice expressing the human tau transgene on a mouse tau knockout background. (Andorfer et al. J Neurochem 86:582–590 (2003)). Primary neurons were generated by papain digestion according to manufacturer's protocol (Worthington Biochemical Corporation, LK0031050). Briefly, forebrains were dissected from hTau mouse E18 BAC-Tg embryos expressing the entire human microtubule-associated protein Tau (MAPT) gene on a murine MAPT-null background and were incubated at 37 °C for 30-45 minutes in papain/DNase/Earle's balanced salt solution (EBSS) solution. After trituration and centrifugation of cell pellet, the reaction was stopped by incubation with EBSS containing protease inhibitors, bovine serum albumin (BSA) and DNase. The cells were triturated and washed with Neurobasal (NB, Invitrogen) supplemented with 2% B-27, 100 µg/ml penicillin, 85 µg/ml streptomycin, and 0.5mM glutamine.

Transgenic Tau mouse (hTau mouse)

Male and female transgenic mice (30-40g) expressing a tau transgene derived from a human PAC, H1 haplotype driven by the tau promoter (Polydoro et. al., *J. Neurosci.* (2009) 29(34): 10741-9), and in which the native mouse Tau gene was deleted, were used to assess tolerability, pharmacodynamic endpoints and tissue drug concentrations.

Animals were held in colony rooms maintained at constant temperature (21 ± 2°C) and humidity (50 ± 10%) and illuminated for 12 hours per day (lights on at 0600 hours). All animals had *ad libitum* access to food and water throughout the studies. Behavioral studies were conducted between 0700 and 1500 hours.

Intracerebroventricular (ICV) injections were performed using a Hamilton micro syringe fitted with a 27 or 30-gauge needle, according to the method of Haley and McCormick. The needle was equipped with a polyethylene guard at 2.5 mm from the tip in order to limit its penetration into the brain. Mice were anesthetized using isoflurane anesthetic (1.5-4%). The mouse to be injected was held by the loose skin at the back of the neck with the thumb and first fingers of one hand. Applying gentle but firm pressure, the head of the animal was then immobilized by pressing against a firm flat level surface. The needle tip was then inserted through the scalp and the skull, about 1 mm lateral and 1 mm caudal to bregma. Once the needle was positioned, ASO was given in a volume of 5 microliters in saline vehicle and injected into the right (or left) lateral ventricle over 20-30 seconds. The needle was left in place for 10 seconds before

removal. This procedure requires no surgery or incision. Animals were warmed on heating pads until they recovered from the procedure.

3 days and/or 4 weeks post administration mice were sacrificed with isoflurane overdose followed by rapid decapitation and brain tissue (right, frontal cortical region) was collected on dry ice for later Tau qPCR.

Media used for cell culturing and differentiation of human stem cell derived neurons

N2B27+ SFA Media=N2B27 + S,F,A cytokines

Cytokines used	Ref	Provider	Stock	Final use in N2B27(dilution)
SHH (sonic hedgehog)	100-45	Peprotech	100 ug/ml in PBS +0.1%BSA	1:500 (200 ng/ml)
FGF8	100-25	Peprotech	100 ug/ml in	1:1000 (100 ng/ml)
AA (Aa2-P)	A8960	Sigma	PBS +0.1% BSA 100 mM in DMEM:F12	1:1000

N2B27+ BGAA Media=N2B27 + B,G,Aa,cA cytokines +P/S+Laminin

Cytokines used	Ref	Provider	Stock	Final use in N2B27(dilution)
BDNF	450-02	Peprotech	20 ug/ml in PBS +0.1%BSA	1:1000
GDNF	450-10	Peprotech	10 ug/ml in PBS +0.1%BSA	1:1000
AA (Aa2-P)	A8960	Sigma	100 mM in DMEM:F12	1:1000
cAMP	D 009	BIOLOG Life Science	200 mM in water	1:400
PenStrep	15140-122	Gibco		1%
Laminin	11243217001	Roche	1mg/ml	1:500

Example 1 *in vitro* screening of ASO's targeting MAPT introns

An antisense oligonucleotide (ASO) screening was performed in primary neuronal cells from humanized Tau mice with 807 ASO's targeting the MAPT introns.

The ability of ASOs to reduce MAPT mRNA *in vitro* was measured by QUANTIGENE® analysis. Each tau mRNA reduction was standardized by subtracting an assay background signal and normalizing each well via the housekeeping gene tubulin mRNA signal.

Primary neuronal cell cultures were prepared as described in the "Materials and Method" section and plated on poly-D-lysine coated 384 well plates at 10,000 cells per well and maintained in Neurobasal media containing B27, glutamax and Penicillin-Streptomycin. ASO's were diluted in water and added to cells at DIV01 to a final concentration of 0.5 µM. Following ASO addition, neurons were incubated at 37°C and 5% CO_2 for 5 days to achieve steady state

reduction of mRNA. Media was removed and cells were washed 1X in DPBS. Measurement of lysate messenger RNA was performed using the QUANTIGENE® 2.0 Reagent System (AFFYMETRIX®), which quantitates RNA using a branched DNA-signal amplification method reliant on the specifically designed RNA capture probe set. The cells were lysed using working cell lysis buffer solution made by adding 50µl proteinase K to 5ml of pre-warmed Lysis mix and diluted to 1:4 final dilution with dH_20. The working lysis buffer was added to the plate (45 µl/ well), triturated to mix, sealed and incubated for 30 min at 55°C. Following lysis the wells were stored at -80°C or assayed immediately.

Lysates were diluted in lysis mix dependent on the specific capture probe used (tau or tubulin). 27 µl/ well total was then added to the capture plate (384 well polystyrene plate coated with capture probes). Working probe sets reagents were generated by combining 2.2 ml of nuclease-free water, 1.2 ml of lysis mixture, 184 µl blocking reagent, and 66.8 µl of specific 2.0 probe set human MAPT catalogue #15486 and mouse beta 3 tubulin, catalogue #SB-17245, per manufacturer instructions (QUANTIGENE® 2.0 AFFYMETRIX®). Then 7 µl working probe set reagents were added to 27 µl lysate dilution (or 27 µl lysis mix for background samples) on the capture plate. Plates were centrifuged and then incubated for 16-20 hours at 55°C to hybridize (target RNA capture). Signal amplification and detection of target RNA began by washing plates with buffer 3 times to remove unbound material. 2.0 Pre-Amplifier hybridization reagent (30 µl/well) was added, incubated at 55°C for 1 hour then aspirated and wash buffer was added and aspirated 3 times. The 2.0 Amplifier hybridization reagent was then added as described (30 µl/well), incubated for 1 hour at 55°C and the wash was repeated as described previously. The 2.0 Label Probe hybridization reagent was added next (30 µl/well), incubated for 1 hour at 50°C and the wash was repeated as described previously. Lastly, the plates were centrifuged to remove any excess wash buffer and 2.0 Substrate was added (30 µl/well). Plates were incubated for 5 minutes at room temperature and plates were imaged on a PerkinElmer Envision multilabel reader in luminometer mode within 15 minutes.

For the gene of interest, the average assay background signal was subtracted from the average signal of each technical replicate. The background-subtracted, average signals for the gene of interest are divided by the background-subtracted average signal for the housekeeping tubulin RNA. The percent inhibition for the treated sample was calculated relative to untreated sample (i.e. the lower the value the larger the inhibition). Variability in background of untreated samples may result in percent inhibition of a treated sample that are equal to or higher than background, and in these cases, percent inhibition is expressed as 100% inhibition of control (i.e. no inhibition).

Figure 1 shows the MAPT mRNA reduction achieved by all 807 ASO's. In the figure three regions A, B and C on the MAPT target nucleic acid are indicated. These regions have a high prevalence of ASO's that reduce the target to 40% or less compared to control (100%).

Example 2 *in vitro* screening of ASO's targeting selected regions on MAPT

Based on the screening in Example 1, a new library of ASO's were designed to target region A, B and C as illustrated in figure 1. The motif sequences and the oligonucleotide compounds are shown in table 5 above.

The screening was conducted as described in Example 1. The results are shown in table 6.

Table 6 *in vitro* screening of anti-MAPT compounds

CMP ID NO	Compound	% MAPT mRNA of control
6_1	TCACtcatgccttaaTC	2
7_1	TAATcactcatgcCTTA	15
8_1	TAATcactcatgCCTT	34
9_1	CtttaatttaaTcaCtCAT	41
9_2	CtttaatttaaTcACtCAT	36
9_3	CtttaatttaaTCactCAT	28
9_4	CtttaatttaaTCacTCAT	31
9_5	CtttaatttaaTCaCtcAT	28
9_6	CtttaatttaaTCaCtCAT	55
9_7	CtttaatttaaTCActcAT	30
9_8	CtttaatttaaTCActCAT	21
9_9	CtttaatttaaTCAcTCAT	61
9_10	CtttaatttaaTCACtcAT	24
9_11	CtttaaTttaatcacTCAT	14
9_12	CtttaaTttaatcaCtCAT	22
9_13	CtttaaTttaatcActCAT	33
9_14	CtttaaTttaatcAcTCAT	9
9_15	CtttaaTttaatcACtCAT	20
9_16	CtttaAtttaatcacTCAT	17
9_18	CtttAatttaatcacTCAT	10
9_19	CtttAatttaatcaCtCAT	17
9_20	CtttAaTttaatcacTCAT	0
9_21	CtttAAtttaatcacTCAT	3
9_22	CtttAATttaatcacTCAT	1
9_23	CttTaatttaatcacTCAT	13
9_24	CttTaatttaatcaCtCAT	13
9_25	CttTaaTttaatcacTCAT	4
9_26	CttTaAtttaatcacTCAT	4
9_27	CttTaATttaatcacTCAT	1
9_28	CttTAatttaatcactCAT	12
9_29	CttTAatttaatcacTCAT	1
9_30	CttTAatttaatcaCtcAT	15
9_31	CttTAatttaatcaCtCAT	4
9_32	CttTAaTttaatcacTCAT	1
9_33	CttTAAtttaatcacTCAT	1
9_34	CttTAATttaatcactcAT	4
9_35	CttTAATttaatcacTCAT	1
9_36	CtTtaaTttaatcacTCAT	5
9_37	CtTtaAtttaatcacTCAT	7
9_38	CtTtaATttaatcacTCAT	2
9_39	CtTtAatttaatcacTCAT	3
9_40	CtTtAatttaatcaCtCAT	9
9_41	CtTtAaTttaatcacTCAT	4

CMP ID NO	Compound	% MAPT mRNA of control
9_42	CtTtAAtttaatcacTCAT	1
9_43	CtTtAATttaatcacTCAT	1
9_44	CtTTaatttaatcacTCAT	2
9_45	CtTTaatttaatcaCtcAT	15
9_46	CtTTaatttaatcaCtCAT	3
9_47	CtTTaaTttaatcacTCAT	2
9_48	CtTTaAtttaatcacTCAT	1
9_49	CtTTaATttaatcactcAT	1
9_50	CtTTaATttaatcacTCAT	1
9_51	CtTTAatttaatcactCAT	1
9_52	CtTTAatttaatcacTCAT	1
9_53	CtTTAatttaatcaCtcAT	6
9_54	CtTTAatttaatcaCtCAT	2
9_56	CtTTAaTttaatcacTCAT	1
9_57	CtTTAAtttaatcactcAT	1
9_58	CtTTAAtttaatcacTCAT	1
9_59	CTttaatttaatcActCAT	39
9_60	CTttaatttaatcAcTCAT	10
9_61	CTttaatttaatcACtCAT	20
9_62	CTttaatttaaTCactcAT	26
9_63	CTttaatttaaTCactCAT	14
9_64	CTttaatttaaTCacTCAT	14
9_65	CTttaatttaaTCaCtcAT	15
9_66	CTttaatttaaTCaCtCAT	38
9_67	CTttaatttaaTCActcAT	9
9_68	CTttaatttaaTCActCAT	12
9_69	CTttaatttaaTCACtcAT	9
9_70	CTttaaTttaatcactCAT	42
9_71	CTttaaTttaatcacTCAT	6
9_72	CTttaaTttaatcaCtcAT	49
9_73	CTttaaTttaatcaCtCAT	15
9_74	CTttaaTttaatcActCAT	16
9_75	CTttaaTttaatcAcTCAT	12
9_76	CTttaaTttaatcACtcAT	32
9_77	CTttaaTttaatcACtCAT	15
9_78	CTttAatttaatcactCAT	21
9_79	CTttAatttaatcacTCAT	3
9_80	CTttAatttaatcaCtCAT	10
9_81	CTttAaTttaatcacTCAT	2
9_82	CTttAAtttaatcacTCAT	1
9_84	CTtTaatttaatcaCtcAT	22
9_85	CTtTaatttaatcaCtCAT	8
9_86	CTtTaAtttaatcacTCAT	2
9_89	CTtTAatttaatcacTCAT	1
9_90	CTtTAatttaatcaCtcAT	5
9_92	CTtTAaTttaatcactcAT	1
9_94	CTtTAAtttaatcacTCAT	1
9_97	CTTtAatttaatcactCAT	0
9_98	CTTtAatttaatcacTCAT	1
9_99	CTTtAatttaatcaCtcAT	7
9_100	CTTtAatttaatcaCtCAT	3
9_101	CTTtAAtttaatcacTCAT	1
9_103	CTTTaatttaatcacTCAT	0

CMP ID NO	Compound	% MAPT mRNA of control
9_105	CTTTaaTttaatcactcAT	0
9_106	CTTTaAtttaatcacTCAT	1
10_1	GctttaatttaaTcaCtCAT	35
10_2	GctttaatttaaTCactcAT	56
10_3	GctttaatttaaTCactCAT	18
10_4	GctttaatttaaTCacTCAT	21
10_5	GctttaatttaaTCaCtcAT	16
10_6	GctttaatttaaTCaCtCAT	35
10_7	GctttaatttaaTCActcAT	22
10_8	GctttaatttaaTCACtcAT	12
10_9	GctttaaTttaatcactCAT	61
10_10	GctttaaTttaatcacTCAT	19
10_11	GctttaaTttaatcaCtcAT	76
10_12	GctttaaTttaatcaCtCAT	12
10_13	GctttaaTttaaTcaCtCAT	15
10_14	GctttaaTttaaTCactCAT	7
10_15	GctttaaTttaaTCaCtcAT	14
10_16	GctttaaTttaaTCActcAT	10
10_17	GctttaAtttaatcacTCAT	28
10_18	GctttAatttaatcacTCAT	16
10_19	GctttAatttaatcaCtCAT	13
10_20	GctttAaTttaatcacTCAT	2
10_21	GctttAAtttaatcacTCAT	3
10_22	GctttAATttaatcacTCAT	1
10_23	GcttTaatttaatcacTCAT	18
10_24	GcttTaatttaatcaCtcAT	51
10_25	GcttTaatttaatcaCtCAT	8
10_26	GcttTaaTttaatcacTCAT	4
10_27	GcttTaAtttaatcacTCAT	3
10_28	GcttTAatttaatcacTCAT	2
10_29	GcttTAatttaatcaCtcAT	13
10_30	GcttTAatttaatcaCtCAT	3
10_31	GctTtaaTttaatcacTCAT	4
10_32	GctTtaAtttaatcacTCAT	6
10_33	GctTtAatttaatcacTCAT	3
10_34	GctTtAatttaatcaCtcAT	18
10_35	GctTtAatttaatcaCtCAT	6
10_36	GctTtAaTttaatcacTCAT	2
10_37	GctTtAAtttaatcacTCAT	1
10_38	GctTTaatttaatcacTCAT	1
10_39	GctTTaatttaatcaCtcAT	12
10_40	GctTTaatttaatcaCtCAT	3
10_41	GctTTaAtttaatcacTCAT	1
10_42	GctTTAatttaatcaCtcAT	5
10_43	GcTttaatttaaTCactcAT	15
10_44	GcTttaatttaaTCactCAT	11
10_45	GcTttaatttaaTCaCtcAT	15
10_46	GcTttaatttaaTCActcAT	7
10_47	GcTttaaTttaatcactCAT	23
10_48	GcTttaaTttaatcacTCAT	6
10_49	GcTttaaTttaatcaCtcAT	34
10_50	GcTttaaTttaatcaCtCAT	12
10_51	GcTttaAtttaatcacTCAT	10

CMP ID NO	Compound	% MAPT mRNA of control
10_52	GcTttAatttaatcacTCAT	5
10_53	GcTttAatttaatcaCtcAT	26
10_54	GcTttAatttaatcaCtCAT	10
10_55	GcTttAaTttaatcacTCAT	3
10_56	GcTttAAtttaatcacTCAT	2
10_57	GcTtTaatttaatcacTCAT	5
10_58	GcTtTaatttaatcaCtCAT	9
10_59	GcTtTaaTttaatcacTCAT	5
10_60	GcTtTaAtttaatcacTCAT	4
10_61	GcTtTAatttaatcaCtcAT	10
10_62	GcTtTAAtttaatcactcAT	4
10_63	GcTTtaaTttaatcacTCAT	2
10_64	GcTTtaAtttaatcactcAT	21
10_65	GcTTtaAtttaatcacTCAT	2
10_66	GcTTtAatttaatcacTCAT	2
10_67	GcTTtAatttaatcaCtCAT	1
10_68	GcTTtAAtttaatcactcAT	4
10_69	GcTTTaatttaatcaCTcAT	1
10_70	GcTTTAatttaatcaCtcAT	5
10_71	GCtttaatttaatCactcAT	71
10_72	GCtttaatttaaTCactcAT	22
10_73	GCtttaaTttaatcactcAT	76
10_74	GCtttaaTttaatcactCAT	25
10_75	GCtttaaTttaatcaCtcAT	43
10_76	GCtttaATttaatcactcAT	25
10_77	GCtttAatttaatcaCtcAT	13
10_78	GCtttAAtttaatcactcAT	22
10_79	GCttTaatttaatcaCtcAT	16
10_80	GCttTaAtttaatcactcAT	8
10_81	GCttTAAtttaatcactcAT	3
10_82	GCtTtaAtttaatcactcAT	21
10_83	GCtTtAatttaatcaCtcAT	7
10_84	GCtTtAAtttaatcactcAT	3
10_85	GCTttaatttaatCactcAT	29
10_86	GCTttaaTttaatcactcAT	32
10_87	GCTttaAtttaatcactcAT	38
10_88	GCTttAAtttaatcactcAT	6
10_89	GCTtTaatttaatcAcTcAT	9
11_1	CTTTaatttaatcaCTCA	0
12_1	CTTTaatttaatcACTC	0
19_1	ACAccatccaagtCAAT	20
20_1	TACaccatccaagTCAA	18
21_1	TTACaccatccaagtCA	0
22_1	TTACaccatccaaGTC	5
23_1	AATAttacaccatCCAA	0
24_1	AgaaTattacaccatCCAA	11
24_2	AgaaTattacaccaTcCAA	8
24_3	AgaaTattacaccaTCcAA	6
24_4	AgaaTattacaccAtcCAA	11
24_5	AgaaTattacaccAtCCAA	14
24_6	AgaaTattacaccATcCAA	6
24_7	AgaaTattacaccATCcAA	2
24_8	AgaaTattacacCaTCcAA	12

CMP ID NO	Compound	% MAPT mRNA of control
24_9	AgaaTattacaCcAtCcAA	11
24_10	AgaaTattacaCcATcCAA	18
24_11	AgaAtattacaccatCCAA	10
24_12	AgaAtattacaccaTcCAA	12
24_13	AgaATattacaccatcCAA	1
24_14	AgaATattacaccaTCcAA	1
24_15	AgaATattacaccAtcCAA	9
24_16	AgaATattacaccAtCcAA	0
24_17	AgaATattacaccATCcAA	10
24_18	AgaATattacacCAtCcAA	3
24_19	AgAatattacaccAtCCAA	10
24_20	AgAatattacaccATCcAA	13
24_21	AgAaTattacaccatcCAA	0
24_22	AgAaTattacaccaTCcAA	3
24_23	AgAaTattacaccAtcCAA	13
24_24	AgAaTattacaccAtCcAA	1
24_25	AgAaTattacaccATCcAA	8
24_26	AgAaTattacacCatcCAA	3
24_27	AgAaTattacaCcatcCAA	1
24_28	AgAaTAttacacCAtccAA	5
24_29	AgAAtattacaccaTCcAA	13
24_30	AgAATattacaccatcCAA	10
24_31	AgAATattacaccatCcAA	4
24_32	AgAATattacaccaTCcAA	12
24_33	AgAATattacaccAtcCAA	13
24_34	AgAATattacaccAtCcAA	5
24_35	AgAATattacacCaTCcAA	4
24_36	AGaatAttacaccaTCcAA	5
24_37	AGaatAttacacCatcCAA	2
24_38	AGaaTattacaccatcCAA	11
24_39	AGaaTattacaccatCcAA	3
24_40	AGaaTattacaccaTCcAA	17
24_41	AGaaTattacaccAtcCAA	9
24_42	AGaaTattacaccAtCcAA	2
24_43	AGaaTattacaccATCcAA	5
24_44	AGaaTattacaCcAtCcAA	9
24_45	AGaaTAttacacCatCcAA	3
24_46	AGaAtattacaccaTCcAA	9
24_47	AGaAtAttacacCaTCcAA	26
24_48	AGaATattacaccatcCAA	8
24_49	AGaATattacaccatCcAA	0
24_50	AGaATattacaccaTCcAA	2
24_51	AGaATattacaccAtcCAA	4
24_52	AGaATattacaccAtCcAA	0
24_53	AGaATAttacaccatCcAA	1
24_54	AGAatattacaccaTCcAA	5
24_55	AGAatattacaccAtcCAA	1
24_56	AGAatattacaccAtCcAA	0
24_57	AGAaTattacaccatCcAA	0
24_58	AGAaTattacaccAtccAA	13
24_59	AGAaTattacaccAtCcAA	11
24_60	AGAAtattacaccatCcAA	11
24_61	AGAAtattacacCatccAA	56

CMP ID NO	Compound	% MAPT mRNA of control
24_62	AGAAtAttacaccatCcAA	4
25_1	CagaaTattacaccaTcCAA	8
25_2	CagaaTattacaccaTCcAA	11
25_3	CagaaTattacacCatCcAA	9
25_4	CagaaTattacaCcAtCcAA	12
25_5	CagaAtattacaccaTCcAA	20
25_6	CagaAtattacaCCatccAA	10
25_7	CagaAtAttacacCAtccAA	6
25_8	CagaATattacaccatcCAA	5
25_9	CagaATattacaccatCcAA	6
25_10	CagaATattacaccaTCcAA	9
25_11	CagaATattacaccAtCcAA	12
25_12	CagAatattacaccaTCcAA	11
25_13	CagAatattacaccAtcCAA	2
25_14	CagAatAttacacCaTCcAA	19
25_15	CagAaTattacaccatcCAA	13
25_16	CagAaTattacaccaTCcAA	7
25_17	CagAaTattacaccAtcCAA	0
25_18	CagAaTattacaccAtCcAA	13
25_19	CagAaTattacacCaTCcAA	6
25_20	CagAaTAttacacCatCcAA	12
25_21	CagAAtattacacCAtccAA	2
25_22	CagAAtattacacCAtCcAA	25
25_23	CaGaaTattacaccatcCAA	2
25_24	CaGaaTattacaccatCcAA	3
25_25	CaGaaTattacaccaTCcAA	5
25_26	CaGaaTattacaccAtcCAA	0
25_27	CaGaaTattacaccAtCcAA	10
25_28	CaGaaTattacaCcatccAA	4
25_29	CaGaAtattacaccatCcAA	6
25_30	CaGaAtattacaccaTCcAA	3
25_31	CaGaAtAttacaccatCcAA	6
25_32	CaGaAtAttacacCAtccAA	2
25_33	CaGAatattacaccAtCcAA	5
25_34	CaGAatattacaCcAtccAA	10
25_35	CAgaaTattacaccatCcAA	5
25_36	CAgaaTattacaccAtccAA	5
25_37	CAgaaTattacaccAtCcAA	3
25_38	CAgaAtattacaccatCcAA	26
25_39	CAgAatattacaccAtccAA	1
25_40	CAgAatattacaccAtCcAA	11
25_41	CAgAaTattacaccAtccAA	6
25_42	CAgAaTattacacCatccAA	73
25_43	CAgAAtattacaccatCcAA	1
26_1	GaatattacacCAtCCAA	11
26_2	GaatattacacCATcCAA	13
26_3	GaatattacacCATCcAA	10
26_4	GaatAttacaccatCCAA	0
26_5	GaaTattacaccatCCAA	2
26_6	GaaTattacaccAtCCAA	0
26_7	GaaTAttacacCAtCcAA	8
26_8	GaAtattacaccatCCAA	1
26_9	GaAtAttacaccatCCAA	1

CMP ID NO	Compound	% MAPT mRNA of control
26_10	GaAtAttacacCATCcAA	22
26_11	GaATattacaccatCCAA	1
26_12	GaATattacaccaTCcAA	2
26_13	GaATattacaccAtCCAA	3
26_14	GaATattacaccATCcAA	3
26_15	GaATattacacCAtcCAA	1
26_16	GAatattacaccAtCCAA	0
26_17	GAatattacaccATCcAA	1
26_18	GAatattacacCATCcAA	8
26_19	GAatAttacacCATCcAA	22
26_20	GAaTattacaccatcCAA	1
26_21	GAaTattacaccaTCcAA	1
26_22	GAaTattacaccAtcCAA	4
26_23	GAaTattacaccATCcAA	5
26_24	GAaTattacacCatcCAA	9
26_25	GAaTattacacCAtccAA	2
26_26	GAAtattacaccatCCAA	3
26_27	GAAtattacaccaTCcAA	3
26_28	GAAtattacacCAtCcAA	5
26_29	GAATattacaccatcCAA	0
26_30	GAATattacaccAtcCAA	0
26_31	GAATattacacCaTCcAA	24
27_1	AATAttacaccaTCCA	0
28_1	AgaaTattacaccatCCA	1
28_2	AgaaTattacaccaTcCA	6
28_3	AgaaTattacaccAtCCA	1
28_4	AgaaTattacaccATcCA	5
28_5	AgaAtattacaccatCCA	5
28_6	AgaAtattacaccaTCCA	6
28_7	AgaAtAttacaccaTcCA	3
28_8	AgaAtAttacacCatcCA	4
28_9	AgaATattacaccatcCA	2
28_10	AgaATattacaccAtcCA	0
28_11	AgAatattacaccaTCCA	8
28_12	AgAatattacaccAtCCA	1
28_13	AgAatattacacCAtcCA	1
28_14	AgAatAttacacCatcCA	3
28_15	AgAatAttacacCatCCA	6
28_16	AgAaTattacaccatcCA	3
28_17	AgAaTattacaccatCCA	1
28_18	AgAaTattacaccAtcCA	3
28_19	AgAaTattacaccAtCCA	0
28_20	AgAaTattacacCatcCA	6
28_21	AgAaTattacaCcatcCA	3
28_22	AgAaTAttacacCatcCA	5
28_23	AgAAtattacaccatCCA	0
28_24	AgAATattacaccatcCA	2
28_25	AgAATattacaccAtcCA	3
28_26	AGaaTattacaccatcCA	2
28_27	AGaaTattacaccAtcCA	1
28_28	AGaAtattacaccatCCA	1
28_29	AGaATattacaccatcCA	0
28_30	AGaATattacaccAtcCA	1

CMP ID NO	Compound	% MAPT mRNA of control
28_31	AGAatattacaccAtcCA	1
28_32	AGAaTattacaccatcCA	1
28_33	AGAaTattacaccAtcCA	5
29_1	CagaaTattacaccaTcCA	1
29_2	CagaAtattacaccatCCA	4
29_3	CagaAtattacaCcatcCA	15
29_4	CagaATattacaccatcCA	6
29_5	CagaATattacaccAtcCA	12
29_6	CagaATattacacCatcCA	3
29_7	CagAaTattacaccatcCA	2
29_8	CagAaTattacaccAtcCA	9
29_9	CagAATattacaccatcCA	0
29_10	CaGaaTattacaccatcCA	0
29_11	CaGaaTattacaccAtcCA	7
29_12	CaGAatattacaccAtcCA	4
29_13	CAgAatattacaccAtcCA	0
29_14	CAgAatattacAccAtcCA	2
30_1	GaatattacacCAtCCA	20
30_2	GaatAttacaccaTCCA	2
30_3	GaaTattacaccatCCA	1
30_4	GaaTattacaccAtCCA	1
30_5	GaAtattacaccatCCA	0
30_6	GaAtattacaccaTCCA	1
30_7	GaAtattacacCAtCCA	4
30_8	GaAtattacaCCatcCA	2
30_9	GaAtAttacacCATcCA	20
30_10	GaATattacaccatCCA	1
30_11	GaATattacaccAtCCA	4
30_12	GAatattacaccaTCCA	1
30_13	GAatattacaccAtCCA	1
30_14	GAatAttacaccatCCA	2
30_15	GAatAttacacCatcCA	3
30_16	GAaTattacaccatcCA	5
30_17	GAaTattacaccatCCA	0
30_18	GAaTattacaccAtcCA	5
30_19	GAaTattacaccAtCCA	3
30_20	GAaTattacacCAtcCA	2
30_21	GAaTattacaCcatcCA	2
30_22	GAAtattacaccatCCA	4
30_23	GAAtattacacCatcCA	2
30_24	GAATattacaccatcCA	1
30_25	GAATattacaccAtcCA	3
31_1	TcAgaaTattacaccatcCA	10
31_2	TcAgaaTattacaccAtcCA	3
31_3	TcAgaAtattacaccaTcCA	7
32_1	AgaaTattacaccaTCC	1
32_2	AgaaTattacaccATCC	1
32_3	AgaaTAttacacCatCC	0
32_4	AgaAtattacaccaTCC	5
32_5	AgaAtattacACcAtCC	39
32_6	AgaAtAttacacCatCC	7
32_7	AgaATattacaccaTCC	1
32_8	AgaATattacaccAtCC	0

CMP ID NO	Compound	% MAPT mRNA of control
32_9	AgaATattacaccATCC	1
32_10	AgAatattacaccaTCC	1
32_11	AgAatattacaccATCC	5
32_12	AgAatattacaCcAtCC	5
32_13	AgAatattacaCcATCC	15
32_14	AgAatattacAccaTCC	3
32_15	AgAatattacACcatCC	0
32_16	AgAatattacACCatCC	18
32_17	AgAaTattacaccaTCC	4
32_18	AgAaTattacaccAtCC	3
32_19	AgAaTattacaccATCC	3
32_20	AgAaTattacacCatCC	10
32_21	AgAaTattacaCcAtCC	18
32_22	AgAAtattacaccaTCC	5
32_23	AgAAtattacaCCatCC	6
32_24	AgAAtattacAcCAtCC	34
32_25	AgAATattacaccatCC	1
32_26	AgAATattacaccaTCC	1
32_27	AgAATattacaccAtCC	2
32_28	AgAATattacaccATCC	2
32_29	AgAATattacaCcAtCC	13
32_30	AGaaTattacaccatCC	5
32_31	AGaaTattacaccaTCC	0
32_32	AGaaTattacaccAtCC	4
32_33	AGaaTattacaccATCC	1
32_34	AGaAtattacaccatCC	2
32_35	AGaAtattacaccaTCC	1
32_36	AGaAtattacacCaTCC	4
32_37	AGaAtattacAccATCC	11
32_38	AGaATattacaccatCC	0
32_39	AGaATattacaccAtCC	0
32_40	AGAatattacaccaTCC	4
32_41	AGAatattacaccAtCC	0
32_42	AGAatattacAccaTCC	2
32_43	AGAatattacAccAtCC	10
32_44	AGAatattacAcCatCC	12
32_45	AGAatAttacaccatCC	3
32_46	AGAaTattacaccatCC	1
32_47	AGAaTattacaccAtCC	1
32_48	AGAAtattacaccatCC	0
32_49	AGAAtattacaccaTCC	0
32_50	AGAAtattacacCatCC	0
32_51	AGAAtattacAcCatCC	5
33_1	CagaaTattacaccaTCC	7
33_2	CagaAtattacaccaTCC	55
33_3	CagaAtattacaCcaTCC	19
33_4	CagaAtattacAccaTCC	8
33_5	CagaAtattacACcatCC	20
33_6	CagaATattacaccatCC	1
33_7	CagaATattacaccaTCC	2
33_8	CagaATattacaccAtCC	3
33_9	CagAatattacaccaTCC	1
33_10	CagAatAttacaccaTCC	10

CMP ID NO	Compound	% MAPT mRNA of control
33_11	CagAaTattacaccaTCC	0
33_12	CagAAtattacaccaTCC	11
33_13	CagAAtattacacCaTCC	4
33_14	CagAATattacaCcatCC	3
33_15	CaGaatAttacacCAtCC	5
33_16	CaGaaTattacaccAtCC	1
33_17	CaGaAtattacaccatCC	1
33_18	CaGaAtattacaccaTCC	14
33_19	CaGaAtattacaCcatCC	6
33_20	CaGaAtattacACcAtCC	53
33_21	CaGAatattacaccAtCC	0
33_22	CAgaaTattacaccatCC	0
33_23	CAgaaTattacaccAtCC	1
33_24	CAgaAtattacaccatCC	3
33_25	CAgaAtattacaccaTCC	61
33_26	CAgaAtAttacacCatCC	5
33_27	CAgAatattacaccaTCC	8
33_28	CAgAatattacaccAtCC	0
33_29	CAgAaTattacaccatCC	0
33_30	CAgAaTattacaccAtCC	1
33_31	CAgAAtattacaccatCC	13
33_32	CAgAAtattacAccatCC	1
33_33	CAGaAtattacaccatCC	10
34_1	GAATattacaccATCC	0
35_1	TCagaaTattacaccatCC	10
35_2	TCagaAtattacaccatCC	11
35_3	TCagaAtattacAccatCC	9
36_1	AGAAtattacacCATC	0
37_1	CAGAatattacaCCAT	0
38_1	CAattctcatttcaacCTTC	14
39_1	TCaattctcatttcaacCTT	35
40_1	ATCaattctcatttcaacCT	17
41_1	AATCaattctcatttcaACC	28
42_1	AAATcaattctcatttCAAC	38
43_1	CAAAtcaattctcattTCAA	22
44_1	TCAaatcaattctcatTTCA	0
45_1	CTCAaatcaattctcatTTC	6
46_1	ACTCaaatcaattctcATTT	5
47_1	AACTcaaatcaattctCATT	37
48_1	TAACtcaaatcaattcTCAT	20
49_1	TtaactCaaatcaattcTCA	46
49_2	TtaactCAaatcaattctCA	35
49_3	TtaactCAaatcaattcTCA	9
49_4	TtaacTCaaatcaattctCA	33
49_5	TtaacTCAaatcaattctCA	6
49_6	TtaaCtcaaatcaattCtCA	63
49_7	TtaaCtcaaatcaattCTCA	18
49_8	TtaaCtcaaatcaatTCtCA	19
49_9	TtaaCtcaaatcaaTtctCA	80
49_10	TtaaCtcaaatcaaTtcTCA	26
49_11	TtaaCtcaaatcaaTtCtCA	30
49_12	TtaaCtcaaatcaaTtCTCA	18
49_13	TtaaCtcaaatcaaTTCtCA	32

CMP ID NO	Compound	% MAPT mRNA of control
49_14	TtaaCtcaaatcAattcTCA	22
49_15	TtaaCtcAaatcaattcTCA	20
49_16	TtaaCtcAaatcaattCtCA	28
49_17	TtaaCtcAaatcaattCTCA	7
49_18	TtaaCtcAaatcaatTctCA	19
49_19	TtaaCtcAaatcaatTCtCA	9
49_20	TtaaCtcAaatcaaTtctCA	33
49_21	TtaaCtcAaatcaaTtcTCA	13
49_22	TtaaCtcAaatcaaTtCtCA	16
49_23	TtaaCtcAaatcaaTtCTCA	12
49_24	TtaaCtcAaatcaaTTCtCA	19
49_25	TtaaCtCaaatcaattctCA	33
49_26	TtaaCtCaaatcaattcTCA	14
49_27	TtaaCtCaaatcaattCtCA	17
49_28	TtaaCtCaaatcaattCTCA	7
49_29	TtaaCtCaaatcaatTCtCA	7
49_30	TtaaCtCAaatcaattctCA	7
49_32	TtaaCtCAaatcaattCtCA	10
49_33	TtaaCtCAaatcaaTtctCA	10
49_34	TtaaCtCAaatcaaTtCtCA	6
49_35	TtaaCTCaaatcaattctCA	10
49_36	TtaaCTCaaatcaattCtCA	7
49_37	TtaaCTCAaatcaattctCA	4
49_39	TtaActcaaatcaatTCtCA	24
49_40	TtaActcaaatcaaTtCtCA	26
49_41	TtaActcaaatcaaTtCTCA	17
49_42	TtaActcAaatcaattCtCA	33
49_43	TtaActcAaatcaatTCtCA	11
49_44	TtaActcAaatcaaTtcTCA	15
49_45	TtaActcAaatcaaTtCtCA	24
49_46	TtaActCaaatcaattCtCA	20
49_47	TtaActCaaatcaattCTCA	6
49_48	TtaActCaaatcaatTCtCA	6
49_49	TtaActCAaatcaattctCA	18
49_50	TtaActCAaatcaattCtCA	9
49_53	TtaActCAaatcaaTtctCA	12
49_54	TtaActCAaatcaaTtCtCA	6
49_55	TtaAcTCaaatcaattCtCA	7
49_56	TtaACtcaaatcaattCtCA	30
49_57	TtaACtcaaatcaattCTCA	7
49_58	TtaACtcaaatcaatTCtCA	11
49_59	TtaACtcaaatcaaTtctCA	47
49_60	TtaACtcaaatcaaTtCtCA	18
49_61	TtaACtcaaatcaaTtCTCA	9
49_62	TtaACtcaaatcaaTTCtCA	17
49_63	TtaACtcaaatcAattctCA	40
49_64	TtaACtcAaatcaattctCA	23
49_65	TtaACtcAaatcaattCtCA	13
49_67	TtaACtcAaatcaatTCtCA	4
49_68	TtaACtcAaatcaaTtctCA	19
49_69	TtaACtcAaatcaaTtCtCA	12
49_70	TtaACtcAaatcaaTtCTCA	9
49_71	TtaACtcAaatcaaTTCtCA	16

CMP ID NO	Compound	% MAPT mRNA of control
49_72	TtaACtCaaatcaattctCA	12
49_73	TtaACtCaaatcaattCtCA	9
49_74	TtaACtCaaatcaattCTCA	4
49_75	TtaACtCaaatcaatTCtCA	4
49_76	TtaACtCAaatcaattctCA	3
49_78	TtaACtCAaatcaaTtctCA	3
49_79	TtaACTCaaatcaattCtCA	6
49_80	TtAactcaaatcaaTtCtCA	11
49_81	TtAactcaaatcaAttCtCA	35
49_82	TtAactcaaatcaAtTCtCA	18
49_83	TtAactcaaatcaATtCtCA	21
49_84	TtAactcaaatcaATTCtCA	36
49_85	TtAactcAaatcaatTCtCA	7
49_86	TtAactcAaatcaaTtCtCA	6
49_87	TtAactCaaatcaattCtCA	19
49_88	TtAactCaaatcaattCTCA	7
49_89	TtAactCaaatcaatTCtCA	6
49_90	TtAactCAaatcaattCtCA	9
49_92	TtAactCAaatcaaTtCtCA	3
49_93	TtAactCAaatcaaTTCtCA	11
49_94	TtAaCtcaaatcaattCtCA	34
49_95	TtAaCtcaaatcaatTCtCA	11
49_96	TtAaCtcaaatcaaTtctCA	56
49_97	TtAaCtcaaatcaaTtCtCA	15
49_98	TtAaCtcaaatcaaTtCTCA	14
49_99	TtAaCtcaaatcaaTTCtCA	30
49_100	TtAaCtcaaatcAattctCA	46
49_101	TtAaCtcAaatcaattctCA	24
49_102	TtAaCtcAaatcaattCtCA	22
49_103	TtAaCtcAaatcaattCTCA	8
49_104	TtAaCtcAaatcaatTCtCA	6
49_105	TtAaCtcAaatcaaTtctCA	28
49_106	TtAaCtcAaatcaaTtCtCA	31
49_107	TtAaCtcAaatcaaTtCTCA	29
49_108	TtAaCtcAaatcaaTTCtCA	38
49_109	TtAaCtCaaatcaattctCA	21
49_110	TtAaCtCaaatcaattCtCA	19
49_111	TtAaCtCaaatcaatTCtCA	9
49_112	TtAaCtCAaatcaattctCA	10
49_113	TtAaCtCAaatcaattCtCA	10
49_114	TtAaCtCAaatcaaTtctCA	6
49_115	TtAActcaaatcaatTCtCA	6
49_116	TtAActcaaatcaaTtCtCA	9
49_117	TtAActcAaatcaattCtCA	11
49_118	TtAActcAaatcaatTCtCA	3
49_119	TtAActcAaatcaaTtCtCA	11
49_120	TtAActCaaatcaattCtCA	33
49_121	TtAActCaaatcaatTCtCA	2
49_123	TtAActCAaatcaatTCtCA	1
49_125	TtAACtcaaatcaattCtCA	6
49_126	TtAACtcaaatcaattCTCA	5
49_127	TtAACtcaaatcaatTCtCA	9
49_128	TtAACtcaaatcaaTtctCA	33

CMP ID NO	Compound	% MAPT mRNA of control
49_129	TtAACtcaaatcaaTtCtCA	12
49_130	TtAACtcaaatcaaTTCtCA	19
49_131	TtAACtcaaatcAattctCA	25
49_132	TtAACtcAaatcaattctCA	15
49_133	TtAACtcAaatcaattCtCA	6
49_134	TtAACtcAaatcaatTCtCA	10
49_135	TtAACtcAaatcaaTtctCA	15
49_136	TtAACtcAaatcaaTtCtCA	22
49_137	TtAACtcAaatcaaTTCtCA	33
49_138	TtAACtCaaatcaattctCA	8
49_139	TtAACtCaaatcaattCtCA	6
49_141	TtAACtCaaatcaatTCtCA	11
49_143	TtAACtCAaatcaaTtctCA	3
49_144	TTaactcAaatcaattCtCA	14
49_145	TTaactcAaatcaatTCtCA	6
49_146	TTaactcAaatcaaTtCtCA	6
49_147	TTaactcAaatcaaTTCtCA	9
49_148	TTaactCAaatcaattCtCA	6
49_149	TTaactCAaatcaatTCtCA	2
49_150	TTaaCtcaaatcaattCtCA	26
49_151	TTaaCtcaaatcaattCTCA	8
49_152	TTaaCtcaaatcaatTCtCA	11
49_153	TTaaCtcaaatcaaTtctCA	41
49_154	TTaaCtcaaatcaaTtCtCA	14
49_155	TTaaCtcaaatcAattctCA	38
49_156	TTaaCtcAaatcaattctCA	23
49_157	TTaaCtcAaatcaattCtCA	13
49_158	TTaaCtcAaatcaattCTCA	4
49_159	TTaaCtcAaatcaatTCtCA	6
49_160	TTaaCtcAaatcaaTtctCA	20
49_161	TTaaCtcAaatcaaTtCtCA	12
49_162	TTaaCtCaaatcaattctCA	18
49_163	TTaaCtCaaatcaattCtCA	10
49_164	TTaaCtCAaatcaattctCA	7
49_166	TTaActcaaatcaaTtCtCA	17
49_167	TTaActCaaatcaattCtCA	7
49_168	TTaActCAaatcaattCtCA	3
49_169	TTaACtcaaatcaaTtCtCA	12
49_170	TTaACtcAaatcaatTCtCA	9
49_171	TTaACtcAaatcaaTtCtCA	25
49_172	TTAactcaaatcaaTtCtCA	16
49_173	TTAactcaaatcaAttCtCA	27
49_174	TTAactcaaatcaAtTCtCA	14
49_175	TTAactcAaatcaatTCtCA	5
49_176	TTAactcAaatcaaTtCtCA	6
49_177	TTAactCaaatcaattCtCA	15
49_178	TTAactCaaatcaattCTCA	4
49_180	TTAactCAaatcaattCtCA	6
49_181	TTAaCtcaaatcaattCtCA	23
49_182	TTAaCtcaaatcaaTtctCA	38
49_183	TTAaCtcaaatcaaTtCtCA	17
49_184	TTAaCtcaaatcAattctCA	40
49_185	TTAaCtcAaatcaattctCA	19

CMP ID NO	Compound	% MAPT mRNA of control
49_186	TTAaCtcAaatcaattCtCA	13
49_187	TTAaCtcAaatcaaTtctCA	13
49_188	TTAaCtCaaatcaattctCA	18
49_189	TTAActcaaatcaattCTCA	3
49_190	TTAActcaaatcaatTCtCA	9
49_191	TTAActcAaatcaatTCtCA	3
49_192	TTAActCaaatcaattCtCA	6
50_1	TTTAactcaaatcaatTCTC	1
51_1	TTTAactcaaatcaaTTCT	10
52_1	CCTTttaattcaTTAG	72
53_1	CAACacctttttaattcATTA	0
54_1	AACAccttttaattCATT	27
55_1	CAtcaacacctttttaaTTCA	100
56_1	CTCAtcaacacctttttaaTT	15
57_1	ACtcatcaacaccttttTAAT	37
58_1	AACtcatcaacaccttTTAA	16
59_1	TAACtcatcaacaccttttTA	18
60_1	TTAActcatcaacacctTTT	12
61_1	TTAactcatcaacacCTTT	4
62_1	TTAactcatcaacaCCTT	3
63_1	TTAActcatcaacACCT	0
64_1	GTTAactcatcaacACC	29
65_1	GTTAactcatcaaCAC	78

Example 3 IC50 values of selected oligonucleotides

The IC50 of some of the best performing oligonucleotides from Example 2 was determined *in vitro* in primary neuronal cells using a 96 well assay.

Primary neuronal cell cultures were prepared as described in the “Materials and Method” section and plated on poly-D-lysine coated 96 well plates at 50,000 cells per well and maintained in Neurobasal media containing B27, glutamax and Penicillin-Streptomycin. ASOs were diluted in water (for IC50 determinations) and added to cells at 1 day post plating (DIV01). For IC_{50} determinations, neurons were treated with a top concentration of 0.5 to 5 µM and a concentration response dilution of about 1:4 was used to define the IC50. CMP ID NO: 66_1, corresponding to ASO-001933 in WO2016/126995, was included as a positive control. Following ASO treatment, neurons were incubated at 37°C for 5 days to achieve steady state reduction of mRNA. Media was removed and cells lysed as follows. Measurement of lysate messenger RNA was performed using the QUANTIGENE® 2.0 Reagent System (AFFYMETRIX®), which quantitated RNA using a branched DNA-signal amplification method reliant on the specifically designed RNA capture probe set. The working cell lysis buffer solution was made by adding 50 µl proteinase K to 5ml of pre-warmed Lysis mix and diluted to 1:4 final dilution with dH_20. The working lysis buffer was added to the plate (150 µl/ well), triturated to mix, sealed and incubated for 30 min at 55°C. Following lysis the wells were stored at -80°C or assayed immediately.

Lysates were diluted in lysis mix dependent on the specific capture probe used (tau or tubulin). 80 µl/ well total were then added to the capture plate (96 well polystyrene plate coated with capture probes). Working probe sets reagents were generated by combining nuclease-free water 12.1 µl, lysis mixture 6.6 µl, blocking reagent 1 µl, specific 2.0 probe set 0.3 µl human *MAPT* catalogue #15486 and either mouse beta 3 tubulin, catalogue #SB-17245, per manufacturer instructions (QUANTIGENE® 2.0 AFFYMETRIX®). Then 20 µl working probe set reagents were added to 80 µl lysate dilution (or 80 µl lysis mix for background samples) on the capture plate. Plates were centrifuged and then incubated for 16-20 hours at 55ºC to hybridize (target RNA capture). Signal amplification and detection of target RNA was begun by washing plates with buffer 3 times to remove unbound material. 2.0 Pre-Amplifier hybridization reagent (100 µl/well) was added, incubated at 55ºC for 1 hour then aspirated and wash buffer was added and aspirated 3 times. The 2.0 Amplifier hybridization reagent was then added as described (100 µl/well), incubated for 1 hour at 55ºC and the wash was repeated as described previously. The 2.0 Label Probe hybridization reagent was added next (100 µl/well), incubated for 1 hour at 50ºC and the wash was repeated as described previously. Lastly, the plates were centrifuged to remove any excess wash buffer and 2.0 Substrate was added (100 µl/well). Plates were incubated for 5 minutes at room temperature and plates were imaged on a PerkinElmer Envision multilabel reader in luminometer mode within 15 minutes.

Data determination: For the gene of interest, the average assay background signal was subtracted from the average signal of each technical replicate. The background-subtracted, average signals for the gene of interest are divided by the background-subtracted average signal for the housekeeping tubulin RNA. The percent inhibition for the treated sample was calculated relative to untreated sample (i.e. the lower the value the larger the inhibition). Variability in background of untreated samples may result in percent inhibition of a treated sample that are equal to or higher than background, and in these cases, percent inhibition is expressed as 100% inhibition of control (i.e. no inhibition). The results are shown in table 7.

Table 7: IC50 of anti-MAPT compounds

CMP ID NO	Compound	Region	IC50 (nM)
9_103	CTTTaatttaatcacTCAT	A	12.2
11_1	CTTTaatttaatcaCTCA	A	9.4
34_1	GAATattacaccATCC	A	32.0
37_1	CAGAatattacaCCAT	A	15.6
49_189	TTAActcaaatcaattCTCA	B	11.8
56_1	CTCAtcaacacctttaaTT	C	44.0
62_1	TTAactcatcaacaCCTT	C	40.5
63_1	TTAActcatcaacACCT	C	37.1
66_1	AtTTCcaaattcactTTtAC	-	44.3

Example 4 *In vivo* tolerability and *in vivo* Tau mRNA reduction

Some of the best performing oligonucleotides from Example 2 were tested *in vivo* in a humanized Tau mouse to assess acute tolerability in CNS as well as MAPT mRNA reduction 3 days or 28 days after a single injection.

Transgenic Tau mice were administered with 100 µg ASO by intracerebroventricular (ICV) injection (see Materials and Method section, Transgenic Tau mouse). CMP ID NO: 66_1, corresponding to ASO-001933 in WO2016/126995, was included as a positive control. Animals were observed for behavioral side effects for one hour following the single injection of ASO ICV. The acute tolerability for the severity of side effects was scored on a scale of zero (no side effects) to 20 (convulsions resulting in euthanasia). The tolerability scale was divided into 5 neurobehavioral categories: 1) hyperactivity 2) decreased activity and arousal 3) motor dysfunction /ataxia 4) abnormal posture and breathing and 5) tremor/convulsions. Each category was scored on a scale of 0-4, with the worst possible total score of 20. Animals were observed for changes in behavior in the home cage, and then they were removed from the home cage for more detailed observations which included measurement of grip strength and righting reflex. Data from acute tolerability of ASO of the invention are presented in table 8.

The MAPT mRNA reduction in right, frontal cortical region was analyzed by qPCR as follows. Collected mouse brain tissue (see Materials and Methods section, Transgenic Tau mouse) was homogenized in a 10x volume of a high salt /sucrose buffer (10 mM Tris-HCl, pH 7.4, 800 mM NaCl, 10% sucrose (w/v), 1 mM EGTA) supplemented with phosphatase inhibitor cocktail sets 2 and 3, 1 mM PMSF (Sigma, Saint Louis, MO), and complete protease inhibitor cocktail EDTA-free (Roche, Indianapolis, IN) using a Quiagen TissueLyzer II. The homogenate was centrifuged at 20,000 x g for 20 minutes at 4°C. The supernatant was centrifuged at 100,000 Xg for 1 hour at 4°C.

For cDNA synthesis and subsequent PCR, 300ng of RNA from brain tissue supernatants was added to 1 well of a 96 well plate (Axygen, PCR-96-C-S). To each well 7.5µl of master mix (5µL of 2.5mM NTP mix and 2.5µL random primers per reaction) was added and the plate was centrifuged at 1000 rpm and placed in thermocycler for 3 min at 70° C. Plates were immediately cooled on ice and 4µl of reaction master mix was added. Prior to PCR, plates were briefly centrifuged to collect sample in bottom of well. cDNA synthesis was carried out at 42° C for 60 min, 95° C for 10 min followed by a hold at 4° C. cDNA Samples were diluted 1:3 with molecular biology grade water and stored at -20° C until further use.

For PCR, each sample was run in triplicate with two probe sets (MAPT: Taqman Expression assays Hs00902193_m1; GAPDH Taqman Expression assays Hs01922876_u1). To each reaction 4 µl of previously diluted cDNA and 6 µL of master mix was added and plates were

centrifuged. Samples were incubated at 95° C for 20 sec follow by 40 cycles at 95° C for 1 sec and 60° C for 20 sec.

Data were analyzed using the delta delta Ct method where each sample was first normalized to GAPDH and then expressed as percent of untreated control (percent inhibition). If the percent inhibition was equal to or higher than in control cells, percent inhibition was expressed as zero inhibition.

Table 8 Acute tolerability in hTau mice and MAPT mRNA reduction 3 days and 4 weeks post treatment *in vivo*

CMP ID NO	Compound	Region	Acute tolerability	% MAPT mRNA of saline	
				Day 3	4 weeks
9_103	CTTTaatttaatcacTCAT	A	0.5	16	16
11_1	CTTTaatttaatcaCTCA	A	0.0	16	18
9_104	CTTTaatttaatcaCtCAT	A	0.25	NA	28
9_102	CTTtAATttaatcactcAT	A	1.75	NA	20
34_1	GAATattacaccATCC	A	0.0	36	20
9_91	CTtTAatttaatcaCtCAT	A	0.50	NA	84
9_83	CTttAATttaatcacTCAT	A	0.75	NA	31
9_17	CtttaATttaatcacTCAT	A	0.50	NA	65
9_88	CTtTAatttaatcactCAT	A	0.50	NA	43
9_96	CTTtaATttaatcactcAT	A	2.50	NA	54
9_95	CTtTAATttaatcactcAT	A	4.13	NA	34
9_93	CTtTAAtttaatcactcAT	A	1.88	NA	52
9_87	CTtTaATttaatcactcAT	A	1.63	NA	46
9_55	CtTTAaTttaatcactcAT	A	2.50	NA	54
37_1	CAGAatattacaCCAT	A	0.0	27	NA
49_189	TTAActcaaatcaattCTCA	B	0.0	29	29
49_38	TtaaCTCAaatcaaTtctCA	B	1.50	NA	18
49_179	TTAactCaaatcaatTCtCA	B	1.0	NA	32
49_51	TtaActCAaatcaattCTCA	B	1.25	NA	31
49_124	TtAActCAaatcaaTtCtCA	B	1.50	NA	48
49_165	TTaaCtCAaatcaaTtctCA	B	0.88	NA	44
49_91	TtAactCAaatcaatTCtCA	B	0.63	NA	60
49_52	TtaActCAaatcaatTCtCA	B	2.88	NA	56
49_140	TtAACtCaaatcaattCTCA	B	0.25	NA	43
49_66	TtaACtcAaatcaattCTCA	B	0.0	NA	36
49_142	TtAACtCAaatcaattCtCA	B	0.5	NA	36
49_122	TtAActCAaatcaattCtCA	B	0.75	NA	56
49_77	TtaACtCAaatcaattCtCA	B	1.13	NA	55
50_1	TTTAactcaaatcaatTCTC	B	NA	26	NA
53_1	CAACacctttttaattcATTA	C	NA	21	NA
56_1	CTCAtcaacacctttttaaTT	C	0.2	25	NA
62_1	TTAactcatcaacaCCTT	C	0.0	39	28
63_1	TTAActcatcaacACCT	C	0.5	13	NA
66_1	AtTTCcaaattcactTTtAC	-	0.83	37	44

NA = not assessed

Example 5: *in vitro* efficacy in human embryonic stem cell (hESC) derived neurons.

Selected ASO's from example 2 were tested at three different concentrations (200 nM, 8 nM and 0.32 nM) in an alternative *in vitro* assay using human embryonic stem cell (hESC) derived neurons. For comparative purposes two prior art oligonucleotides targeting MAPT were included, namely CMP ID NO: 66_1 corresponding to ASO-001933 in WO2016/126995 and CPM ID NO: 67:1 corresponding to compound No 814907 in WO2018/064593.

Culturing and ASO treatment of human embryonic stem cells (ESCs):

Neural stem cells (NSCs) were derived from human ESCs according to published procedures (Chambers et al. 2009 Nat. Biotech. 7, 275–280). The neural stem cells (NSCs) were proliferated into ventralized progenitors during 1 week in SFA medium, and was then differentiated into neurons in BGAA medium during 6 weeks, for media content, please see the Materials and methods section.

Cells were seeded at a density of 10,000 cells/cm^2 in N2B27 + SFA medium in a flask coated with poly-ornithine and laminin. Media was changed at day 4. After 7 days in N2B27 + SFA medium cells were trypsinized, and seeded as ventralized progenitors in N2B27+BGAA media at a density of 50,000 cell/well in 96 well plates.

Media was changed twice a week and treatment with ASO was started at the first media change and continued for 6 weeks. Then cells were harvested as decribed below.

qPCR analysis:

Treated neurons were harvested as follows: removal of media followed by addition of 125 µL PURELINK®Pro 96 Lysis buffer and 125 µL 70% ethanol. RNA was purified according to the manufacture's instruction and eluted in a final volume of 50 µL water, resulting in an RNA concentration of 10-20 ng/µL. Next, RNA was diluted 10 fold in water prior to the one-step qPCR reaction.

For the one-step qPCR reaction, qPCR-mix (qScriptTMXLE 1-step RT-qPCR TOUGHMIX®Low ROX from QauntaBio) was mixed with two Taqman probes at a ratio 10:1:1 (qPCR mix: probe1:probe2) to generate the mastermix. The qPCR was performed as technical replicates and Taqman probes were acquired from LifeTechnologies: MAPT_Hs00902193_m1; GAPDH 4325792 (house keeping gene used for normalization).

The mastermix (6 µL) and RNA (4µL, 1-2 ng/µL) were then mixed in a qPCR plate (MICROAMP®optical 384 well, catalog no. 4309849). After sealing the plate, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a ViiaTM 7 system (Applied Biosystems, Thermo). The following PCR conditions were used: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec, followed by a temperature decrease of 1.6 °C/sec, followed by 60 °C for 45 sec. The data was analyzed using the QuantStudioTM Real_time PCR Software. The percent inhibition for the ASO treated samples was calculated relative to the

control treated samples (low values indicate high reduction of MAPT). The results are shown in table 9 as the average of the two technical repeats.

Tau protein and pTau protein measurement in hESC neurons:

PBS-washed cells were extracted into a buffer containing Cytobuster protein extraction reagent (Merck-Millipore #71009), 1% Phosphatase Inhibitor Cocktail 3 (Sigma #P0044), 1% Proteases Inhibitor Set III (Calbiochem #539134), 1% DNAse-I (Roche # 4536282001) and 10 mM $MgCl_2$. The cell extract wss lysed by pipetting up and down and then stored at -20°C until use.

Total Tau levels in the cell extracts were measured by AlphaLISA using an in house assay format comprising the Tau-specific antibodies 5A6 (DSHB Antibody Registry ID: AB_528487) and Roche in house Tau monoclonal antibody Tau 4/2. The latter antibody was generated by immunizing mice with human full-length Tau i.e. longest human brain isoform, 441 amino acids. Tau 4/2 binds to an C-terminal epitope in Tau located between amino acids 369 and 441. Briefly, cell extracts were diluted into AlphaLISA Hi Block assay buffer (PerkinElmer AL004C) and mixed with biotinylated 5A6 and Tau 4/2-coated AlphaLISa acceptor beads. After incubation for 1hr at room temperature, streptavidin-coated donor beads are added to the mixture. After incubation for 30 min, the samples were measured in an Envision plate reader (ex 680 nm, em 615 nm). A standard curve was constructed using recombinant human Tau (Merck-Millipore #AG960).

PhosphoTau (Tau-pS422) levels in the cell extracts were measured by AlphaLISA using the Roche in house assay format comprising Tau-specific antibody 5A6 (DSHB Antibody Registry ID: AB_528487) and Tau-pS422-specific antibody 5.6.11 (described in WO2010/142423 and Collin et al 2014 Brain vol 137 P 2834-2846). Cell extracts are diluted into assay buffer B before assay. Buffer B comprises 25 mM HEPES pH7.4, 0.5% Triton X-100, 0.1% Top Block (LuBio Science), 1 mg/ml Dextran500, 10 % ELISA Blocking Reagent (Roche). A standard curve was prepared using ERK-phosphorylated Tau prepared as follows: recombinant human Tau was produced as described in Grueninger *et al* (Neurobiology of Disease 37 [2010] pp294-306). Recombinant His-tagged ERK2 (produced in house) was activated by incubation with activated MEKK1 (produced in house). Activated ERK2 was then incubated with Tau at a molar ratio of 1:50 in buffer containing 2mM ATP. ERk2 was subsequently removed by passage over Ni-NTA agarose (Qiagen). The extent of phosphorylation at S422 was subsequently determined by mass spectroscopy.

The results are shown in table 9.

Table 9 MAPT reduction and Tau protein reduction in hESC derived neurons following treatment at three different concentrations.

CMP ID NO	MAPT as % of control			Total Tau protein % of control			PhosphoTau protein % of control		
ASO conc (nM)	200	8	0.32	200	8	0.32	200	8	0.32
9_104	5.4	36.6	100.9	7.0	40.3	88.3	0.6	12.0	54.0
9_103	1.2	15.6	71.8	1.8	23.2	66.2	0.1	19.8	92.9
11_1	1.0	12.5	72.3	1.5	25.9	65.1	0.1	17.5	70.4
49_38	5.7	36.3	83.5	6.8	45.5	79.6	1.3	51.6	116.6
49_189	7.0	36.5	90.2	10.4	48.1	102.9	5.0	59.6	137.3
53_1	4.8	32.9	79.4	8.8	45.7	79.0	3.1	48.6	127.6
66_1	11.0	40.2	81.9	10.9	48.4	69.9	3.6	57.9	94.2
9_102	2.0	34.9	99.0	3.0	44.3	87.4	0.3	37.7	113.8
49_179	10.5	53.6	96.4	12.4	70.7	91.7	3.5	76.0	112.0
49_51	6.7	39.8	76.1	5.9	60.2	92.2	1.3	68.2	161.6
56_1	2.8	36.8	93.2	3.6	49.3	96.6	0.3	37.9	111.9
62_1	4.5	38.6	86.2	5.8	48.4	88.1	1.5	47.8	119.0
67_1	31.1	57.0	86.0	35.9	58.4	79.2	26.2	65.8	115.5

Example 6: IC50 of selected compounds from Example 5

A selection of the efficacious ASO's from example 5 were tested in the same hESC derived neuron assay together with the two prior art controls (CMP ID 66_1 and CMP ID 67_1) to determine IC50 of the target mRNA reduction as well as the Tau protein reduction.

The experiment was conducted as described in example 5 using the following oligonucleotide concentrations: 1000, 200, 40, 8, 1.6, 0.32, 0.064, 0.0128, 0.00256 nM.

The IC50 values were fitted using the GraphPad PRISM software. The results are shown in table 10.

Table 10 IC50 and max efficacy (as % of control) with respect to MAPT and TAU protein

CMP ID NO	Compound	IC50 MAPT (nM)	Max efficacy MAPT	IC50 TAU (nM)	Max efficacy MAPT
9_103	CTTTaatttaatcacTCAT	2.0	0.6	1.4	1.1
49_38	TtaaCTCAaatcaaTtctCA	8.2	2.6	6.1	1.6
53_1	CAACacctttttaattcATTA	7.6	1.7	15.0	1.9
66_1	AtTTCcaaattcactTTtAC	9.7	8.1	11.8	4.9
67_1	$CC_oGTTttcettacceeAC_oCCT$	17.7	22.6	43.3	23.4

From these data it can be seen that CMP ID NO 9_103 and 49_38 of the invention are more efficacious and have a better IC50 than the prior art compounds on all parameter, whereas CMP ID NO 53_1 seems to have a better maximal knockdown than the prior art compounds and a similar IC50 as CMP ID NO: 66_1.

Example 7 *in vivo* activity in specific brain regions of hTau mouse

A selection of the ASO's from example 5 were tested for their ability to reduce the target *in vivo* in specific brain regions of a humanized Tau mouse (hTau mouse) four weeks after a single low dose ICV administration.

The humanized Tau mouse used in this example is an in house Roche hTau P301S transgenic mouse line which overexpresses human Tau (longest human brain isoform) with the point mutation P301S on a mouse Tau background.

Humanized Tau mice were administered with 25 µg ASO by intracerebroventricular (ICV) injection as described below. CMP ID NO: 66_1, corresponding to ASO-001933 in WO2016/126995, was included for comparative purposes.

In vivo ICV mouse evaluation:

Animal Care:

Animals of mixed sex with a weight of 16-23-grams were held in colony rooms maintained at constant temperature (22 ± 2°C) and humidity (55 ± 10%) and illuminated for 12 hours per day (lights on at 0600 hours). All animals had ad libitum access to food and water throughout the studies. All mouse protocols were approved by the Danish National Committee for Ethics in Animal Experiments.

Intra-cerebroventricular injections:

The compounds were administered to mice by intracerebroventricular (ICV) injections. 6-8 mice of mixed sexes were included in each treatment group. Prior to the ICV dosing, the mice were weighed and anaesthetized with isofluran or Propofol (30mg/kg). Intracerebroventricular injections were performed using a Hamilton micro syringe with a FEP catheter fitted with a 23 gauge needle fixed in a stand adjusted to penetrate the correct distance (3.9mm) through the skin and skull and into the right lateral ventricle. The mouse to be injected was held at the scruff of the neck with the thumb and first fingers of one hand. Applying gentle but firm pressure, the head was pressed upwards so that the needle pierced the skull 1-2mm right of the midline (medio lateral) and 1-2mm behind the eye. The 5 µl bolus of test compound or vehicle was injected over 30 seconds with a previously determined infusion rate. To avoid reflux the mouse was held in this position for another 5 seconds before carefully being pulled downwards, away from the needle. This procedure required no surgery or incision. Animals were placed under a heating lamp until they recovered from the procedure.

At study termination (4 weeks), brain tissue (cortex, medulla/pons and midbrain) was collected on dry ice for analysis of tau mRNA and protein.

Tissue homogenization:

Mouse brain tissue samples were homogenized in the MagNA Pure LC RNA Isolation Tissue Lysis Buffer (Roche, Indianapolis, IN) using a Qiagen TissueLyzer II. The homogenates were incubated for 30 minutes at room temperature for complete lysis. After lysis the homogenates were centrifuged for 3 minutes at 13000rpm and the supernatant used for analysis.

RNA purification from tissue:

RNA was purified from 350µL of supernatant using the MagNA Pure 96 instrument using the kit Cellular RNA Large Volume Kit (Roche, Indianapolis, IN). RNA samples were normalized to 2ng/µL in RNase-Free water and stored at -20° C until further use. MAPT mRNA levels were quantified as described in example 5.

Tau protein measurement from mouse brain tissue:

Pre-weighed frozen tissue was extracted with 10 volumes (wt/vol) of extraction buffer comprising 10 mM TrisCl pH 7.4, 800 mM NaCl, 1 mM EGTA, 10 % sucrose, 1% Phosphatase Inhibitor Cocktail 3 (Sigma #P0044), 1% Proteases Inhibitor Set III (Calbiochem #539134). A homogenate was prepared using the PreCellys tissue disruptor (20 sec, 6500 rpm). The homogenate was then centrifuged at 10'000x*g* for 20 min at 4°C and the supernatant retained for analysis.

Tau levels in the extracts were measured by AlphaLISA using the total Tau AlphaLISA kit supplied by Perkin Elmer (Cat. Nr. AL271C). The antibodies used in this assay were BT2 and Tau-12 provided with the kit, both of which bind to the central region of tau. Extracts were diluted into HiBlock assay buffer and 5 µl of each sample was then used in assay. The assay was otherwise performed as described by the supplier

Results from mRNA and protein quatification are shown in table 11

Table 11: *in vivo* efficacy in selected brain regions 4 weeks after a single ICV dose of 25 µg ASO. MAPT mRNA as % control are shown for four brain regions and Tau protein as % of control is shown for one brain region

CMP ID NO	mRNA %ctrl								Protein %ctrl	
	Cortex A1		Cortex A2		Medulla-Pons		Midbrain		CortexB2	
	Avg	Std	Avg	Std	Avg	Std	Avf	Std	Avg	Std
9_104	74	12	77	14	68	19	65	18	73	18
9_103	80	13	80	10	66	17	64	12	69	16
11_1	58	12	62	15	54	16	48	19	63	11
49_38	63	12	67	9	55	18	49	16	76	15
49_189	75	5	70	10	54	4	55	6	84	13
53_1	80	10	93	7	81	12	81	16	101	11
66_1	94	20	98	6	101	4	99	11	112	8

From these data it can be observed that even at the fairly low concertation of 25 µg, reduction of more than 20 % is seen in most brain regions for the compounds of the invention, where as the control compound show vertually no reduction of the target at this concentration.

Example 8 in vivo dose response and time course in the hTau mouse

The dose response of two ASO's (CMP ID NO: 9_103 and 49_189) was evaluated using three different doses (25, 50 and 100 µg) and target reduction was measure in specific brain regions 1 week and 4 weeks after administration. For comparative purposes two prior art compounds (CMP ID NO: 66_1_103 and 67_1) were included at some of the doses in the one-week study.

The experiment was essentially conducted as described in example 7. Tau protein was however not measured in the dose response study which was run for 1 week since the Tau protein has a half life beyond one week. The results are shown in Tables 12 and 13.

Table 12 *in vivo* efficacy in selected brain regions 1 week after a single ICV dose at 25 µg, 50 µg or 100 µg ASO or 4weeks after a single ICV dose at 100 µg ASO. MAPT mRNA as % control are shown for four brain regions.

Brain region	ASO conc µg	CMP ID NO	9_103	49_38	66_1	67_1	9_103	49_38
		Time	1 week				4 weeks	
Cortex A1	25	Avg	51	69	NA	NA	NA	NA
		Std	13	8	NA	NA	NA	NA
	50	Avg	52	52	68	NA	NA	NA
		Std	12	14	14	NA	NA	NA
	100	Avg	33	39	60	71	36	37
		Std	10	24	12	25	17	26
Cortex A2	25	Avg	73	59	NA	NA	NA	NA
		Std	12	12	NA	NA	NA	NA
	50	Avg	68	39	73	NA	NA	NA
		Std	15	7	8	NA	NA	NA
	100	Avg	42	43	77	63	51	46
		Std	21	30	12	20	13	30
Midbrain	25	Avg	79	43	NA	NA	NA	NA
		Std	20	4	NA	NA	NA	NA
	50	Avg	50	26	68	NA	NA	NA
		Std	14	6	11	NA	NA	NA
	100	Avg	51	38	78	76	60	38
		Std	29	31	21	27	28	35
Medulla-Pons	25	Avg	81	41		NA	NA	NA
		Std	21	6		NA	NA	NA
	50	Avg	57	26	70	NA	NA	NA
		Std	18	5	10	NA	NA	NA
	100	Avg	58	37	80	82	61	40
		Std	34	31	23	28	29	33

NA = not assessed

Table 13 *in vivo* reduction of Tau protein as % of control 4 weeks after a single ICV dose at 100 µg ASO.

Brain region	**Cortex B1**	
CMP ID NO	Avg	Std
9_103	56	18
49_38	43	35

From the data in table 12 and 13 it can be seen that the compounds of the invention perform significantly better than the prior art compounds, in particular when dosed at 100 µg. It can also be observed that the MAPT reduction is maintained over the 4 weeks. Furthermore, the compounds of the invention show a significant reduction of Tau protein after 4 weeks treatment with a single dose of 100 µg compound.

CLAIMS

1. An antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of at least 10 nucleotides in length with at least 90% complementarity, to contiguous nucleotides within position 12051 to 12111, 39562 to 39593 or 72837 to 72940 of SEQ ID NO: 1.

2. The antisense oligonucleotide of claim 1, wherein the contiguous nucleotide sequence is at least 16 nucleotides and 100% complementary to contiguous nucleotides within position12060 to 12078, 39573 to 39592 or position 72862-72890 of SEQ ID NO: 1.

3. The antisense oligonucleotide of claim 1 or 2, wherein the oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NO: 9, 11, 49, 53, 56 and 62.

4. The antisense oligonucleotide of any one of claims 1-3, wherein the oligonucleotide is capable of reducing the expression of Tau.

5. The antisense oligonucleotide of any one of claims 1-4, wherein the contiguous nucleotide sequence comprises one or more 2' sugar modified nucleosides.

6. The antisense oligonucleotide of claim 5, wherein the one or more 2' sugar modified nucleoside is 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.

7. The antisense oligonucleotide of any one of claims 5 or 6, wherein the contiguous nucleotide sequence comprises 4 to 8 LNA nucleosides.

8. The antisense oligonucleotide of any one of claims 1-7, wherein at least 80% of the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

9. The antisense oligonucleotide of any one of claims 1-8, wherein the oligonucleotide is capable of recruiting RNase H.

10. The antisense oligonucleotide of claim 9, wherein the antisense oligonucleotide, or contiguous nucleotide sequence thereof, consists or comprises a gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise 1 - 8 nucleosides, of which 2 - 5 are 2' sugar modified and defines the 5' and 3' end of the F and F' region, and the G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH, such as a region comprising 6 – 16 DNA nucleosides.

11. The antisense oligonucleotide according to any one of claims 1 – 10, wherein the antisense oligonucleotide is a compound selected from the group consisting of

CTTtAATttaatcactcAT	SEQ ID NO: 9; CMP ID NO: 9_102
CTTTaatttaatcacTCAT	SEQ ID NO: 9; CMP ID NO: 9_103

CTTTaatttaatcaCtCAT	SEQ ID NO: 9; CMP ID NO: 9_104
CTTTaatttaatcaCTCA	SEQ ID NO: 11; CMP ID NO: 11_1
TtaaCTCAaatcaaTtctCA	SEQ ID NO: 49; CMP ID NO: 49_38
TtaActCAaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_51
TTAactCaaatcaatTCtCA	SEQ ID NO: 49; CMP ID NO: 49_179
TTAActcaaatcaattCTCA	SEQ ID NO: 49; CMP ID NO: 49_189
CAACacctttttaattcATTA	SEQ ID NO: 53; CMP ID NO: 53_1
CTCAtcaacacctttttaaTT	SEQ ID NO: 56; CMP ID NO: 56_1
TTAactcatcaacaCCTT	SEQ ID NO: 62; CMP ID NO: 62_1

wherein capital letters are beta-D-oxy LNA nucleosides, lowercase letters are DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

12. The antisense oligonucleotide according to any one of claims 1 – 11, wherein the antisense oligonucleotide is CMP ID NO: 9_103 as shown in Fig. 2.

13. The antisense oligonucleotide according to any one of claims 1 – 11, wherein the antisense oligonucleotide is CMP ID NO: 9_104 as shown in Fig. 3.

14. The antisense oligonucleotide according to any one of claims 1 – 11, wherein the antisense oligonucleotide is CMP ID NO: 11_1 as shown in Fig. 4.

15. The antisense oligonucleotide according to any one of claims 1 – 11, wherein the antisense oligonucleotide is CMP ID NO: 49_38 as shown in Fig. 5.

16. The antisense oligonucleotide according to any one of claims 1 – 11, wherein the antisense oligonucleotide is CMP ID NO: 49_189 as shown in Fig. 6.

17. A conjugate comprising the antisense oligonucleotide according to any one of claims 1 – 16, and at least one conjugate moiety covalently attached to said oligonucleotide.

18. A pharmaceutically acceptable salt of the antisense oligonucleotide according to any one of claims 1 – 16, or the conjugate according to claim 17.

19. A pharmaceutical composition comprising the antisense oligonucleotide of any one of claims 1-16 or the conjugate of claim 17 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

20. An *in vivo* or *in vitro* method for modulating Tau expression in a target cell which is expressing Tau, said method comprising administering an antisense oligonucleotide of any one of claims 1-16 or the conjugate according to claim 17 or the pharmaceutical composition of claim 19 in an effective amount to said cell.

21. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of any one of claims 1 - 16

or the conjugate according to claim 17 or the pharmaceutical composition of claim 19 to a subject suffering from or susceptible to the disease.

22. The method of claim 21, wherein the disease is selected from the group consisting of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

23. The method of claim 22, wherein the disease is progressive supranuclear palsy (PSP).

24. The antisense oligonucleotide of any one of claims 1 - 16 or the conjugate according to claim 17 or the pharmaceutical composition of claim 19 for use in medicine.

25. The antisense oligonucleotide of any one of claims 1 - 16 or the conjugate according to claim 17 or the pharmaceutical composition of claim 19 for use in the treatment or prevention of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto-temporal dementia (FTD) or FTDP-17.

26. The antisense oligonucleotide, conjugate or pharmaceutical composition for use in the treatment of claim 25, wherein the diseas is progressive supranuclear palsy (PSP).

27. Use of the antisense oligonucleotide of claim 1 - 16 or the conjugate according to claim 17 or the pharmaceutical composition of claim 19, for the preparation of a medicament for treatment or prevention of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.