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

The present disclosure 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.

The disclosure 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.

In one aspect, the disclosure provides an antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of at least ~~10~~ 16 nucleotides ~~in length~~ with ~~at least 90%~~100% complementarity~~,~~ to contiguous nucleotides within position ~~12051 to 12111, 39562 to 39593 or 72837 to 72940~~12060 to 12078 of SEQ ID NO: 1, and wherein the antisense oligonucleotide is capable of reducing the expression of Tau.

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 another aspect, the disclosure provides a conjugate comprising the antisense oligonucleotide as defined herein, and at least one conjugate moiety covalently attached to said oligonucleotide.

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

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

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

The disclosure 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 disclosure in an effective amount to said cell.

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

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

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

The oligonucleotide or composition of the disclosure is used for the treatment or prevention of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

In another aspect, the disclosure provides the antisense oligonucleotide as defined herein, or the conjugate as defined herein, or the pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein for use in the treatment or prevention of a disease selected from the group consisting of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

In another aspect, the disclosure provides use of the antisense oligonucleotide as defined herein or the conjugate as defined herein, or the pharmaceutically acceptable salt as defined herein, or the pharmaceutical composition as defined herein, in the preparation of a medicament for treatment or prevention of a disease selected from the group consisting 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)

CLAIMS

1. An antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of at least ~~10~~ 16 nucleotides ~~in length~~ with ~~at least 90%~~100% complementarity~~,~~ to contiguous nucleotides within position ~~12051 to 12111, 39562 to 39593 or 72837 to 72940~~12060 to 12078 of SEQ ID NO: 1, and wherein the antisense oligonucleotide is capable of reducing the expression of Tau.

~~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.~~2. The antisense oligonucleotide of claim 1 ~~or 2~~, wherein the oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NO: 9~~,~~ and SEQ ID NO: 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.~~3. The antisense oligonucleotide of ~~any one of claims 1-4~~claim 1 or claim 2, wherein the contiguous nucleotide sequence comprises one or more 2’ sugar modified nucleosides.

~~6.~~4. The antisense oligonucleotide of claim ~~5~~3, 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.~~5. The antisense oligonucleotide of any one of claim~~s~~ ~~3~~5 or claim~~6~~ 4, wherein the contiguous nucleotide sequence comprises 4 to 8 LNA nucleosides.

~~8.~~6. The antisense oligonucleotide of any one of claims ~~1-7~~1-5, wherein at least 80% of the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

~~9.~~7. The antisense oligonucleotide of any one of claims ~~1-8~~1-6, wherein the oligonucleotide is capable of recruiting RNase H.

~~10.~~8. The antisense oligonucleotide of claim ~~9~~7, 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.~~9. The antisense oligonucleotide ~~according to~~of any one of claims 1 – ~~10~~8, 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.~~

10. The antisense oligonucleotide of any one of claims 1 – 9, wherein the antisense oligonucleotide is CMP ID NO: 9_102.

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

~~14.~~12. The antisense oligonucleotide ~~according to~~of any one of claims 1 – ~~11~~9, 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.~~13. A conjugate comprising the antisense oligonucleotide ~~according to~~of any one of claims 1 – ~~16~~12, and at least one conjugate moiety covalently attached to said oligonucleotide.

~~18.~~14. A pharmaceutically acceptable salt of the antisense oligonucleotide ~~according to~~of any one of claims 1 – ~~16~~12, or the conjugate ~~according to~~of claim ~~17~~13.

~~19.~~15. A pharmaceutical composition comprising the antisense oligonucleotide of any one of claims ~~1-16~~1-12, or the conjugate of claim ~~17~~ 13, or the pharmaceutically acceptable salt of claim 14, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

~~20.~~16. An *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~~1-12, or the conjugate ~~according to~~of claim ~~17~~ 13, or the pharmaceutically acceptable salt of claim 14, or the pharmaceutical composition of claim ~~19~~ 15 in an effective amount to said cell.

~~21.~~17. The antisense oligonucleotide of any one of claims ~~1 - 16~~1 – 12, or the conjugate ~~according to~~of claim ~~17~~ 13, or the pharmaceutically acceptable salt of claim 14, or the pharmaceutical composition of claim ~~19~~ 15 for use in medicine.

~~22.~~18. The antisense oligonucleotide of any one of claims 1 - ~~16~~ 12, or the conjugate ~~according to~~of claim ~~17~~ 13, or the pharmaceutically acceptable salt of claim 14, or the pharmaceutical composition of claim ~~19~~ 15 for use in the treatment or prevention of a disease selected from the group consisting of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

~~23.~~19. The antisense oligonucleotide, conjugate, pharmaceutically acceptable salt, or pharmaceutical composition for use in the treatment of claim ~~22~~18, wherein the disease is progressive supranuclear palsy (PSP).

20. The antisense oligonucleotide, conjugate, pharmaceutically acceptable salt, or pharmaceutical composition for use in the treatment of claim 18, wherein the disease is Alzheimer’s disease (AD).

~~24.~~21. Use of the antisense oligonucleotide of claim ~~1 - 16~~1 - 12 or the conjugate ~~according to~~of claim ~~17~~ 13, or the pharmaceutically acceptable salt of claim 14, or the pharmaceutical composition of claim ~~19~~15, in the preparation of a medicament for treatment or prevention of a disease selected from the group consisting of Alzheimer's disease (AD), progressive supranuclear palsy (PSP), fronto- temporal dementia (FTD) or FTDP-17.

~~25.~~22. The use of claim ~~24~~ 21, wherein the disease is progressive supranuclear palsy (PSP).

23. The use of claim 21, wherein the disease is Alzheimer’s disease (AD).