ALPHA-SYNUCLEIN ANTISENSE OLIGONUCLEOTIDES AND USES THEREOF

FIELD OF DISCLOSURE

The present disclosure relates to antisense oligomeric compounds (ASOs) that target alpha-synuclein (*SNCA*) transcript in a cell, leading to reduced expression of alpha-synuclein (SNCA) protein. Reduction of SNCA protein expression can be beneficial for a range of medical disorders, such as multiple system atrophy, Parkinson's disease, Parkinson's Disease Dementia (PDD), and dementia with Lewy bodies.

BACKGROUND

Alpha-synuclein (SNCA), a member of the synuclein protein family, is a small soluble protein that is expressed primarily within the neural tissues. *See* Marques O *et al.*, *Cell Death Dis*. 19: e350 (2012). It is expressed in many cell types but is predominantly localized within the presynaptic terminals of neurons. While the precise function has yet to be fully elucidated, SNCA has been suggested to play an important role in the regulation of synaptic transmission. For instance, SNCA functions as a molecular chaperone in the formation of SNARE complexes, which mediate the docking of synaptic vesicles with the presynaptic membranes of neurons. SNCA can also interact with other proteins like the microtubule-associated protein tau, which helps stabilize microtubules and regulate vesicle trafficking.

Due to SNCA's role in the regulation of synaptic transmission, alterations of SNCA expression and/or function can disrupt critical biological processes. Such disruptions have been thought to contribute to α-synucleinopathies, which are neurodegenerative diseases characterized by abnormal accumulation of SNCA protein aggregates within the brain. Accordingly, insoluble inclusions of misfolded, aggregated, and phosphorylated SNCA protein are a pathological hallmark for diseases such as Parkinson's disease (PD), Parkinson's Disease Dementia (PDD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). *See* Galvin JE *et al.*, *Archives of Neurology* 58: 186-190 (2001); and Valera E *et al.*, *J Neurochem* 139 Suppl 1: 346-352 (Oct. 2016)

α-Synucleinopathies, such as Parkinson's disease, are highly prevalent progressive neurodegenerative brain disorders, especially among the elderly. *See* Recchia A *et al.*, *FASEB J.* 18: 617-26 (2004). It is estimated that approximately seven to ten million people worldwide are living with such disorders, with about 60,000 new cases each year in the United States alone. Medication costs for an individual person can easily exceed $2,500 a year and therapeutic surgery

can cost up to $100,000 per patient. Therefore, a more robust and cost-effective treatment options are greatly needed.

US 2008/0003570 describes translation enhancer elements on alpha-synuclein methods for identifying compounds that modulate alpha-synuclein.

WO 2012/068405 discloses modified antisense oligonucleotides targeting alpha-synuclein.

WO 2005/004794, WO 2005/045034, WO 2006/039253, WO 2007/135426, US 2008/0139799, WO 2008/109509, WO 2009/079399, WO 2012/027713 all describe nucleic acid molecules acting via the RISC complex in the cytosol, such as siRNA molecules. Such molecules are not capable of targeting introns in the SNCA transcript.

WO 2011/041897, WO 2011/131693 and WO 2014/064257 describe conjugations of nucleic acid molecules for delivery to CNS to modulate target molecules in the CNS one of these being alpha-synuclein.

SUMMARY OF DISCLOSURE

The present disclosure is directed to antisense oligonucleotide (ASOs) comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is at least 90% complementary to an intron nucleic acid region within an alpha-synuclein (*SNCA*) transcript. In some embodiments, the *SNCA* transcript comprises SEQ ID NO: 1 and the ASOs of the present disclosure are capable of inhibiting the expression of the human *SNCA* transcript in a cell which is expressing the human *SNCA* transcript.

In some embodiments the intron region is selected from intron 1 corresponding to nucleotides 6336 - 7604 of SEQ ID NO: 1; intron 2 corresponding to nucleotides 7751 - 15112 of SEQ ID NO: 1; intron 3 corresponding to nucleotides 15155 - 20908 of SEQ ID NO: 1 or intron 4 corresponding to nucleotides 21052 - 114019 of SEQ ID NO: 1.

In further embodiments the antisense oligonucleotides (ASOs) comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is at least 90% complementary to a nucleic acid sequence within an alpha-synuclein (*SNCA*) transcript, wherein the nucleic acid sequence is selected from the group consisting of ; i) nucleotides 21052 - 29654 of SEQ ID NO: 1;; ii) nucleotides 30931 – 33938 of SEQ ID NO: 1;; iii)nucleotides 44640 – 44861 of SEQ ID NO: 1; ; iv)nucleotides 47924 – 58752 of SEQ ID NO: 1; ; v) nucleotides 4942 – 5343 of SEQ ID NO: 1; ; vi) nucleotides 6336 – 7041 of SEQ ID NO: 1;; vii) nucleotides 7329 – 7600 of SEQ ID NO: 1; ; viii)nucleotides 7751 – 7783 of SEQ ID NO: 1; ; ix)nucleotides 8277 – 8501 of SEQ ID NO: 1; ; x) nucleotides 9034 – 9526 of SEQ ID NO: 1; ; xi) nucleotides 9982 –

14279 of SEQ ID NO: 1; ; xii)nucleotides 15204 – 19041 of SEQ ID NO: 1; ; xiii) nucleotides 20351 – 20908 of SEQ ID NO: 1; xiv) nucleotides 34932 – 37077 of SEQ ID NO: 1; ; xv)nucleotides 38081 – 42869 of SEQ ID NO: 1;; xvi) nucleotides 38081 – 38303 of SEQ ID NO: 1; xvii)nucleotides 40218 – 42869 of SEQ ID NO: 1; xvii) nucleotides 46173 – 46920 of SEQ ID NO: 1; ; xix) nucleotides 60678 – 60905 of SEQ ID NO: 1; ; xx) nucleotides 62066 – 62397 of SEQ ID NO: 1; ; xxi) nucleotides 67759 – 71625 of SEQ ID NO: 1; ; xxii) nucleotides 72926 – 86991 of SEQ ID NO: 1; ; xxiii) nucleotides 88168 – 93783 of SEQ ID NO: 1; ; xxiv) nucleotides 94976 – 102573 of SEQ ID NO: 1; ; xxv) nucleotides 104920 – 107438 of SEQ ID NO: 1; ; xxvi) nucleotides 106378 – 106755 of SEQ ID NO: 1;; xxvii) nucleotides 106700 – 106755 of SEQ ID NO: 1; ; xxviii) nucleotides 108948 – 114019 of SEQ ID NO: 1; and; xxix) nucleotides 114292 – 116636 of SEQ ID NO: 1.

In certain embodiments, the contiguous nucleotide sequence comprises or consists of consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353.

In some embodiments, the contiguous nucleotide sequence comprises at least one nucleotide analogue. In some embodiments, the antisense oligonucleotide is a gapmer. The gapmer can be comprised of the formula of 5'-A-B-C-3', wherein, (i) region B is a contiguous sequence of at least 6 DNA units, which are capable of recruiting RNase; (ii) region A is a first wing sequence of 1 to 10 nucleotides, wherein the first wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 3' end of A; and (iii) region C is a second wing sequence of 1 to 10 nucleotides, wherein the second wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 5' end of C.

In certain embodiments, the nucleotide analogue or analogues are high affinity analogues such as the 2’ sugar modified nucleosides selected from the group consisting of Locked Nucleic Acid (LNA); 2'-O-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), constrained ethyl nucleoside (cEt), 2'-O-methyl nucleic acid (2'-OMe), 2'-O-methoxyethyl nucleic acid (2'-MOE), and any combination thereof. In some embodiments, the nucleotide analogue or analogues comprise a bicyclic sugar. In certain embodiments, the bicyclic sugar comprises cEt, 2',4'-constrained 2′-O-methoxyethyl (cMOE), LNA, α-L-LNA, β-D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, or thio-LNA. In some embodiments, the nucleotide analogue or analogues comprise an LNA.

In some embodiments, the antisense oligonucleotide has an *in vivo* tolerability less than or equal to a total score of 4, wherein the total score is the sum of a unit score of five categories, which are 1) hyperactivity; 2) decreased activity and arousal; 3) motor dysfunction and/or ataxia; 4) abnormal

posture and breathing; and 5) tremor and/or convulsions, and wherein the unit score for each category is measured on a scale of 0-4. In certain embodiments, the *in vivo* tolerability is less than or equal to the total score of 3, the total score of 2, the total score of 1, or the total score of 0.

In some embodiments, the nucleotide sequence of the antisense oligonucleotides comprises, consists essentially of, or consists of a sequence selected from the group consisting of from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 with a design selected from the group consisting of the designs in Figures 1A to 1C, wherein the upper case letter is a sugar modified nucleoside and the lower case letter is DNA. In certain embodiments, the antisense oligonucleotide or the contiguous nucleotide sequence thereof has a the chemical structure selected from the group consisting of ASO-008387; ASO-008388; ASO-008501; ASO-008502; ASO-008529; ASO-008530; ASO-008531; ASO-008532; ASO-008533; ASO-008534; ASO-008535; ASO-008536; ASO-008537; ASO-008543; ASO-008545; ASO-008584; ASO-008226 and ASO-008261.

Also provided herein is a pharmaceutical composition comprising the antisense oligonucleotide or a conjugate thereof as disclosed herein and a pharmaceutically acceptable carrier.

The present disclosure further provides a kit comprising the antisense oligonucleotide, a conjugate thereof, or the composition as disclosed herein.

Provided herein is a method for treating a synucleinopathy in a subject in need thereof, comprising administering an effective amount of the antisense oligonucleotide, a conjugate thereof, or the composition of the present disclosure. In some embodiments, the synucleinopathy is selected from the group consisting of Parkinson’s disease, Parkinson's Disease Dementia (PDD), multiple system atrophy, dementia with Lewy bodies, and any combinations thereof.

Also provided herein is a use of the antisense oligonucleotide, a conjugate thereof, or the composition of the present disclosure for the manufacture of a medicament. The present disclosure also provides the use of the antisense oligonucleotide, a conjugate thereof, or the composition for the manufacture of a medicament for the treatment of a synucleinopathy in a subject in need thereof. In some embodiments, the antisense oligonucleotide, a conjugate thereof, or the composition of the present disclosure are for use in therapy of a synucleinopathy in a subject in need thereof. In other embodiments, the antisense oligonucleotide, a conjugate thereof, or the composition of the present disclosure are for use in therapy.

In some embodiments, the subject is a human. In some embodiments, the antisense oligonucleotide, a conjugate thereof, or the compositions are administered orally, parenterally, intrathecally, intra-cerebroventricularly, pulmorarily, topically, or intraventricularly.

BRIEF DESCRIPTION OF FIGURES

Figures 1A to 1C show exemplary ASOs targeting a region of the *SNCA* pre-mRNA. FIG. 1A provides exemplary ASOs that target the wild-type *SNCA* mRNA (SEQ ID NO: 2). FIG. 1B provides exemplary ASOs that target a variant *SNCA* mRNA ("variant 4"/SEQ ID NO: 5; or "variant 2"/SEQ ID NO: 3). FIG. 1C provides exemplary ASOs that target another variant *SNCA* mRNA ("variant 3"/SEQ ID NO: 4). Each column of figures 1A to 1C show the Sequence ID number (SEQ ID No.) designated for the sequence only, the target start and end positions on the *SNCA* pre-mRNA sequence, the target start and end positions on the *SNCA* mRNA sequence, the design number (DES No.), the ASO sequence with a design, the ASO number (ASO No.), and the ASO sequence with a chemical structure. In the figures, the annotation of ASO chemistry is as follows Beta-D-oxy LNA nucleotides are designated by OxyB where B designates a nucleotide base such as thymine (T), uridine (U), cytosine (C), 5-methylcytosine (MC), adenine (A) or guanine (G), and thus include OxyA, OxyT, OxyMC, OxyC and OxyG. DNA nucleotides are designated by DNAb, where the lower case b designates a nucleotide base such as thymine (T), uridine (U), cytosine (C), 5-methylcytosine (Mc), adenine (A) or guanine (G), and thus include DNAa, DNAt, DNA and DNAg. The letter M before C or c indicates 5-methylcytosine. The letter s is a phosphorothioate internucleotide linkage.

Figure 2 shows ASOs targeting *SNCA* pre-mRNA with exemplary wing design modification. Each column of FIG. 2 shows the Sequence ID number (SEQ ID No.) designated for the sequence only, the target start and end positions on the *SNCA* pre-mRNA sequence, the design number (DES No.), the ASO sequence with a design, the ASO number (ASO No.), and the ASO sequence with a chemical structure and wing design modification identified. DES-287033, DES-287041, DES-287053, DES-287965, DES-288902, DES-288903, DES-288905, DES-290315, and DES-292378 show various ASO designs possible for SEQ ID NO: 1467. DES-286762, DES-286785, and DES-286783 show various ASO designs possible for SEQ ID NO: 1764. For the ASO designs, the upper case letters indicate nucleotide analogues (*e.g.,* LNA or 2'-O-Methyl (OMe)), and the lower case letters indicate DNAs. The upper case letters with or without underlines indicate the two letters can be different nucleotide analogues, *e.g.,* LNA and 2'-O-Methyl. For example, the underlined upper letters can be 2'-O-Methyl while the upper letters without underlines are LNA. In the ASOs with chemical structure column, OMe is 2'-O-Methyl nucleotide, L is LNA, D is DNA, and the numbers followed by L or D mean the number of LNAs or DNAs

Fugure 3 shows the relative *SNCA* mRNA expression level (as a percentage of the vehicle control) in cyno monkeys after ASO-003179 administration. The animals received the vehicle control (circle), 8 mg of ASO-003179 (square), or 16 mg of ASO-003179 (triangle) via ICV injection. The

animals were then sacrificed at 2 weeks post-dosing and the *SNCA* mRNA expression levels were assessed in the following tissues: medulla (top left panel), caudate putamen (top middle panel), pons (top right panel), cerebellum (bottom left panel), lumbar spinal cord (bottom middle panel), and frontal cortex (bottom right panel). Both the data for the individual animals and the mean are shown. The horizontal line marks the reference value of 100% (i.e., value at which the *SNCA* mRNA expression would be equivalent to expression level observed in the vehicle control group).

Figure 4 shows the effect of ASO-003092 on *SNCA* mRNA expression level in the brain tissues of cyno monkeys. The animals were dosed with either 4 mg (square) or 8 mg (triangle) of ASO-003092 and then the *SNCA* mRNA expression level in the different brain tissues was assessed at 2 weeks post-dosing. Animals receiving the vehicle control were used as controls (circle). The *SNCA* mRNA expression level was assessed in the following tissues: medulla (top left panel), caudate putamen (top middle panel), pons (top right panel), cerebellum (bottom left panel), lumbar spinal cord (bottom middle panel), and frontal cortex (bottom right panel). The *SNCA* mRNA expression levels were normalized to the GAPDH and then shown as a percentage of the vehicle control. Both the data for the individual animals and the mean are shown. The horizontal line marks the reference value of 100% (i.e., value at which the *SNCA* mRNA expression would be equivalent to expression level observed in the vehicle control group).

DETAILED DESCRIPTION OF DISCLOSURE

I Definitions

It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, *e.g.*, 10 percent, up or down (higher or lower). For example, if it is stated that "the ASO reduces expression of SNCA protein in a cell following administration of the ASO by at least about 60%," it is implied that the SNCA levels are reduced by a range of 50% to 70%.

The term "antisense oligonucleotide" (ASO) refers to an oligomer or polymer of nucleosides, such as naturally-occurring nucleosides or modified forms thereof, that are covalently linked to each other through internucleotide linkages. The ASO useful for the disclosure includes at least one non-naturally occurring nucleoside. An ASO is complementary to a target nucleic acid, such that the ASO hybridizes to the target nucleic acid sequence. The terms "antisense ASO," "ASO," and "oligomer" as used herein are interchangeable with the term "ASO."

The term "nucleic acids" or "nucleotides" is intended to encompass plural nucleic acids. In some embodiments, the term "nucleic acids" or "nucleotides" refers to a target sequence, *e.g.,* pre-mRNAs, mRNAs, or DNAs *in vivo* or *in vitro*. When the term refers to the nucleic acids or nucleotides in a target sequence, the nucleic acids or nucleotides can be naturally occurring sequences within a cell. In other embodiments, "nucleic acids" or "nucleotides" refer to a sequence in the ASOs of the disclosure. When the term refers to a sequence in the ASOs, the nucleic acids or nucleotides are not naturally occurring, *i.e.,* chemically synthesized, enzymatically produced,

recombinantly produced, or any combination thereof. In one embodiment, the nucleic acids or nucleotides in the ASOs are produced synthetically or recombinantly, but are not a naturally occurring sequence or a fragment thereof. In another embodiment, the nucleic acids or nucleotides in the ASOs are not naturally occurring because they contain at least one nucleotide analogue that is not naturally occurring in nature. The term "nucleic acid" or "nucleoside" refers to a single nucleic acid segment, *e.g.*, a DNA, an RNA, or an analogue thereof, present in a polynucleotide. "Nucleic acid" or "nucleoside" includes naturally occurring nucleic acids or non-naturally occurring nucleic acids. In some embodiments, the terms "nucleotide", "unit" and "monomer" are used interchangeably. It will be recognized that when referring to a sequence of nucleotides or monomers, what is referred to is the sequence of bases, such as A, T, G, C or U, and analogues thereof.

The term "nucleotide" as used herein, refers to a glycoside comprising a sugar moiety, a base moiety and a covalently linked group (linkage group), such as a phosphate or phosphorothioate internucleotide linkage group, and covers both naturally occurring nucleotides, such as DNA or RNA, and non-naturally occurring nucleotides comprising modified sugar and/or base, which are also referred to as "nucleotide analogues" herein. Herein, a single nucleotide (unit) can also be referred to as a monomer or nucleic acid unit. In certain embodiments, the term "nucleotide analogues" refers to nucleotides having modified sugar moieties. Non-limiting examples of the nucleotides having modified sugar moieties (*e.g.,* LNA) are disclosed elsewhere herein. In other embodiments, the term "nucleotide analogues" refers to nucleotides having modified nucleobase moieties. The nucleotides having modified nucleobase moieties include, but are not limited to, 5-methylcytosine, isocytosine, pseudoisocytosine, 5-bromouracil, 5-propynyluracil, 6-aminopurine, 2-aminopurine, inosine, diaminopurine, and 2-chloro-6-aminopurine.

The term "nucleoside" as used herein is used to refer to a glycoside comprising a sugar moiety and a base moiety, which can be covalently linked by the internucleotide linkages between the nucleosides of the ASO. In the field of biotechnology, the term "nucleoside" is often used to refer to a nucleic acid monomer or unit. In the context of an ASO, the term "nucleoside" can refer to the base alone, *i.e.,* a nucleobase sequence comprising cytosine (DNA and RNA), guanine (DNA and RNA), adenine (DNA and RNA), thymine (DNA) and uracil (RNA), in which the presence of the sugar backbone and internucleotide linkages are implicit. Likewise, particularly in the case of oligonucleotides where one or more of the internucleotide linkage groups are modified, the term "nucleotide" can refer to a "nucleoside." For example, the term "nucleotide" can be used, even when specifying the presence or nature of the linkages between the nucleosides.

The term "nucleotide length" as used herein means the total number of the nucleotides (monomers) in a given sequence. For example, the sequence of ctaacaacttctgaacaaca (SEQ ID NO: 1436) has 20 nucleotides; thus the nucleotide length of the sequence is 20. The term "nucleotide length" is therefore used herein interchangeably with "nucleotide number."

As one of ordinary skill in the art would recognize, the 5' terminal nucleotide of an oligonucleotide does not comprise a 5' internucleotide linkage group, although it can comprise a 5' terminal group.

As used herein, a "coding region" or "coding sequence" is a portion of polynucleotide which consists of codons translatable into amino acids. Although a "stop codon" (TAG, TGA, or TAA) is typically not translated into an amino acid, it can be considered to be part of a coding region, but any flanking sequences, for example promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), and the like, are not part of a coding region. The boundaries of a coding region are typically determined by a start codon at the 5' terminus, encoding the amino terminus of the resultant polypeptide, and a translation stop codon at the 3' terminus, encoding the carboxyl terminus of the resulting polypeptide.

The term "non-coding region" as used herein means a nucleotide sequence that is not a coding region. Examples of non-coding regions include, but are not limited to, promoters, ribosome binding sites, transcriptional terminators, introns, untranslated regions ("UTRs"), non-coding exons and the like. Some of the exons can be wholly or part of the 5' untranslated region (5' UTR) or the 3' untranslated region (3' UTR) of each transcript. The untranslated regions are important for efficient translation of the transcript and for controlling the rate of translation and half-life of the transcript.

The term "region" when used in the context of a nucleotide sequence refers to a section of that sequence. For example, the phrase "region within a nucleotide sequence" or "region within the complement of a nucleotide sequence" refers to a sequence shorter than the nucleotide sequence, but longer than at least 10 nucleotides located within the particular nucleotide sequence or the complement of the nucleotides sequence, respectively. The term "sub-sequence" or "subsequence" or “target region” can also refer to a region of a nucleotide sequence.

The term "downstream," when referring to a nucleotide sequence, means that a nucleic acid or a nucleotide sequence is located 3' to a reference nucleotide sequence. In certain embodiments, downstream nucleotide sequences relate to sequences that follow the starting point of transcription. For example, the translation initiation codon of a gene is located downstream of the start site of transcription.

The term "upstream" refers to a nucleotide sequence that is located 5' to a reference nucleotide sequence.

Unless otherwise indicated, the sequences provided herein are listed from 5' end (left) to 3' end (right).

As used herein, the term "regulatory region" refers to nucleotide sequences located upstream (5' non-coding sequences), within, or downstream (3' non-coding sequences) of a coding region, and which influence the transcription, RNA processing, stability, or translation of the associated coding region. Regulatory regions can include promoters, translation leader sequences, introns, polyadenylation recognition sequences, RNA processing sites, effector binding sites, UTRs, and stem-loop structures. If a coding region is intended for expression in a eukaryotic cell, a polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence.

The term "transcript" as used herein can refer to a primary transcript that is synthesized by transcription of DNA and becomes a messenger RNA (mRNA) after processing, *i.e.,* a precursor messenger RNA (pre-mRNA), and the processed mRNA itself. The term "transcript" can be interchangeably used with "pre-mRNA" and "mRNA." After DNA strands are transcribed to primary transcripts, the newly synthesized primary transcripts are modified in several ways to be converted to their mature, functional forms such as mRNA, tRNA, rRNA, lncRNA, miRNA and others. Thus, the term "transcript" can include exons, introns, 5' UTRs, and 3' UTRs.

The term "expression" as used herein refers to a process by which a polynucleotide produces a gene product, for example, a RNA or a polypeptide. It includes, without limitation, transcription of the polynucleotide into messenger RNA (mRNA) and the translation of an mRNA into a polypeptide. Expression produces a "gene product." As used herein, a gene product can be either a nucleic acid, *e.g.*, a messenger RNA produced by transcription of a gene, or a polypeptide which is translated from a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, *e.g.*, polyadenylation or splicing, or polypeptides with post translational modifications, *e.g.*, methylation, glycosylation, the addition of lipids, association with other protein subunits, or proteolytic cleavage.

The terms "identical" or percent "identity" in the context of two or more nucleic acids refer to two or more sequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences.

One such non-limiting example of a sequence alignment algorithm is the algorithm described in Karlin *et al.*, 1990, *Proc. Natl. Acad. Sci.*, 87:2264-2268, as modified in Karlin *et al.*, 1993, *Proc. Natl. Acad. Sci.*, 90:5873-5877, and incorporated into the NBLAST and XBLAST programs (Altschul *et al.*, 1991, *Nucleic Acids Res.*, 25:3389-3402). In certain embodiments, Gapped BLAST can be used as described in Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402. BLAST-2, WU-BLAST-2 (Altschul *et al.*, 1996, *Methods in Enzymology*, 266:460-480), ALIGN, ALIGN-2 (Genentech, South San Francisco, California) or Megalign (DNASTAR) are additional publicly available software programs that can be used to align sequences. In certain embodiments, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (*e.g.*, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 90 and a length weight of 1, 2, 3, 4, 5, or 6). In certain alternative embodiments, the GAP program in the GCG software package, which incorporates the algorithm of Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) can be used to determine the percent identity between two amino acid sequences (*e.g.*, using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5). Alternatively, in certain embodiments, the percent identity between nucleotide or amino acid sequences is determined using the algorithm of Myers and Miller (CABIOS, 4:11-17 (1989)). For example, the percent identity can be determined using the ALIGN program (version 2.0) and using a PAM120 with residue table, a gap length penalty of 12 and a gap penalty of 4. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain embodiments, the default parameters of the alignment software are used.

In certain embodiments, the percentage identity "X" of a first nucleotide sequence to a second nucleotide sequence is calculated as 100 x (Y/Z), where Y is the number of amino acid residues scored as identical matches in the alignment of the first and second sequences (as aligned by visual inspection or a particular sequence alignment program) and Z is the total number of residues in the second sequence. If the length of a first sequence is longer than the second sequence, the percent identity of the first sequence to the second sequence will be higher than the percent identity of the second sequence to the first sequence.

Different regions within a single polynucleotide target sequence that align with a polynucleotide reference sequence can each have their own percent sequence identity. It is noted that the percent sequence identity value is rounded to the nearest tenth. For example, 80.11, 80.12, 80.13, and 80.14 are rounded down to 80.1, while 80.15, 80.16, 80.17, 80.18, and 80.19 are rounded up to 80.2. It also is noted that the length value will always be an integer.

As used herein, the terms "homologous" and "homology" are interchangeable with the terms "identity" and "identical."

The term "naturally occurring variant thereof" refers to variants of the SNCA polypeptide sequence or *SNCA* nucleic acid sequence (*e.g.,* transcript) which exist naturally within the defined taxonomic group, such as mammalian, such as mouse, monkey, and human. Typically, when referring to "naturally occurring variants" of a polynucleotide the term also can encompass any allelic variant of the *SNCA* -encoding genomic DNA which is found at Chromosomal position 17q21 by chromosomal translocation or duplication, and the RNA, such as mRNA derived therefrom. "Naturally occurring variants" can also include variants derived from alternative splicing of the *SNCA* mRNA. When referenced to a specific polypeptide sequence, *e.g.*, the term also includes naturally occurring forms of the protein, which can therefore be processed, *e.g.,* by co- or post-translational modifications, such as signal peptide cleavage, proteolytic cleavage, glycosylation, etc.

In determining the degree of "complementarity" between ASOs of the disclosure (or regions thereof) and the target region of the nucleic acid which encodes mammalian SNCA protein (*e.g.,* the *SNCA* gene), such as those disclosed herein, the degree of "complementarity" (also, "homology" or "identity") is expressed as the percentage identity (or percentage homology) between the sequence of the ASO (or region thereof) and the sequence of the target region (or the reverse complement of the target region) that best aligns therewith. The percentage is calculated by counting the number of aligned bases that are identical between the two sequences, dividing by the total number of contiguous monomers in the ASO, and multiplying by 100. In such a comparison, if gaps exist, it is preferable that such gaps are merely mismatches rather than areas where the number of monomers within the gap differs between the ASO of the disclosure and the target region.

The term "complement" as used herein indicates a sequence that is complementary to a reference sequence. It is well known that complementarity is the base principle of DNA replication and transcription as it is a property shared between two DNA or RNA sequences, such that when they are aligned antiparallel to each other, the nucleotide bases at each position in the sequences will be complementary, much like looking in the mirror and seeing the reverse of things. Therefore, for example, the complement of a sequence of 5'"ATGC"3' can be written as 3'"TACG"5' or 5'"GCAT"3'. The terms "reverse complement", "reverse complementary" and "reverse complementarity" as used herein are interchangeable with the terms "complement", "complementary" and "complementarity."

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 terms "corresponding to" and "corresponds to," when referencing two separate nucleic acid or nucleotide sequences can be used to clarify regions of the sequences that correspond or are similar to each other based on homology and/or functionality, although the nucleotides of the specific sequences can be numbered differently. For example, different isoforms of a gene transcript can have similar or conserved portions of nucleotide sequences whose numbering can differ in the respective isoforms based on alternative splicing and/or other modifications. In addition, it is recognized that different numbering systems can be employed when characterizing a nucleic acid or nucleotide sequence (*e.g.*, a gene transcript and whether to begin numbering the sequence from the translation start codon or to include the 5'UTR). Further, it is recognized that the nucleic acid or nucleotide sequence of different variants of a gene or gene transcript can vary. As used herein, however, the regions of the variants that share nucleic acid or nucleotide sequence homology and/or functionality are deemed to "correspond" to one another. For example, a nucleotide sequence of a *SNCA* transcript corresponding to nucleotides X to Y of SEQ ID NO: 1 ("reference sequence") refers to an *SNCA* transcript sequence (*e.g., SNCA* pre-mRNA or mRNA) that has an identical sequence or a similar sequence to nucleotides X to Y of SEQ ID NO: 1. A person of ordinary skill in the art can identify the corresponding X and Y residues in the *SNCA* transcript sequence by aligning the *SNCA* transcript sequence with SEQ ID NO: 1.

The terms "corresponding nucleotide analogue" and "corresponding nucleotide" are intended to indicate that the nucleobase in the nucleotide analogue and the naturally occurring nucleotide have the same pairing, or hybridizing, ability. For example, when the 2-deoxyribose unit of the nucleotide

is linked to an adenine, the "corresponding nucleotide analogue" contains a pentose unit (different from 2-deoxyribose) linked to an adenine.

The term "DES Number" or "DES No." as used herein refers to a unique number given to a nucleotide sequence having a specific pattern of nucleosides (*e.g.,* DNA) and nucleoside analogues (*e.g.,* LNA). As used herein, the design of an ASO is shown by a combination of upper case letters and lower case letters. For example, DES-003092 refers to an ASO sequence of ctaacaacttctgaacaaca (SEQ ID NO: 1436) with an ASO design of LDDLLDDDDDDDDDDLDLLL (*i.e.,* CtaACaacttctgaaCaACA), wherein the L (*i.e.,* upper case letter) indicates a nucleoside analogue (*e.g.,* LNA) and the D (*i.e.,* lower case letter) indicates a nucleoside (*e.g.,* DNA).

The term "ASO Number" or "ASO No." as used herein refers to a unique number given to a nucleotide sequence having the detailed chemical structure of the components, *e.g.*, nucleosides (*e.g.*, DNA), nucleoside analogues (*e.g.*, beta-D-oxy-LNA), nucleobase (*e.g.*, A, T, G, C, U, or MC), and backbone structure (*e.g.*, phosphorothioate or phosphorodiester). For example, ASO-003092 refers to OxyMCs DNAts DNAas OxyAs OxyMCs DNAas DNAas DNAcs DNAts DNAts DNAcs DNAts DNAgs DNAas DNAas OxyMCs DNAas OxyAs OxyMCs OxyA.

"Potency" is normally expressed as an IC_{50} or EC_{50} value, in μM, nM, or pM unless otherwise stated. Potency can also be expressed in terms of percent inhibition. IC_{50} is the median inhibitory concentration of a therapeutic molecule. EC_{50} is the median effective concentration of a therapeutic molecule relative to a vehicle or control (*e.g.,* saline). In functional assays, IC_{50} is the concentration of a therapeutic molecule that reduces a biological response, *e.g.,* transcription of mRNA or protein expression, by 50% of the biological response that is achieved by the therapeutic molecule. In functional assays, EC_{50} is the concentration of a therapeutic molecule that produces 50% of the biological response, *e.g.,* transcription of mRNA or protein expression. IC_{50} or EC_{50} can be calculated by any number of means known in the art.

By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. Mammalian subjects include humans, domestic animals, farm animals, sports animals, and zoo animals including, *e.g.*, humans, non-human primates, dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, bears, and so on.

The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the composition would be administered. Such composition can be sterile.

An "effective amount" of an ASO as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. In certain embodiments, a subject is successfully "treated" for a disease or condition disclosed elsewhere herein according to the methods provided herein if the patient shows, *e.g.*, total, partial, or transient alleviation or elimination of symptoms associated with the disease or disorder.

II. Antisense Oligonucleotides

The present disclosure employs antisense oligonucleotides for use in modulating the function of nucleic acid molecules encoding mammalian α-Syn, such as the *SNCA* nucleic acid, *e.g.*, *SNCA* transcript, including *SNCA* pre-mRNA, and *SNCA* mRNA, or naturally occurring variants of such nucleic acid molecules encoding mammalian α-Syn. The term "ASO" in the context of the present disclosure, refers to a molecule formed by covalent linkage of two or more nucleotides (*i.e.,* an oligonucleotide).

The ASO comprises a contiguous nucleotide sequence of from about 10 to about 30, such as 10–20, 16–20, or 15–25 nucleotides in length. The terms "antisense ASO," "antisense oligonucleotide," and "oligomer" as used herein are interchangeable with the term "ASO."

A reference to a SEQ ID number includes a particular nucleobase sequence, but does not include any design or full chemical structure shown in FIG. 1A to C or 2. Furthermore, the ASOs disclosed in the figures herein show a representative design, but are not limited to the specific design shown in the figures unless otherwise indicated. Herein, a single nucleotide (unit) can also be referred to as a monomer or unit. When this specification refers to a specific ASO number, the reference includes the sequence, the specific ASO design, and the chemical structure. When this specification refers to a specific DES number, the reference includes the sequence and the specific ASO design. For example, when a claim (or this specification) refers to SEQ ID NO: 1436, it includes the nucleotide sequence of ctaacaacttctgaacaaca only. When a claim (or the specification) refers to DES-003092, it includes the nucleotide sequence of ctaacaacttctgaacaaca with the ASO design shown in the figures (*i.e.,* CtaACaacttctgaaCaACA). Alternatively, the design of ASO-

003092 can also be written as SEQ ID NO: 1436, wherein each of the 1st nucleotide, 4th nucleotide, 5th nucleotide, 16th nucleotide and 18th-20th nucleotides from the 5' end is a modified nucleotide, *e.g.,* LNA, and each of the other nucleotides is a non-modified nucleotide (*e.g.,* DNA). The ASO number includes the sequence and the ASO design as well as the specific details of the ASO. Therefore, ASO-003092 referred in this application indicates OxyMCs DNAts DNAas OxyAs OxyMCs DNAas DNAas DNAcs DNAts DNAts DNAcs DNAts DNAgs DNAas DNAas OxyMCs DNAas OxyAs OxyMCs OxyA , wherein "s" indicates a phosphorothioate linkage.

In various embodiments, the ASO of the disclosure does not comprise RNA (units). In some embodiments, the ASO comprises one or more DNA units. In one embodiment, the ASO according to the disclosure is a linear molecule or is synthesized as a linear molecule. In some embodiments, the ASO is a single stranded molecule, and does not comprise short regions of, for example, at least 3, 4 or 5 contiguous nucleotides, which are complementary to equivalent regions within the same ASO (*i.e.* duplexes) - in this regard, the ASO is not (essentially) double stranded. In some embodiments, the ASO is essentially not double stranded. In some embodiments, the ASO is not a siRNA. In various embodiments, the ASO of the disclosure can consist entirely of the contiguous nucleotide region. Thus, in some embodiments the ASO is not substantially self-complementary.

In one embodiment, the ASO of the disclosure can be in the form of any pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" as used herein refers to derivatives of the ASOs of the disclosure wherein the ASO is modified (e.g., addition of a cation) by making salts thereof. Such salts retain the desired biological activity of the ASOs without imparting undesired toxicological effects. In some embodiments, the ASO of the disclosure is in the form of a sodium salt. In other embodiments, the ASO is in the form of a potassium salt.

II.A. The Target

Suitably the ASO of the disclosure is capable of down-regulating (*e.g.,* reducing or removing) expression of the *SNCA* mRNA or SNCA protein. In this regard, the ASO of the disclosure can affect indirect inhibition of SNCA protein through the reduction in *SNCA* mRNA levels, typically in a mammalian cell, such as a human cell, such as a neuronal cell. In particular, the present disclosure is directed to ASOs that target one or more regions of the *SNCA* pre-mRNA.

Synonyms of *SNCA* are known and include NACP, non A-beta component of AD amyloid, PARK1, PARK4, and PD1. The sequence for the *SNCA* gene can be found under publicly available Accession Number NC_000004.12 and the sequence for the *SNCA* pre-mRNA transcript can be found under publicly available Accession Number NG_011851.1 (SEQ ID NO: 1). The sequence for SNCA protein can be found under publicly available Accession Numbers: P37840, A8K2A4,

Q13701, Q4JHI3, and Q6IAU6, each of which is incorporated by reference herein in its entirety. Natural variants of the *SNCA* gene product are known. For example, natural variants of SNCA protein can contain one or more amino acid substitutions selected from: A30P, E46K, H50Q, A53T, and any combinations thereof. Therefore, the ASOs of the present disclosure can be designed to reduce or inhibit expression of the natural variants of the SNCA protein.

Mutations in SNCA are known to cause one or more pathological conditions. The ASOs of the disclosure can be used to reduce or inhibit the expression of a SNP or alternatively spliced *SNCA* transcript containing one or more mutations and consequently reduce the formation of a mutated SNCA protein. Examples of SNCA protein mutants include, but are not limited to a SNCA protein comprising one or more mutations selected from: D2A, E35K, Y39F, H50A, E57K, G67_V71del, V71_V82del, A76_V77del, A76del, V77del, A78del, A85_F94del, Y125F, Y133F, Y136F , and any combination thereof. The ASO of the disclosure can be designed to reduce or inhibit expression of any mutants of SNCA proteins.

An example of a target nucleic acid sequence of the ASOs is *SNCA* pre-mRNA. SEQ ID NO: 1 represents a *SNCA* genomic sequence. SEQ ID NO: 1 is identical to a *SNCA* pre-mRNA sequence except that the nucleotide "t" in SEQ ID NO: 1 is shown as "u" in the pre-mRNA. In certain embodiments, the "target nucleic acid" comprises an intron region of an SNCA protein-encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom, *e.g.*, pre-mRNA. In other embodiments, the "target nucleic acid" comprises an exon region of an SNCA protein-encoding nucleic acids or naturally occurring variants thereof, and RNA nucleic acids derived therefrom, such as a mRNA, pre-mRNA, or a mature mRNA. In some embodiments, for example when used in research or diagnostics the "target nucleic acid" can be a cDNA or a synthetic oligonucleotide derived from the above DNA or RNA nucleic acid targets. In one embodiment, the *SNCA* genomic sequence is shown as GenBank Accession No. NG_011851.1 (SEQ ID NO: 1). The mature mRNA encoding SNCA protein is shown as SEQ ID NO: 2 (NM_000345.3) Variants of this sequence are shown in SEQ ID NO: 3 (NM_001146054.1) SEQ ID NO: 4 (NM_001146055.1), and SEQ ID NO: 5 (NM_007308.2), variants 2-4, respectively. Variant 2 corresponds to GenBank Accession No. NM_001146054.1. Variant 3 corresponds to GenBank Accession No. NM_001146055.1. Variant 4 corresponds to GenBank Accession No. NM_007308.2. The SNCA protein sequence encoded by the *SNCA* mRNA (SEQ ID NO: 2) is shown as SEQ ID NO: 6.

The target nucleic acid sequences to which the oligonucleotides of the invention are complementa are summarized in the table below:

Species	type	Length (nt)	SEQ ID NO	NCBI ref.	Alternative name/comments
Human	premRNA	121198	1	NG_011851.1	Human (GRCh38.p12) Chromosome 4: position 89,724,099 - 89,838,315 reverse strand
Human	mRNA	3215	2	NM_000345.3	Transcript of SEQ ID NO:1
Human	mRNA	3211	3	NM_001146054.1	Variant 2
Human	mRNA	3022	4	NM_001146055.1	Variant 3
Human	mRNA	3127	5	NM_007308.2	Variant 4

The oligonucleotide of the invention may for example target an exon region of a mammalian *SNCA*, or may for example target an intron region in the *SNCA* pre-mRNA as indicated in the table below:

Exonic regions in the human *SNCA* premRNA (SEQ ID NO 1)			Intronic regions in the human *SNCA* premRNA (SEQ ID NO 1)		
ID	**start**	**end**	**ID**	**start**	**end**
			i0	1	6097
e1	6098	6335	i1	6336	7604
e2	7605	7750	i2	7751	15112
e3	15113	15154	i3	15155	20908
e4	20909	21051	i4	21052	114019
e5	114020	114103	i5	114104	116636
e6	116637	119198	i6	119199	121198

In one embodiment, the ASO according to the disclosure comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length that are complementary to a nucleic acid sequence within a *SNCA* transcript, *e.g.,* a region corresponding to an exon, intron, or any combination thereof of SEQ ID NO: 1 or a region within SEQ ID NOs: 2, 3, 4, or 5, wherein the nucleic acid sequence corresponds to (i) nucleotides 4942 – 5343 of SEQ ID NO: 1; (ii) nucleotides 6326 – 7041 of SEQ ID NO: 1; (iia) nucleotides 6336 – 7041 of SEQ ID NO: 1; (iii) nucleotides 7329 – 7600 of SEQ ID NO: 1; (iv) nucleotides 7630 – 7783 of SEQ ID NO: 1; (iva) nucleotides 7750 – 7783 of SEQ ID NO: 1; (v) nucleotides 8277 – 8501 of SEQ ID NO: 1; (vi) nucleotides 9034 – 9526 of SEQ ID NO: 1; (vii) nucleotides 9982 – 14279 of SEQ ID NO: 1; (viii) nucleotides 15204 – 19041 of SEQ ID NO: 1; (ix) nucleotides 20351 – 29654 of SEQ ID NO: 1; (ixa) nucleotides 20351 – 20908 of SEQ ID NO: 1; (ixb) nucleotides 21052 - 29654 of SEQ ID NO: 1; (x) nucleotides 30931 – 33938 of SEQ ID NO: 1; (xi) nucleotides 34932 – 37077 of SEQ ID NO: 1; (xii) nucleotides 38081 – 42869 of SEQ ID NO: 1; (xiii) nucleotides 44640 – 44861 of SEQ ID NO: 1; (xiv) nucleotides 46173 – 46920 of SEQ ID NO: 1; (xv) nucleotides 47924 – 58752 of SEQ ID NO: 1; (xvi) nucleotides 60678 – 60905 of SEQ ID NO: 1; (xvii) nucleotides 62066 – 62397 of SEQ ID NO: 1; (xviii) nucleotides 67759 – 71625 of SEQ ID NO: 1; (xix) nucleotides 72926 – 86991 of SEQ ID NO: 1; (xx) nucleotides 88168 – 93783 of SEQ ID NO: 1; (xxi) nucleotides 94976 – 102573 of SEQ ID NO: 1;

(xxii) nucleotides 104920 – 107438 of SEQ ID NO: 1; (xxiii) nucleotides 108948 – 119285 of SEQ ID NO: 1; (xxiiia) nucleotides 108948 – 114019 of SEQ ID NO: 1; (xxiib) nucleotides 114292 – 116636 of SEQ ID NO: 1; (xxiv) nucleotides 131 - 678 of SEQ ID NO: 5; (xxv) nucleotides 131-348 of SEQ ID NO: 3; (xxvi) nucleotides 1 - 162 of SEQ ID NO: 4; (xxvii) nucleotides 126 – 352 of SEQ ID NO: 2; (xxviii) nucleotides 276 – 537 of SEQ ID NO: 2; (xxix) nucleotides 461 – 681 of SEQ ID NO: 2; and (xxx) nucleotides 541 – 766 of SEQ ID NO: 2.

In another embodiment, the ASO according to the disclosure comprises a contiguous nucleotide sequence of 10-30 nucleotides that hybridizes to or is complementary, such as at least 90% complementary, such as fully complementary, to a region within an intron of a *SNCA* transcript, *e.g.,* a region corresponding to an intron of SEQ ID NO: 1 (*e.g.,* intron 1, 2, 3, or 4).

In some embodiments the ASO comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length that is at least 90% complementary, such as fully complementary, to an intron region present in the pre-mRNA of human SNCA , selected from intron i0 (nucleotides 1-6097 of SEQ ID NO: 1); i1 (nucleotides 6336 - 7604 of SEQ ID NO: 1); i2 (nucleotides 7751 - 15112 of SEQ ID NO: 1); i3 (nucleotides 15155 - 20908 of SEQ ID NO: 1); i4 (nucleotides 21052 - 114019 of SEQ ID NO: 1); i5 (nucleotides 114104 - 116636 of SEQ ID NO: 1) or i6 (nucleotides 119199 - 121198 of SEQ ID NO: 1).

In some embodiments the ASO comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length that is at least 90% complementary, such as fully complementary to a of human SNCA, wherein the nucleic acid sequence corresponds to nucleotides 21052 -20351 – 29654 of SEQ ID NO: 1; nucleotides 30931 – 33938 of SEQ ID NO: 1; nucleotides 44640 – 44861 of SEQ ID NO: 1; or nucleotides 47924 – 58752 of SEQ ID NO: 1.

In particular, an ASO complementary to intron 4 (nucleotides 21052 - 114019 of SEQ ID NO: 1), such as intron 4 regions selected from nucleotides 21052 - – 29654 of SEQ ID NO: 1; nucleotides 24483 - 28791 of SEQ ID NO: 1; nucleotides 30931 – 33938 of SEQ ID NO: 1; nucleotides 32226 - 32242 of SEQ ID NO: 1; nucleotides 44640 – 44861 of SEQ ID NO: 1; nucleotides 44741 - 44758 of SEQ ID NO: 1; nucleotides 47924 – 58752 of SEQ ID NO: 1 or nucleotides 48641 - 48659 of SEQ ID NO: 1 are advantageous.

In another embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence of 10-30 nucleotides that hybridizes to or is complementary, such as at least 90% complementary, such as fully complementary, to a nucleic acid sequence, or a region within the sequence, of a *SNCA* transcript, wherein the nucleic acid sequence corresponds to nucleotides 6,426-6,825; 18,569-20,555; or 31,398-107,220 of SEQ ID NO: 1, and wherein the ASO has one of the designs

described herein (*e.g.,* Section II.G. *e.g.,* a gapmer design, *e.g.,* an alternating flank gapmer design) or a chemical structure shown elsewhere herein (*e.g.,* FIGs. 1A to 1C and 2).

In another embodiment, the target region corresponds to nucleotides 5,042-5,243 of SEQ ID NO: 1.

In other embodiments, the target region corresponds to nucleotides 6336 – 7604 of SEQ ID NO: 1.

In other embodiments, the target region corresponds to nucleotides 6336 – 7041 of SEQ ID NO: 1

In other embodiments, the target region corresponds to nucleotides 6,426-6,941 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 7,429-7,600 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 7,630-7,683 of SEQ ID NO: 1.

In other embodiments, the target region corresponds to nucleotides 7751 – 15112 of SEQ ID NO: 1.

In other embodiments, the target region corresponds to nucleotides 7751 – 7783 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 8,377-8,401 of SEQ ID NO: 1.

In another embodiment, the target region corresponds to nucleotides 9,134-9,426 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 10,082-14,179 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 15,304-18,941 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 15155 - 20908 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 20,451-29,554 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 20351 – 20908 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 21052 - 114019 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 21052 - 29654 of SEQ ID NO: 1

In one embodiment, the target region corresponds to nucleotides 31,031-33,838 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 30931 – 33938 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 35032-36977 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 38181-42769 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 44640 – 44861 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 44740-44761 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 46273-46820 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 47924 – 58752 of SEQ ID NO: 1.

In other embodiments, the target region corresponds to nucleotides 48024-58752 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 60778-60805 of SEQ ID NO: 1.

In some embodiment, the target region corresponds to nucleotides 62,166-62,297 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 67,859-71,525 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 73026-86891 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 88268-93683 of SEQ ID NO: 1.

In some embodiment, the target region corresponds to nucleotides 95076-102473 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 105020-107338 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 109,048-119,185 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides 108948 – 114019 of SEQ ID NO: 1.

In some embodiments, the target region corresponds to nucleotides nucleotides 114292 – 116636 of SEQ ID NO: 1.

In one embodiment, the target region corresponds to nucleotides 231 – 248 or 563 - 578 of SEQ ID NO: 5.

In another embodiment, the target region corresponds to nucleotides 231 – 248 of SEQ ID NO: 3.

In some embodiments, the target region corresponds to nucleotides 38 – 62 of SEQ ID NO: 4.

In other embodiments, the target region corresponds to nucleotides 226-252 of SEQ ID NO: 2.

In one embodiment, the target region corresponds to nucleotides 376-437 of SEQ ID NO: 2.

In another embodiment, the target region corresponds to nucleotides 561-581 of SEQ ID NO: 2.

In one embodiment, the target region corresponds to nucleotides 641-666 of SEQ ID NO: 2.

In certain embodiments, the ASOs hybridize to or are complementary, such as at least 90% complementary, such as fully complementary, to a region within a *SNCA* transcript, *e.g.,* SEQ ID

NO: 1, and have a sequence score equal to or greater than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0. Calculation methods of the sequence score are disclosed elsewhere herein.

In one embodiment, the ASO according to the disclosure comprises a contiguous nucleotide sequence that hybridizes to a region within an exon of a *SNCA* transcript, *e.g.,* a region corresponding to an exon of SEQ ID NO: 1, *e.g.,* exon 2, 4, 5, or 6. In another embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence that hybridizes to a nucleic acid sequence, or a region within the sequence, of a *SNCA* transcript ("target region"), wherein the nucleic acid sequence corresponds to nucleotides 7,630-7,683; 20,932-21,032; 114,059-114,098; or 116,659-119,185 of SEQ ID NO: 1. In another embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence that hybridizes to a nucleic acid sequence, or a region within the sequence, of a *SNCA* transcript, wherein the nucleic acid sequence corresponds to nucleotides 7,630-7,683; 20,926-21,032; 114,059-114,098; or 116,659-119,185 of SEQ ID NO: 1, and wherein the ASO has one of the designs described herein (*e.g.,* Section II.G. *e.g.,* a gapmer design, *e.g.,* an alternating flank gapmer design) or a chemical structure shown elsewhere herein (*e.g.,* FIGs. 1A to 1C and 2).

In another embodiment, the target region corresponds to nucleotides 7,630-7,683 of SEQ ID NO: 1. In some embodiments, the target region corresponds to nucleotides 20,932-21,032 of SEQ ID NO: 1. In certain embodiments, the target region corresponds to nucleotides 114,059-114,098 of SEQ ID NO: 1. In one embodiment, the target region corresponds to nucleotides 116,659-119,185 of SEQ ID NO: 1. In another embodiment, the target region corresponds to nucleotides 116,981-117,212 of SEQ ID NO: 1. In some embodiments, the target region corresponds to nucleotides 116,981-117,019 of SEQ ID NO: 1. In other embodiments, the target region corresponds to nucleotides 117,068-117,098 of SEQ ID NO: 1. In certain embodiments, the target region corresponds to nucleotides 117,185-117,212 of SEQ ID NO: 1. In another embodiment, the target region corresponds to nucleotides 118,706-118,725 of SEQ ID NO: 1. In certain embodiments, the ASOs hybridize to a region within an exon of a *SNCA* transcript, *e.g.,* SEQ ID NO: 1, and have a sequence score equal to or greater than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0. Calculation methods of the sequence score are disclosed elsewhere herein.

In other embodiments, the target region corresponds to nucleotides 6,426-6,825 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In some embodiments, the target region corresponds to nucleotides 18,569-20,555 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In another embodiment, the target region corresponds to nucleotides 20,926-21,032 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both.

In other embodiments, the target region corresponds to nucleotides 31,398-31,413 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In some embodiments, the target region corresponds to nucleotides 35,032-35,049 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In certain embodiments, the target region corresponds to nucleotides 68,373-69,827 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In another embodiment, the target region corresponds to nucleotides 78,418-78,487 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In other embodiments, the target region corresponds to nucleotides 91,630-91,646 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In some embodiments, the target region corresponds to nucleotides 100,028-101,160 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In certain embodiments, the target region corresponds to nucleotides 107,205-107,220 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In another embodiment, the target region corresponds to nucleotides 114,059-114,098 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In other embodiments, the target region corresponds to nucleotides 116,659-119,185 of SEQ ID NO: 1 ± 10, ± 20, ± 30, ± 40, ± 50, ± 60, ± 70, ± 80, or ± 90 nucleotides at the 3' end, the 5' end, or both. In other embodiments, the target region corresponds to nucleotides 7,604-7,620 of SEQ ID NO: 1 ± 1, ± 2, ± 3, ± 4, ± 5, ± 6, ± 7, ± 8, or ± 9 nucleotides at the 3' end, the 5' end, or both.

In certain embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *SNCA* transcript) under physiological condition, *i.e., in vivo* condition. In some embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *SNCA* transcript) *in vitro*. In some embodiments, the ASO of the disclosure is capable of hybridizing to the target nucleic acid (*e.g.*, *SNCA* transcript) *in vitro* under stringent conditions. Stringency conditions for hybridization *in vitro* are dependent on, *inter alia*, productive cell uptake, RNA accessibility, temperature, free energy of association, salt concentration, and time (*see, e.g.,* Stanley T Crooks, Antisense Drug Technology: Principles, Strategies and Applications, 2nd Edition, CRC Press (2007)). Generally, conditions of high to moderate stringency are used for *in vitro* hybridization to enable hybridization between substantially similar nucleic acids, but not between dissimilar nucleic acids. An example of stringent hybridization conditions include hybridization in 5X saline-sodium citrate (SSC) buffer (0.75 M sodium chloride/0.075 M sodium citrate) for 1 hour at 40° C, followed by washing the sample 10 times in 1X SSC at 40° C and 5 times in 1X SSC buffer at room temperature. *In vivo* hybridization conditions consist of intracellular conditions (*e.g.*,

physiological pH and intracellular ionic conditions) that govern the hybridization of antisense oligonucleotides with target sequences. *In vivo* conditions can be mimicked *in vitro* by relatively low stringency conditions. For example, hybridization can be carried out *in vitro* in 2X SSC (0.3 M sodium chloride/0.03 M sodium citrate), 0.1% SDS at 37°C. A wash solution containing 4X SSC, 0.1% SDS can be used at 37° C, with a final wash in 1X SSC at 45° C.

II.B. ASO Sequences

The ASOs of the disclosure comprise a contiguous nucleotide sequence which corresponds to the complement of a region of *SNCA* transcript, *e.g.*, a nucleotide sequence corresponding to SEQ ID NO: 1.

In certain embodiments, the disclosure provides an ASO which comprises a contiguous nucleotide sequence of a total of from 10-30 nucleotides, such as 10-25 nucleotides, such as 16 to 22, such as 10-20 nucleotides, such as 14 to 20 nucleotides, such as 17 to 20 nucleotides, such as 10-15 nucleotides, such as 12-14 nucleotides in length, wherein the contiguous nucleotide sequence has at least about 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99% sequence identity to a region within the complement of a mammalian *SNCA* transcript, such as SEQ ID NO: 1 or SEQ ID NO: 2 or naturally occurring variant thereof (SEQ ID NO: 3, 4, or 5). Thus, for example, the ASO hybridizes to a single stranded nucleic acid molecule having the sequence of SEQ ID NOs: 1 to 5 or a portion thereof.

In some embodiments, the oligonucleotide comprises a contiguous sequence of 10 to 30 nucleotides such as 10-25 nucleotides, such as 16 to 22, such as 10-20 nucleotides, such as 14 to 20 nucleotides, such as 17 to 20 nucleotides, such as 10-15 nucleotides, such as 12-14 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 a mammalian *SNCA* transcript, such as SEQ ID NO: 1, 2, 3, 4 and/or 5.

The ASO can comprise a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to the equivalent region of a target nucleic acid which encodes a mammalian SNCA protein (*e.g.*, SEQ ID NOs: 1-5). The ASO can comprise a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a target nucleic acid sequence, or a region within the sequence, such as an intron region, corresponding to nucleotides X-Y of SEQ ID NO: 1, wherein X and Y are the pre-mRNA start site and the pre-mRNA end site of NG_011851.1, respectively. Examples of such regions are liseted in section II.A “The Target”. Furthermore, the ASO can have a design described elsewhere herein (*e.g.,* Section II.G. *e.g.,* a gapmer design, *e.g.,*

an alternating flank gapmer design) or a chemical structure shown elsewhere herein (*e.g.,* FIGs. 1A to 1C and 2). In some embodiments, the ASO comprises a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a target nucleic acid sequence, or a region within the sequence, corresponding to nucleotides X-Y of SEQ ID NO: 2, wherein X and Y are the mRNA start site and the mRNA end site, respectively. Examples of such regions are liseted in section II.A "The Target". In other embodiments, the ASO comprises a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a target nucleic acid sequence, or a region within the sequence, corresponding to nucleotides X-Y of SEQ ID NO: 3, wherein X and Y are the mRNA start site and the mRNA end site, respectively. Examples of such regions are liseted in section II.A "The Target". In other embodiments, the ASO comprises a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a target nucleic acid sequence, or a region within the sequence, corresponding to nucleotides X-Y of SEQ ID NO: 4, wherein X and Y are the mRNA start site and the mRNA end site, respectively. Examples of such regions are liseted in section II.A "The Target". In other embodiments, the ASO comprises a contiguous nucleotide sequence which is fully complementary (perfectly complementary) to a target nucleic acid sequence, or a region within the sequence, corresponding to nucleotides X-Y of SEQ ID NO: 5, wherein X and Y are the mRNA start site and the mRNA end site, respectively. Examples of such regions are liseted in section II.A "The Target".

In certain embodiments, the nucleotide sequence of the ASOs of the disclosure or the contiguous nucleotide sequence has at least about 80% sequence identity to a sequence selected from SEQ ID NOs: 7 to 1878 (*i.e.,* the sequences in FIGs. 1A to 1C and 2), such as at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96% sequence identity, at least about 97% sequence identity, at least about 98% sequence identity, at least about 99% sequence identity, such as about 100% sequence identity (homologous). In some embodiments, the ASO has a design described elsewhere herein (*e.g.,* Section II.G.I, *e.g.,* a gapmer design, *e.g.,* an alternating flank gapmer design) or a nucleoside chemical structure shown elsewhere herein (*e.g.,* FIGs. 1A to 1C and 2).

In certain embodiments, the nucleotide sequence of the ASOs of the disclosure or the contiguous nucleotide sequence has at least about 80% sequence identity to a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 such as at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96% sequence identity, at least about 97% sequence identity, at least about 98% sequence identity, at least about 99% sequence identity, such as about 100% sequence identity (homologous). In some embodiments, the ASO has a design described elsewhere herein

(*e.g.,* Section II.G.I, *e.g.,* a gapmer design, *e.g.,* an alternating flank gapmer design) or a nucleoside chemical structure shown elsewhere herein (*e.g.,* FIGs. 1A to 1C and 2)

In a further embodiment the nucleotide sequence of the ASOs of the disclosure or the contiguous nucleotide sequence consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353.

In one embodiment the nucleotide sequence of the ASOs of the disclosure or the contiguous nucleotide sequence comprises or consists of a sequence selected from the group consisting of SEQ ID NO: 276; 278; 296; 295; 325; 328; 326; 329; 330; 327; 332; 333; 331; 339; 341; 390; 522 and 559.

In some embodiments, the ASO of the disclosure comprises at least one ASO with the design (*e.g.,* DES number) disclosed in FIGs. 1A to 1C and 2. In some embodiments, the ASO of the disclosure comprises at least one ASO with the design (*e.g.,* DES number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 3' end than the ASOs disclosed in FIGs. 1A to 1C and 2. In other embodiments, the ASO of the disclosure comprises at least one ASO with the design (*e.g.,* DES number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 5' end than the ASOs disclosed in FIGs. 1A to 1C and 2. In yet other embodiments, the ASO of the disclosure comprises at least one ASO with the design (*e.g.,* DES number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 5' end and/or the 3' end than the ASOs disclosed in FIGs. 1A to 1C and 2.

In one embodiment the contiguous nucleotide sequence comprises or consists a sequence and a design selected from the group consisting of:
TTCtctatataacatCACT (SEQ ID NO: 276)
TTTCtctatataacaTCAC (SEQ ID NO: 278);
AACTtttacataccACAT (SEQ ID NO: 296);
AACTtttacataccaCATT (SEQ ID NO: 295);
ATTAttcatcacaatCCA (SEQ ID NO: 325);
ATTAttcatcacaATCC (SEQ ID NO:328);
CattattcatcacaaTCCA (SEQ ID NO:326);
CATtattcatcacaATCC (SEQ ID NO:329);
ACAttattcatcacaaTCC (SEQ ID NO: 330);
AcattattcatcacaaTCCA (SEQ ID NO: 327);
ACATtattcatcacAATC (SEQ ID NO: 332);

TACAttattcatcacAATC (SEQ ID NO: 333);
TAcattattcatcacaaTCC (SEQ ID NO: 331);
TTCaacatttttatttCACA (SEQ ID NO:339);
ATTCaacatttttattTCAC (SEQ ID NO: 341);
ACTAtgatacttcACTC (SEQ ID NO: 390);
ACACattaactactCATA (SEQ ID NO: 522) and
GTCAaaatattcttaCTTC (SEQ ID NO:559),
wherein the upper case letters indicate a sugar modified nucleoside analouge and the lower case letters indicate DNAs.

In other embodiments, the ASO of the disclosure comprises at least one ASO with the chemical structure (*e.g.,* ASO number) disclosed in FIGs. 1A to 1C and 2. In some embodiments, the ASO of the disclosure comprises at least one ASO with the chemical structure (*e.g.,* ASO number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 3' end than the ASOs disclosed in FIGs. 1A to 1C and 2. In other embodiments, the ASO of the disclosure comprises at least one ASO with the chemical structure (*e.g.,* ASO number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 5' end than the ASOs disclosed in FIGs. 1A to 1C and 2. In yet other embodiments, the ASO of the disclosure comprises at least one ASO with the chemical structure (*e.g.,* ASO number) disclosed in FIGs. 1A to 1C and 2, wherein the ASO is one nucleotide, two nucleotides, three nucleotides, or four nucleotides shorter at the 5' end and/or the 3' end than the ASOs disclosed in FIGs. 1A to 1C and 2.

In some embodiments the ASO (or contiguous nucleotide portion thereof) is selected from, or comprises, one of the sequences selected from the group consisting of SEQ ID NOs: 7 to 1878 and a region of at least 10 contiguous nucleotides thereof, wherein the ASO (or contiguous nucleotide portion thereof) can optionally comprise one, two, three, or four mismatches when compared to the corresponding *SNCA* transcript. It is advantageous if there are with no more than 1 mismatch or no more than 2 mismatches.

In some embodiments the ASO (or contiguous nucleotide portion thereof) is selected from, or comprises, one of the sequences selected from the group consisting of SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 and a region of at least 10 contiguous nucleotides thereof, wherein the ASO (or contiguous nucleotide portion thereof) can optionally comprise one, two, three, or four mismatches when compared to the corresponding *SNCA* transcript. It is advantageous if there are with no more than 1 mismatch or no more than 2 mismatches.

In one embodiment, the ASO comprises a sequence selected from the group consisting of SEQ ID NO: 1436 (the sequence of ASO-003092) and SEQ ID NO: 1547 (the sequence of ASO-003179)).

In another embodiment, the ASO comprises a sequence selected from the group consisting of ASO-008387; ASO-008388; ASO-008501; ASO-008502; ASO-008529; ASO-008530; ASO-008531; ASO-008532; ASO-008533; ASO-008534; ASO-008535; ASO-008536; ASO-008537; ASO-008543; ASO-008545; ASO-008584; ASO-008226 and ASO-008261.

In some embodiments, an ASO of the disclosure binds to the target nucleic acid sequence (*e.g.*, *SNCA* transcript) and is capable of inhibiting or reducing expression of the *SNCA* transcript by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a mouse expressing a human *SNCA* gene (*e.g.*, A53T-PAC) when administered *in vivo* at doses of 3.13 µg, 12.5 µg, 25 µg, 50 µg, or 100 µg compared to the control (*e.g.*, an internal control such as GADPH or tubulin, or a mouse administered with vehicle control alone), as measured by an assay, *e.g.*, quantitative PCR or QUANTIGENE® analysis disclosed herein.

In some embodiments, an ASO of the disclosure is capable of reducing expression of SNCA protein by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a mouse expressing a human *SNCA* gene (*e.g.*, A53T-PAC) when administered *in vivo* at doses of 3.13 µg, 12.5 µg, 25 µg, 50 µg, or 100 µg compared to the control (*e.g.*, an internal control such as GADPH or tubulin, or a mouse administered with vehicle control alone), as measured by an assay, *e.g.*, High Content Assay disclosed herein (*see* Example 2A).

In some embodiments, an ASO of the disclosure binds to the target nucleic acid sequence (*e.g.*, *SNCA* transcript) and is capable of inhibiting or reducing expression of the *SNCA* transcript by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a cyno expressing the wild-type *SNCA* gene when administered once or twice *in vivo* at doses of 4 mg, 8 mg, or 16 mg compared to the control (*e.g.*, an internal control such as GADPH or tubulin, or a cyno administered with vehicle control alone), as measured by an assay, *e.g.*, quantitative PCR or QUANTIGENE® analysis disclosed herein.

In some embodiments, an ASO of the disclosure is capable of reducing expression of SNCA protein by at least about 10%, at least about 20% , at least about 30%, at least about 40%, at least

about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in a tissue (*e.g.*, a brain region) of a cyno expressing the wild-type *SNCA* gene when administered once or twice *in vivo* at doses of 4 mg, 8 mg, or 16 mg compared to the control (*e.g.*, an internal control such as GADPH or tubulin, or a cyno administered with vehicle control alone), as measured by an assay, *e.g.*, High Content Assay disclosed herein (*see* Example 2A).

In other embodiments, an ASO of the disclosure is capable of reducing expression of *SNCA* mRNA *in vitro* by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in mouse primary neurons expressing a full-length human *SNCA* gene (*e.g.*, PAC neurons) when the neurons are in contact with 5 μM, 3.3 μM, 1 μM, 4 nM, 40 nM, or 200 nM of the antisense oligonucleotide compared to a control (*e.g.*, an internal control such as GADPH or tubulin, or mouse primary neurons expressing a full-length human *SNCA* gene in contact with saline alone), as measured by an assay, *e.g.*, QUANTIGENE® analysis disclosed herein.

In yet other embodiments, an ASO of the disclosure is capable of reducing expression of SNCA protein *in vitro* by at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% in mouse primary neurons expressing a full-length human *SNCA* gene (*e.g.*, PAC neurons) when the neurons are in contact with 5 μM, 3.3 μM, 1 μM, 4 nM, 40 nM, or 200 nM of the antisense oligonucleotide compared to a control (*e.g.*, an internal control such as GADPH or tubulin, or mouse primary neurons expressing a full-length human *SNCA* gene in contact with saline alone), as measured by an assay, *e.g.*, High Content Assay disclosed herein (*see* Example 2A).

In some embodiments, an ASO of the disclosure is capable of reducing expression of *SNCA* mRNA *in vitro* by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in human neuroblastoma cell line (*e.g.*, SK-N-BE(2)) expressing a full-length human *SNCA* gene when the neuroblastoma cells are in contact with 25 μM of the antisense oligonucleotide compared to control (*e.g.*, an internal control such as GADPH or tubulin, or neuroblastoma cells expressing a full-length human *SNCA* gene in contact with saline alone), as measured by an assay, *e.g.*, quantitative PCR disclosed herein.

In some embodiments, an ASO disclosed herein is capable of reducing expression of SNCA protein *in vitro* by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% in human neuroblastoma cell line (*e.g.*, SK-N-BE(2)) expressing a full-length human *SNCA* gene when the neuroblastoma cells are in contact with 25 μM of the antisense

oligonucleotide compared to control (*e.g.*, an internal control such as GADPH or tubulin, or neuroblastoma cells expressing a full-length human *SNCA* gene in contact with saline alone), as measured by an assay, *e.g.*, High Content Assay analysis disclosed herein (*see* Example 2A).

In certain embodiments, an ASO of the disclosure binds to the *SNCA* transcript and inhibit or reduce expression of the *SNCA* mRNA by at least about 10% or about 20% compared to the normal (*i.e.* control) expression level in the cell, *e.g.,* at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or about 95% compared to the normal expression level (such as the expression level in the absence of the ASO(s) or conjugate(s)) in the cell. In certain embodiments, the ASO reduces expression of SNCA protein in a cell following administration of the ASO by at least 60%, at least 70%, at least 80%, or at least 90% compared to a cell not exposed to the ASO (*i.e.*, control). In some embodiments, the ASO reduces expression of SNCA protein in a cell following administration of the ASO by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the ASO (*i.e.*, control).

In certain embodiments, an ASO of the disclosure has at least one property selected from: (1) reduces expression of *SNCA* mRNA in a cell, compared to a control cell that has not been exposed to the ASO; (2) does not significantly reduce calcium oscillations in a cell; (3) does not significantly reduce tubulin intensity in a cell; (4) reduces expression of α-Syn protein in a cell; and (5) any combinations thereof compared to a control cell that has not been exposed to the ASO.

In some embodiments, the ASO of the disclosure does not significantly reduce calcium oscillations in a cell, *e.g.,* neuronal cells. If the ASO does not significantly reduce calcium oscillations in a cell, this property of the ASO corresponds with a reduced neurotoxicity of the ASO. In some embodiments, calcium oscillations are greater than or equal to 95%, greater than or equal to 90%, greater than or equal to 85%, greater than or equal to 80%, greater than or equal to 75%, greater than or equal to 70%, greater than or equal to 65%, greater than or equal to 60%, greater than or equal to 55%, or greater than or equal to 50% of oscillations in a cell not exposed to the ASO.

Calcium oscillations are important for the proper functions of neuronal cells. Networks of cortical neurons have been shown to undergo spontaneous calcium oscillations resulting in the release of the neurotransmitter glutamate. Calcium oscillations can also regulate interactions of neurons with associated glia, in addition to other associated neurons in the network, to release other neurotransmitters in addition to glutamate. Regulated calcium oscillations are required for homeostasis of neuronal networks for normal brain function. (*See*, Shashank *et al.*, *Brain Research*, 1006(1): 8–17 (2004); Rose *et al.*, *Nature Neurosci.*, 4:773 – 774 (2001); Zonta *et al.*, *J Physiol Paris.*, 96(3-4):193-8 (2002); Pasti *et al.*, *J. Neurosci.*, 21(2): 477-484 (2001).) Glutamate

also activates two distinct ion channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors.

In some embodiments, the calcium oscillations measured in the present methods are AMPA-dependent calcium oscillations. In some embodiments, the calcium oscillations are NMDA-dependent calcium oscillations. In some embodiments, the calcium oscillations are gamma-aminobutyric acid (GABA)-dependent calcium oscillations. In some embodiments, the calcium oscillations can be a combination of two or more of AMPA-dependent, NMDA-dependent or GABA-dependent calcium oscillations.

In certain embodiments, the calcium oscillations measured in the present methods are AMPA-dependent calcium oscillations. In order to measure AMPA-dependent calcium oscillations, the calcium oscillations can be measured in the presence of Mg^{2+} ions (*e.g.,* $MgCl_2$). In certain embodiments, the method further comprises adding Mg^{2+} ions (*e.g.,* $MgCl_2$) at an amount that allows for detection of AMPA-dependent calcium oscillations. In some embodiments, the effective ion concentration allowing for detection of AMPA-dependent calcium oscillations is at least about 0.5 mM. In other embodiments, the effective ion concentration to induce AMPA-dependent calcium oscillations is at least about 0.6 mM, at least about 0.7 mM, at least about 0.8 mM, at least about 0.9 mM, at least about 1 mM, at least about 1.5 mM, at least about 2.0 mM, at least about 2.5 mM, at least about 3.0 mM, at least about 4 mM, at least about 5 mM, at least about 6 mM, at least about 7 mM, at least about 8 mM, at least about 9 mM, or at least about 10mM. In a particular embodiment, the concentration of Mg^{2+} ions (*e.g.,* $MgCl_2$) useful for the methods is 1mM. In certain embodiments, the concentration of Mg^{2+} ions (*e.g.,* $MgCl_2$) useful for the present methods is about 1 mM to about 10 mM, about 1 mM to about 15mM, about 1 mM to about 20 mM, or about 1 mM to about 25 mM. Mg^{2+} ions can be added by the addition of magnesium salts, such as magnesium carbonate, magnesium chloride, magnesium citrate, magnesium hydroxide, magnesium oxide, magnesium sulfate, and magnesium sulfate heptahydrate.

In some embodiments, calcium oscillations are measured in the present method through the use of fluorescent probes which detect the fluctuations of intracellular calcium levels. For example, detection of intracellular calcium flux can be achieved by staining the cells with fluorescent dyes which bind to calcium ions (known as fluorescent calcium indicators) with a resultant, detectable change in fluorescence (*e.g.,* Fluo-4 AM and Fura Red AM dyes available from Molecular Probes. Eugene, OR, United States of America).

In other embodiments, the ASO of the disclosure does not significantly reduce the tubulin intensity in a cell. In some embodiments, tubulin intensity is greater than or equal to 95%, greater than or equal to 90%, greater than or equal to 85%, greater than or equal to 80%, greater than or equal to

75%, greater than or equal to 70%, greater than or equal to 65%, greater than or equal to 60%, greater than or equal to 55%, or greater than or equal to 50% of tubulin intensity in a cell not exposed to the ASO (or exposed to saline).

In some embodiments, such property is observed when using from 0.04 nM to 400 µM concentration of the ASO of the disclosure. In the same or a different embodiment, the inhibition or reduction of expression of *SNCA* mRNA and/or SNCA protein in the cell results in less than 100%, such as less than 98%, less than 95%, less than 90%, less than 80%, such as less than 70%, mRNA or protein levels compared to cells not exposed to the ASO. Modulation of expression level can be determined by measuring SNCA protein levels, *e.g.*, by methods such as SDS-PAGE followed by western blotting using suitable antibodies raised against the target protein. Alternatively, modulation of expression levels can be determined by measuring levels of *SNCA* mRNA, *e.g.,* by northern blot or quantitative RT-PCR. When measuring inhibition via mRNA levels, the level of down-regulation when using an appropriate dosage, such as from about 0.04 nM to about 400 µM concentration, is, in some embodiments typically to a level of from about 10-20% the normal levels in the cell in the absence of the ASO.

In certain embodiments, the ASO of the disclosure has an *in vivo* tolerability less than or equal to a total score of 4, wherein the total score is the sum of a unit score of five categories, which are 1) hyperactivity; 2) decreased activity and arousal; 3) motor dysfunction and/or ataxia; 4) abnormal posture and breathing; and 5) tremor and/or convulsions, and wherein the unit score for each category is measured on a scale of 0-4. In certain embodiments, the *in vivo* tolerability is less than or equal to the total score of 3, the total score of 2, the total score of 1, or the total score of 0. In some embodiment, the assessment for *in vivo* tolerability is determined as described in the examples below.

In some embodiments, the ASO can tolerate 1, 2, 3, or 4 (or more) mismatches, when hybridizing to the target sequence and still sufficiently bind to the target to show the desired effect, *i.e.,* down-regulation of the target mRNA and/or protein. Mismatches can, for example, be compensated by increased length of the ASO nucleotide sequence and/or an increased number of nucleotide analogues, which are disclosed elsewhere herein.

In some embodiments, the ASO of the disclosure comprises no more than 3 mismatches when hybridizing to the target sequence. In other embodiments, the contiguous nucleotide sequence comprises no more than 2 mismatches when hybridizing to the target sequence. In other embodiments, the contiguous nucleotide sequence comprises no more than 1 mismatch when hybridizing to the target sequence.

In some embodiments the ASO according to the disclosure comprises a nucleotide sequence, or a region within the sequence, according to any one of SEQ ID NOs: 7 to 1878, the ASO sequences with the design as described in FIGs. 1A to 1C and 2, and the ASO sequence with the chemical structure as described in FIGs. 1A to 1C and 2.

However, it is recognized that, in some embodiments, the nucleotide sequence of the ASO can comprise additional 5' or 3' nucleotides, such as, 1 to 5, such as 2 to 3 additional nucleotides, such as independently, 1, 2, 3, 4 or 5 additional nucleotides. The additional 5' and/or 3' nucleotides are preferably non-complementary to the target sequence. In this respect the ASO of the disclosure, can, in some embodiments, comprise a contiguous nucleotide sequence which is flanked 5' and/or 3' by additional nucleotides. In some embodiments the additional 5' and/or 3' nucleotides are naturally occurring nucleotides, such as DNA or RNA. In a further embodiment the natural occurring nucleotides at the 5'- or 3'-end are linked with phosphodiester (PO) internucleotide linkages. Such terminal PO linkages are cleavable by nucleases upon entry into the target cell, and are also termed biocleavable linkers and are describe in detail in WO 2014/076195.

In some embodiments, the ASO of the disclosure has a sequence score greater than or equal to 0.2, wherein the sequence score is calculated by formula I:

$$\frac{\#\text{ of C nucleotides and analogues thereof} - \#\text{ of G nucleotides and analogues thereof}}{\text{Total nucleotide length.}} \quad \text{(I)}$$

In other embodiments, the ASO of the disclosure has a sequence score greater than or equal to 0.2, wherein the sequence score is calculated by formula IA:

$$\frac{\#\text{ of C nucleotides and 5-methylcytosine nucleotides} - \#\text{ of G nucleotides}}{\text{Total nucleotide length.}} \quad \text{(IA)}$$

In these embodiments, a sequence score of greater than or equal to a cut off value corresponds to a reduced neurotoxicity of the ASO.

In certain embodiments, the ASO of the disclosure has a sequence score greater than or equal to about 0.1, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1.0.

In one embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence hybridizing to a non-coding region of a *SNCA* transcript, wherein the sequence score of the ASO is greater than or equal to about 0.1, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1.0.

In another embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence hybridizing to an intron region of a *SNCA* transcript, wherein the sequence score of the ASO is

greater than or equal to about 0.1, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1.0.

In another embodiment, the ASO of the disclosure comprises a contiguous nucleotide sequence hybridizing to an intron exon junction of a *SNCA* transcript, wherein the sequence score of the ASO is greater than or equal to about 0.1, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1.0.

In all of these embodiments, when the sequence score is greater than or equal to the cut off value, the ASO is considered to have reduced neurotoxicity.

II.C. ASO Length

The ASOs can comprise a contiguous nucleotide sequence of a total 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 some embodiments, the ASOs comprise a contiguous nucleotide sequence of a total of about 10–22, such as 10-21, such as 12-20, such as15-20, such as 17-20, such as 12–18, such as 13–17 or 12–16, such as 13, 14, 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides in length.

In some embodiments, the ASOs comprise a contiguous nucleotide sequence of a total of 10, 11, 12, 13, or 14 contiguous nucleotides in length.

In some embodiments, the ASOs comprise a contiguous nucleotide sequence of a total of 16, 17, 18, 19 or 20 contiguous nucleotides in length.

In some embodiments, the ASO according to the disclosure consists of no more than 22 nucleotides, such as no more than 21 or 20 nucleotides, such as no more than 18 nucleotides, such as 15, 16 or 17 nucleotides. In some embodiments the ASO of the disclosure comprises less than 22 nucleotides. It should be understood that when a range is given for an ASO, or contiguous nucleotide sequence length, the range includes the lower and upper lengths provided in the range, for example from (or between) 10–30, includes both 10 and 30.

II.D. Nucleosides and Nucleoside analogues

In one aspect of the disclosure, the ASOs comprise one or more non-naturally occurring nucleotide analogues. "Nucleotide analogues" as used herein are variants of natural nucleotides, such as DNA or RNA nucleotides, by virtue of modifications in the sugar and/or base moieties. Analogues could in principle be merely "silent" or "equivalent" to the natural nucleotides in the context of the oligonucleotide, *i.e.* have no functional effect on the way the oligonucleotide works to inhibit target gene expression. Such "equivalent" analogues can nevertheless be useful if, for example, they are easier or cheaper to manufacture, or are more stable to storage or manufacturing conditions, or

represent a tag or label. In some embodiments, however, the analogues will have a functional effect on the way in which the ASO works to inhibit expression; for example by producing increased binding affinity to the target and/or increased resistance to intracellular nucleases and/or increased ease of transport into the cell. Specific examples of nucleoside analogues are described by *e.g.* Freier & Altmann; *Nucl. Acid Res.*, 1997, 25, 4429-4443 and Uhlmann; *Curr. Opinion in Drug Development*, 2000, 3(2), 293-213, and illustrated in section II.D.a and in Scheme 1 (section IID.2b).

II.D.1. 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 disclosure the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In some embodiments the nucleobase moiety is modified by modifying or replacing the nucleobase. 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 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 nucleobase 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 (MC) nucleosides may be used.

II.D.2. Sugar Modification

The ASO of the disclosure can 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 biradical 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 RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions. Nucleosides with modified sugar moieties also include 2' modified nucleosides, such as 2' substituted nucleosides. Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides, such as enhanced nucleoside resistance and enhanced affinity.

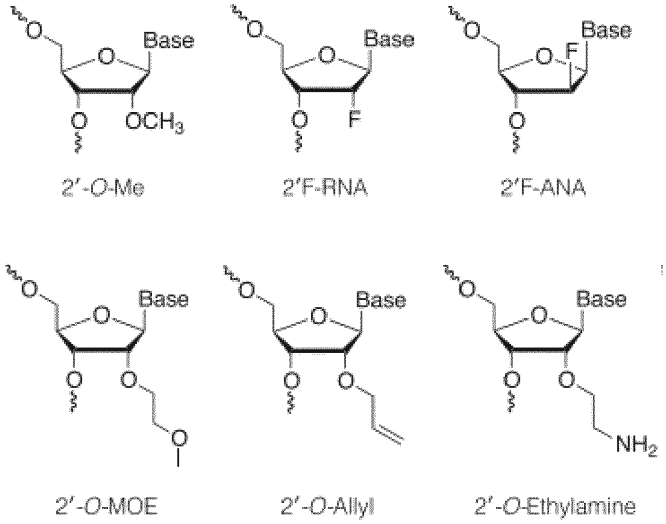
In some embodiments, the sugar modification comprises an affinity enhancing sugar modification, *e.g.*, LNA. An affinity enhancing sugar modification increases the binding affinity of the ASOs to the target RNA sequence. In some embodiments, an ASO comprising a sugar modification disclosed herein has a binding affinity to a target RNA sequence that is enhanced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% compared to a control (*e.g.*, an ASO without such sugar modification).

II.D.2.a 2' modified nucleosides

A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or –OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradical capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2' – 4' biradical 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, *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.

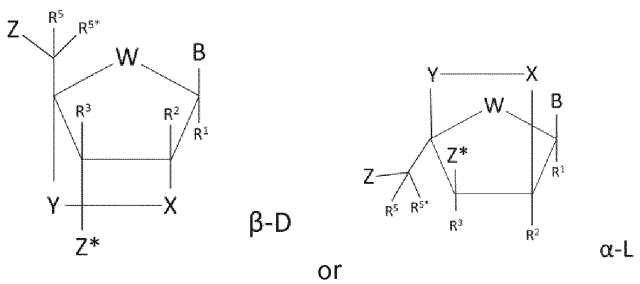


In relation to the present invention 2' substituted sugar modified nucleosides does not include 2' bridged nucleosides like LNA.

II.D.2.b Locked Nucleic Acid Nucleosides (LNA).

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

In some embodiments, the modified nucleoside or the LNA nucleosides of the ASO of the disclosure has a general structure of the formula II or III:



Formula II Formula III

wherein W is selected from -O-, -S-, -N(R^a)-, -C(R^aR^b)-, such as, in some embodiments –O-; B designates a nucleobase or modified nucleobase moiety; Z designates an internucleoside linkage to an adjacent nucleoside, or a 5'-terminal group; Z* designates an internucleoside linkage to an adjacent nucleoside, or a 3'-terminal group; and X designates a group selected from the group consisting of -C(R^aR^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO_2-, -N(R^a)-, and >C=Z.

In some embodiments, X is selected from the group consisting of: –O-, -S-, NH-, NR^aR^b, -CH_2-, CR^aR^b, -C(=CH_2)-, and -C(=CR^aR^b)-. In some embodiments, X is -O-.

In some embodiments, Y designates a group selected from the group consisting of -C(R^aR^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO_2-, -N(R^a)-, and >C=Z. In some embodiments, Y is selected from the group consisting of: –CH_2-, -C(R^aR^b)-, –CH_2CH_2-, -C(R^aR^b)-C(R^aR^b)-, –$CH_2CH_2CH_2$-, -C(R^aR^b)C(R^aR^b)C(R^aR^b)-, -C(R^a)=C(R^b)-, and -C(R^a)=N-.

In some embodiments, Y is selected from the group consisting of: -CH_2-, -CHR^a-, -$CHCH_3$-, CR^aR^b-, and -X-Y- together designate a bivalent linker group (also referred to as a radicle) together designate a bivalent linker group consisting of 1, 2, 3 or 4 groups/atoms selected from the group consisting of -C(R^aR^b)-, -C(R^a)=C(R^b)-, -C(R^a)=N-, -O-, -Si(R^a)$_2$-, -S-, -SO_2-, -N(R^a)-, and >C=Z.

In some embodiments, -X-Y designates a biradical selected from the groups consisting of: -X-CH_2-, -X-CR^aR^b-, -X-CHR^{a-}, -X-C(HCH_3)$^-$, -O-Y-, -O-CH_2-, -S-CH_2-, -NH-CH_2-, -O-$CHCH_3$-, -CH_2-O-CH_2, -O-CH(CH_3CH_3)-, -O-CH_2-CH_2-, OCH_2-CH_2-CH_2-,-O-CH_2OCH_2-, -O-NCH_2-, -C(=CH_2)-CH_2-, -NR^a-CH_2-, N-O-CH_2, -S-CR^aR^b- and -S-CHR^a-.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In some embodiments, one or both of R^5 and R^{5*} is hydrogen and, when substituted the other of R^5 and R^{5*} is C_{1-6} alkyl such as methyl. In such an embodiment, R^1, R^2, R^3, may all be hydrogen, and the biradical –X-Y- may be selected from –O-CH2- or –O-CH(CR^a)-, such as –O-CH(CH3)-.

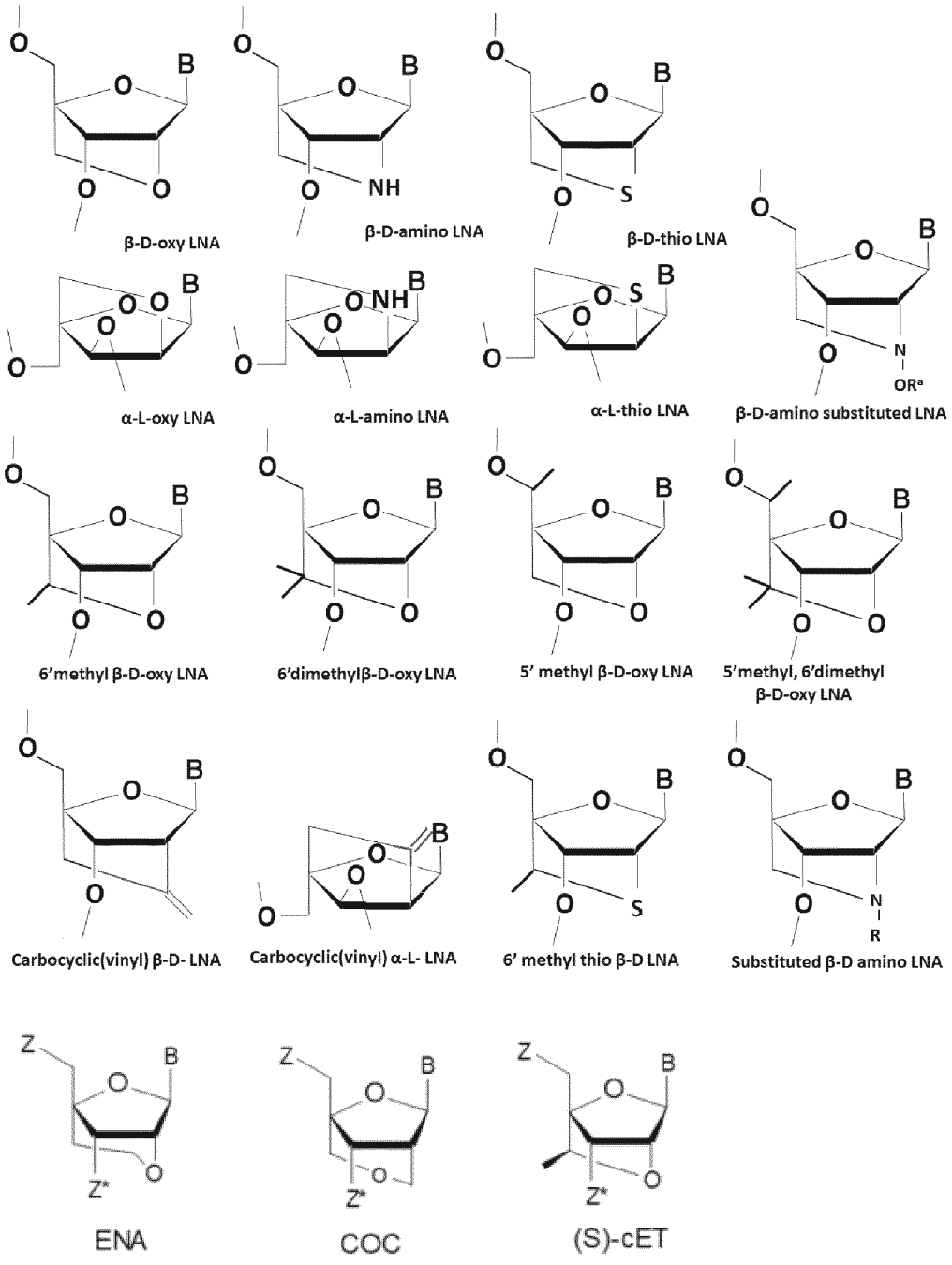
In some embodiments, the biradical is –CR^aR^b-O-CR^aR^b-, such as CH_2-O-CH_2-, W is O and all of R^1, R^2, R^3, R^5 and R^{5*} are all hydrogen. In some embodiments R^a is C_{1-6} alkyl such as methyl. Such LNA nucleosides are also known as conformationally restricted nucleotides (CRNs) and are disclosed in WO2013036868.

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

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

Certain examples of LNA nucleosides are presented in Scheme 1.

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.

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

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.

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.

II.E. 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 disclosure are capable of recruiting a nuclease, particularly and endonuclease, preferably endoribonuclease (RNase), such as RNase H. Examples of oligonucleotide designs which operate via nuclease mediated mechanisms are oligonucleotides which typically comprise a region of at least 5 or 6 DNA nucleosides and are flanked on one side or both sides by affinity enhancing nucleosides, for example gapmers.

II.F. 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 and induce cleavage and subsequent degradation of the complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNase H activity, which may be used to determine the ability to recruit RNase H. 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.

In some embodiments, an oligonucleotide is deemed essentially incapable of recruiting RNaseH if, when provided with the complementary target nucleic acid, the RNaseH initial rate, as measured in pmol/l/min, is less than 20%, such as less than 10%, such as less than 5% of the initial rate determined when using a oligonucleotide having the same base sequence as the oligonucleotide being tested, but containing only DNA monomers, with no 2' substitutions, with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613.

II.G. ASO Design

The ASO of the disclosure can comprise a nucleotide sequence which comprises both natural nucleotides and nucleotide analogues, and can be in the form of a gapmer. Examples of configurations of a gapmer that can be used with the ASO of the disclosure are described in U.S. Patent Appl. Publ. No. 2012/0322851.

The term gapmer as used herein refers to an antisense oligonucleotide which comprises a region of RNase H recruiting oligonucleotides (gap) which is flanked 5' and 3' by one or more affinity enhancing modified nucleosides (flanks). Various gapmer designs are described herein. The term LNA gapmer is a gapmer oligonucleotide wherein at least one of the affinity enhancing modified nucleosides is an LNA nucleoside. The term mixed wing gapmer refers to a LNA gapmer wherein the flank regions comprise at least one LNA nucleoside and at least one DNA nucleoside or non-LNA modified nucleoside, such as at least one 2' substituted modified nucleoside, such as, for example, 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA and 2'-F-ANA nucleoside(s). In some embodiments the mixed wing gapmer has one flank which comprises LNA nucleosides (*e.g.,* 5' or 3') and the other flank (3' or 5' respectfully) comprises 2' substituted modified nucleoside(s).

In some embodiments, in addition to enhancing affinity of the ASO for the target region, some nucleoside analogues also mediate RNase (*e.g.,* RNaseH) binding and cleavage. Since α-L-LNA monomers recruit RNaseH activity to a certain extent, in some embodiments, gap regions (*e.g.,* region B as referred to herein) of ASOs containing α-L-LNA monomers consist of fewer monomers recognizable and cleavable by the RNaseH, and more flexibility in the mixmer construction is introduced.

II.G.1. Gapmer Design

In one embodiment, the ASO of the disclosure is a gapmer. A gapmer ASO is an ASO which comprises a contiguous stretch of nucleotides which is capable of recruiting an RNase, such as RNaseH, such as a region of at least 6 DNA nucleotides, referred to herein in as region B (B), wherein region B is flanked both 5' and 3' by regions of affinity enhancing nucleotide analogues, such as from 1–10 nucleotide analogues 5' and 3' to the contiguous stretch of nucleotides which is capable of recruiting RNase – these regions are referred to as regions A (A) and C (C) respectively.

In certain embodiments, the gapmer is an alternating flank gapmer, examples of which are discussed below. In certain embodiments, the alternating flank gapmer exhibits less off target binding than a traditional gapmer. In certain embodiments, the alternating flank gapmer has better long term tolerability than a traditional gapmer.

An alternating flank gapmer can comprise a (poly)nucleotide sequence of formula (5' to 3'), A-B-C, wherein: region A (A) (5' region or a first wing sequence) comprises at least one nucleotide analogue, such as at least one LNA unit, such as from 1-10 nucleotide analogues, such as LNA units, and; region B (B) comprises at least six consecutive nucleotides which are capable of recruiting RNase (when formed in a duplex with a complementary RNA molecule, such as the pre-mRNA or mRNA target), such as DNA nucleotides, and; region C (C) (3'region or a second wing sequence) comprises at least one nucleotide analogue, such as at least one LNA unit, such as from 1-10 nucleotide analogues, such as LNA units; wherein regions A and C can include at any position in A and C 1-3 insertions of DNA nucleotide regions (*e.g.,* DNA Insertions), in which these DNA insertions can each be 1-6 DNA units long.

In certain other embodiments, the gapmer, *e.g.,* an alternating flank gapmer, comprises a (poly)nucleotide sequence of formula (5' to 3'), A-B-C, or optionally A-B-C-D or D-A-B-C, wherein: region A (A) (5' region) comprises at least one nucleotide analogue, such as at least one LNA unit, such as from 1-10 nucleotide analogues, such as LNA units, and; region B (B) comprises at least five consecutive nucleotides which are capable of recruiting RNase (when formed in a duplex with a complementary RNA molecule, such as the mRNA target), such as DNA nucleotides, and; region C (C) (3'region) comprises at least one nucleotide analogue, such as at least one LNA unit, such as from 1-10 nucleotide analogues, such as LNA units, and; region D (D), when present comprises 1, 2 or 3 nucleotide units, such as DNA nucleotides.

In some embodiments, region A comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide analogues, such as LNA units, such as from 2-5 nucleotide analogues, such as 2-5 LNA units, such as 2-5 nucleotide analogues, such as 3-5 LNA units; and/or region C consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide analogues, such as LNA units, such as from 2-5 nucleotide analogues, such as 2-5 LNA units, such as 2-5 nucleotide analogues, such as 3-5 LNA units.

In some embodiments B comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 consecutive nucleotides which are capable of recruiting RNase, or from 6-14, 7-14, 8-14, or from 7-10, or from 7-9, such as 8, such as 9, such as 10, or such as 14 consecutive nucleotides which are capable of recruiting RNase. In some embodiments region B comprises at least five DNA nucleotide unit, such as 5-23 DNA units, such as from 5-20 DNA units, such as from 5-18 DNA units, such as from 6-14 DNA units, such as from 8-14 DNA units, such as 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 DNA units.

In some embodiments region A comprises 3, 4, or 5 nucleotide analogues, such as LNA, region B consists of 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 DNA units, and region C consists of 3, 4, or 5 nucleotide analogues, such as LNA. Such designs include (A-B-C) 5-10-5, 3-14-3, 3-10-3, 3-10-4,

4-10-3, 3-9-3, 3-9-4, 4-9-3, 3-8-3, 3-8-4, 4-8-3, 3-7-3, 3-7-4, and 4-7-3, and can further include region D, which can have one to 3 nucleotide units, such as DNA units.

In some embodiments, the ASO of the disclosure, *e.g.,* an alternating flank gapmer, comprises the formula of 5'-A-B-C-3', wherein

(i) region B is a contiguous sequence of at least 5, 6, 7, or 8, *e.g.,* 5 to 18 DNA units, which are capable of recruiting RNase;

(ii) region A is a first wing sequence of 1 to 10 nucleotides, wherein the first wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units (*e.g.,* DNA insertion) and wherein at least one of the nucleotide analogues is located at the 3' end of A; and

(iii) region C is a second wing sequence of 1 to 10 nucleotides, wherein the second wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units (*e.g.,* DNA insertion) and wherein at least one of the nucleotide analogues is located at the 5' end of C.

In some embodiments, the first wing sequence (region A in the formula) comprises a combination of nucleotide analogues and DNA units selected from (i) 1-9 nucleotide analogues and 1 DNA unit; (ii) 1-8 nucleotide analogues and 1-2 DNA units; (iii) 1-7 nucleotide analogues and 1-3 DNA units; (iv) 1-6 nucleotide analogues and 1-4 DNA units; (v) 1-5 nucleotide analogues and 1-5 DNA units; (vi) 1-4 nucleotide analogues and 1-6 DNA units; (vii) 1-3 nucleotide analogues and 1-7 DNA units; (viii) 1-2 nucleotide analogues and 1-8 DNA units; and (ix) 1 nucleotide analogue and 1-9 DNA units.

In certain embodiments, the second wing sequence (region C in the formula) comprises a combination of nucleotide analogues and DNA unit selected from (i) 1-9 nucleotide analogues and 1 DNA unit; (ii) 1-8 nucleotide analogues and 1-2 DNA units; (iii) 1-7 nucleotide analogues and 1-3 DNA units; (iv) 1-6 nucleotide analogues and 1-4 DNA units; (v) 1-5 nucleotide analogues and 1-5 DNA units; (vi) 1-4 nucleotide analogues and 1-6 DNA units; (vii) 1-3 nucleotide analogues and 1-7 DNA units; (viii) 1-2 nucleotide analogues and 1-8 DNA units; and (ix) 1 nucleotide analogue and 1-9 DNA units.

In some embodiments, region A in the ASO formula has a sub-formula selected from the first wing design of any ASOs in FIGs. 1A to 1C and 2, and/or region C in the ASO formula has a sub-formula selected from the second wing design of any ASOs in FIGs. 1A to 1C and 2, wherein the upper letter is a nucleotide analogue (*e.g.*, sugar modified analogue, which can also be written as L) and the lower letter is DNA (which can also be written as D).

In certain embodiments, the ASO, *e.g.,* an alternating flank gapmer, has the formula of 5' A-B-C 3', wherein region B is a contiguous sequence of 5 to 18 DNA units, region A has a formula of LLDLL, LDLLL, or LLLDL and region C has a formula of LLDLL or LDLDLL, and wherein L is an LNA unit and D is a DNA unit.

In some embodiments, the ASO has the formula of 5' A-B-C 3', wherein region B is a contiguous sequence of 10 DNA units, region A has the formula of LDL, and region C has the formula of LLLL, wherein L is an LNA unit and D is a DNA unit.

Further gapmer designs are disclosed in WO2004/046160, which is hereby incorporated by reference in its entirety. WO2008/113832 hereby incorporated by reference in its entirety, refers to 'shortmer' gapmer ASOs. In some embodiments, ASOs presented herein can be such shortmer gapmers.

In some embodiments the ASO, *e.g.,* an alternating flank gapmer, comprises a contiguous nucleotide sequence of a total of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotide units, wherein the contiguous nucleotide sequence is of formula (5' – 3'), A-B-C, or optionally A-B-C-D or D-A-B-C, wherein; region A consists of 1, 2, 3, 4, or 5 nucleotide analogue units, such as LNA units; region B consists of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 contiguous nucleotide units which are capable of recruiting RNase when formed in a duplex with a complementary RNA molecule (such as a mRNA target); and region C consists of 1, 2, 3, 4, or 5 nucleotide analogue units, such as LNA units. When present, region D consists of a single DNA unit.

In some embodiments A comprises 1 LNA unit. In some embodiments region A comprises 2 LNA units. In some embodiments region A comprises 3 LNA units. In some embodiments region A comprises 4 LNA units. In some embodiments region A comprises 5 LNA units. In some embodiments region C comprises 1 LNA unit. In some embodiments C comprises 2 LNA units. In some embodiments region C comprises 3 LNA units. In some embodiments region C comprises 4 LNA units. In some embodiments region C comprises 5 LNA units. In some embodiments region B comprises 6 nucleotide units. In some embodiments region B comprises 7 nucleotide units. In some embodiments region B comprises 8 nucleotide units. In some embodiments region B comprises 9 nucleotide units. In certain embodiments, region B comprises 10 nucleoside units. In certain embodiments, region B comprises 11 nucleoside units. In certain embodiments, region B comprises 12 nucleoside units. In certain embodiments, region B comprises 13 nucleoside units. In certain embodiments, region B comprises 14 nucleoside units, region B comprises 15 nucleoside units. In certain embodiments, region B comprises 7–23 DNA monomers or 5-18 DNA monomers. In some embodiments region B comprises from 6–23 DNA units, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 DNA units. In some embodiments region B consists of DNA units.

In some embodiments region B comprises at least one LNA unit which is in the alpha-L configuration, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 LNA units in the alpha-L-configuration. In some embodiments region B comprises at least one alpha-L-oxy LNA unit or wherein all the LNA units in the alpha-L- configuration are alpha-L-oxy LNA units.

In some embodiments the number of nucleotides present in A-B-C are selected from (nucleotide analogue units – region B – nucleotide analogue units): 1-8-1, 1-8-2, 2-8-1, 2-8-2, 3-8-3, 2-8-3, 3-8-2, 4-8-1, 4-8-2, 1-8-4, 2-8-4, or 1-9-1, 1-9-2, 2-9-1, 2-9-2, 2-9-3, 3-9-2, 1-9-3, 3-9-1, 4-9-1, 1-9-4, 4-9-4 or 1-10-1, 1-10-2, 2-10-1, 2-10-2, 1-10-3, 3-10-1 and 4-10-4 or 3-11-4, 4-11-3 and 4-11-4 or 3-12-4 and 4-12-4, or 3-13-3 and 3-13-4 or 1-14-4, or 1-15-4 and 2-15-3. In some embodiments the number of nucleotides in A-B-C is selected from: 2-7-1, 1-7-2, 2-7-2, 3-7-3, 2-7-3, 3-7-2, 3-7-4, and 4-7-3.

In other embodiments, the ASO contains 10 DNA units in B, LDLLL in A (first wing) and LLDLL in C (second wing). In yet other embodiments, the ASO contains 9 DNA units in B, LDDLL in A, and LDLDLL in C. In still other embodiments, the ASO contains 10 DNA units in B, LLDLL in A, and LLDLL in C. In further embodiments, the ASO contains 9 DNA units in B, LLLLL in A, and LDDLL in C. In certain embodiments, each of regions A and C comprises three LNA monomers, and region B consists of 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleoside monomers, for example, DNA monomers. In some embodiments both A and C consist of two LNA units each, and B consists of 7, 8, or 9 nucleotide units, for example DNA units. In various embodiments, other gapmer designs include those where regions A and/or C consists of 3, 4, 5 or 6 nucleoside analogues, such as monomers containing a 2'-O-methoxyethyl-ribose sugar (2'-MOE) or monomers containing a 2'-fluoro-deoxyribose sugar, and region B consists of 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 nucleosides, such as DNA monomers, where regions A-B-C have 3-8-3, 3-9-3, 3-10-3, 5-10-5 or 4-12-4 monomers. Further gapmer designs are disclosed in WO 2007/146511A2, hereby incorporated by reference in its entirety.

In some embodiments, the alternating flank ASO has at least 10 contiguous nucleotides, comprising region A, region B, and region C (A-B-C), wherein region B comprises at least 5 consecutive nucleoside units and is flanked at 5' by region A of 1-8 contiguous nucleoside units and at 3' by region C of 1-8 contiguous nucleoside units, wherein region B, when formed in a duplex with a complementary RNA, is capable of recruiting RNaseH, and wherein region A and region C are selected from the group consisting of:

(i) region A comprises a 5' LNA nucleoside unit and a 3' LNA nucleoside unit, and at least one DNA nucleoside unit between the 5' LNA nucleoside unit and the 3' LNA nucleoside unit, and, region C comprises at least two 3' LNA nucleosides;

(ii) region A comprises at least one 5' LNA nucleoside and region C comprises a 5' LNA nucleoside unit, at least two terminal 3' LNA nucleoside units, and at least one DNA nucleoside unit between the 5' LNA nucleoside unit and the 3' LNA nucleoside units, and

(iii) region A comprises a 5' LNA nucleoside unit and a 3' LNA nucleoside unit, and at least one DNA nucleoside unit between the 5' LNA nucleoside unit and the 3' LNA nucleoside unit; and region C comprises a 5' LNA nucleoside unit, at least two terminal 3' LNA nucleoside units, and at least one DNA nucleoside unit between the 5' LNA nucleoside unit and the 3' LNA nucleoside units.

In some embodiments, region A or region C comprises 1, 2, or 3 DNA nucleoside units. In other embodiments, region A and region C comprise 1, 2, or 3 DNA nucleoside units. In yet other embodiments, region B comprises at least five consecutive DNA nucleoside units. In certain embodiments, region B comprises 6, 7, 8, 9, 10, 11, 12, 13 or 14 consecutive DNA nucleoside units. In some embodiments, region B is 8, 9 10, 11, or 12 nucleotides in length. In other embodiments, region A comprises two 5' terminal LNA nucleoside units. In some embodiments, region A has formula 5'$[LNA]_{1-3}[DNA]_{1-3}[LNA]_{1-3}$, or 5'$[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2}$. In other embodiments, region C has formula $[LNA]_{1-3}[DNA]_{1-3}[LNA]_{2-3}$ 3', or $[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2}[DNA]_{1-2}[LNA]_{2-3}$3'. In yet other embodiments, region A has formula 5'$[LNA]_{1-3}[DNA]_{1-3}[LNA]_{1-3}$, or 5'$[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2,}$ and region C comprises 2, 3, 4 or 5 consecutive LNA nucleoside units. In some embodiments, region C has formula $[LNA]_{1-3}[DNA]_{1-3}[LNA]_{2-3}$3' or $[LNA]_{1-2}[DNA]_{1-2}[LNA]_{1-2}[DNA]_{1-2}[LNA]_{2-3}$3', and region A comprises 1, 2, 3, 4 or 5 consecutive LNA nucleoside units. In still other embodiments, region A has a sequence of LNA and DNA nucleosides, 5' – 3' selected from the group consisting of L, LL, LDL, LLL, LLDL, LDLL, LDDL, LLLL, LLLLL, LLLDL, LLDLL, LDLLL, LLDDL, LDLDL, LDDLL, LDDLLL, LDLLDL, LDLDLL, LDDDLL, LLDDDL, and LDLDLD, wherein L represents a LNA nucleoside, and D represents a DNA nucleoside. In yet other embodiments, region C has a sequence of LNA and DNA nucleosides, 5' – 3' selected from the group consisting of LL, LLL, LLLL, LDLL, LLLLL, LLDLL, LDLLL, LDDLL, LDDLLL, LLDDLL, LDLDLL, LDDDLL, LDLDDLL, LDDLDLL, LDDDLLL, and LLDLDLL. In a further embodiment, region A has a sequence of LNA and DNA nucleosides, 5' – 3' selected from the group consisting of LDL, LLDL, LDLL, LDDL, LLLDL, LLDLL, LDLLL, LLDDL, LDDLL, LLDLD, LDLLD, LDDDL, LLLLDL, LLLDLL, LLDLDL, LDLLLL, LLLDDL, LLDLDL, LLDDLL, LDDLLL, LDLLDL, LDLDLL, LDDDLL, LLDDDL, and LDLDLD, and region C has a sequence of LNA and

DNA nucleosides, 5' – 3' selected from the group consisting of LDLL, LLDL, LLLLL, LLDLL, LDLLL, LDDLL, LDDLLL, LLDDLL, LDLDLL, LDDDLL, LDLDDLL, LDDLDLL, LDDDLLL, and LLDLDLL.

In certain embodiments, the alternating flank ASO has contiguous nucleotides comprising a sequence of nucleosides, 5'–3', selected from the group consisting of LDLDDDDDDDDDLLLL, LLDDDLLDDDDDDDDLL, LDLLDLDDDDDDDDDLL, LLLDDDDDDDDDDLDLL, LLLDDDDDDDDDLDDLL, LLLDDDDDDDDLDDDLL, LLLDDDDDDDDLDLDLL, LLLDLDDDDDDDDDLLL, LLLDLDDDDDDDDLDLL, LLLLDDDDDDDDDLDLL, LLLLDDDDDDDDLDDLL, LLLDDDLDDDDDDDDLL, LLLDDLDDDDDDDDDLL, LLLDDLLDDDDDDDDLL, LLLDDLLDDDDDDDLLL, LLLLLDDDDDDDLDDLL, LDLLLDDDDDDDDDDLL, LDLLLDDDDDDDLDDLL, LDLLLLDDDDDDDDDLL, LLDLLLDDDDDDDDDLL, LLLDLDDDDDDDDDDLL, LLLDLDDDDDDDLDDLL, LLLDLLDDDDDDDDDLL, LLLLDDDDDDDLDDDLL, LLLLLDDDDDDDDDLDLL, LLLLDDDDDDDDDDLDLL, LLLDDDDDDDDDDLDLL, LDLLDDDDDDDDDDLDLL, LDLLLDDDDDDDDLDLL, LLLDDDDDDDDDLDDLL, LLLDDDDDDDDDLDDDLL, LLLDDDDDDDDLDLDDLL, LLLLDDDDDDDDDLDDLL, LLLLDDDDDDDDDLDLLL, LLLLDDDDDDDDLDDLL, LLLLDDDDDDDDDLDDLLL, LLLLDDDDDDDDDLDLDLL, LLLLDDDDDDDDLDDLDLL, LLLDLDDDDDDDDDDDLL, LLDLLDDDDDDDDDDLL, LLDLLLDDDDDDDDLDLL, LLLDLDDDDDDDDDDDLL, LLLDLDDDDDDDDDLDLL, LLLDLDDDDDDDDLDDLL, LLLDLDDDDDDDLDLDLL, LLLLDDDDDDDDDLLDLL, LLLLLDDDDDDDDLDDLL, LLLLDDDDDDDDDDLLDL, LLLLDDDDDDDDLDLDLL, LLLLDDDDDDDDDLDDLL, LLLLDDDDDDDDDLDLLL, LLLLLDDDDDDDDLDDLL, LLLLDDDDDDDDDLLDLL, LLLDDDDDDDDDDDDLLLL, LDLLLDDDDDDDDDDLLDLL, LDDLLDDDDDDDDDDLDLLL, LLDLLDDDDDDDDDDLLDLL, LLDLDDDDDDDDDDDDLLLL, LLDDLDDDDDDDDDDDLLLL, LLLDLDDDDDDDDDDLLLL, LLDLDDDDDDDDDDDDLLLL, LLDLLDDDDDDDDDDLLLL, LLDDLDDDDDDDDDDDLLL, LLLLDDDDDDDDDDLDDLL, LLLDLDDDDDDDDDDLDDLLL, LLDLLDDDDDDDDDDLLLL, LLLLDDDDDDDDDDLDLDDLL, LLLDLDDDDDDDDDDLDDLLL, LLDLDLDDDDDDDDDDLLLL, LLDLLDDDDDDDDDDLDLLL, LLDLDLDDDDDDDDDDLLDLL, LLDDLLDDDDDDDDDDLLDLL, LLLLDDDDDDDDDLDDLDLL, LLLDDLDDDDDDDDDDLLDLL, LLDLLDDDDDDDDDDLLDDLL, LLDLDLDDDDDDDDDDLLLL, LLLDLDDDDDDDDDDLLDDLL, LLDDLLDDDDDDDDDDDLLLL,

LLDLLDDDDDDDDLDLDLL, LLLLDDDDDDDDDDLDDLLL, LLLDDLDDDDDDDDDDLLLL, LLLDLDDDDDDDDDDLLDLL, LLLLDDDDDDDDDDLDLDLL, LLLLDDDDDDDDDDDLDLLL, and LLDDLLDDDDDDDDDDLDLL; wherein L represents a LNA nucleoside, and D represents a DNA nucleoside. In other embodiments, the LNA nucleoside is beta-D-oxy LNA.

In yet other embodiments, an alternating flank ASO has contiguous nucleotides comprising an alternating sequence of LNA and DNA nucleoside units , 5'–3', selected from the group consisting of : **2**-3-**2**-8-**2**, **1**-1-**2**-1-**1**-9-**2**, **3**-10-**1**-1-**2**, **3**-9-**1**-2-**2**, **3**-8-**1**-3-**2**, **3**-8-**1**-1-**1**-1-**2**, **3**-1-**1**-9-**3**, **3**-1-**1**-8-**1**-1-**2**, **4**-9-**1**-1-**2**, **4**-8-**1**-2-**2**, **3**-3-**1**-8-**2**, **3**-2-**1**-9-**2**, **3**-2-**2**-8-**2**, **3**-2-**2**-7-**3**, **5**-7-**1**-2-**2**, **1**-1-**3**-10-**2**, **1**-1-**3**-7-**1**-2-**2**, **1**-1-**4**-9-**2**, **2**-1-**3**-9-**2**, **3**-1-**1**-10-**2**, **3**-1-**1**-7-**1**-2-**2**, **3**-1-**2**-9-**2**, **4**-7-**1**-3-**2**, **5**-9-**1**-1-**2**, **4**-10-**1**-1-**2**, **3**-11-**1**-1-**2**, **2**-1-**1**-10-**1**-1-**2**, **1**-1-**3**-9-**1**-1-**2**, **3**-10-**1**-2-**2**, **3**-9-**1**-3-**2**, **3**-8-**1**-1-**1**-2-**2**, **4**-9-**1**-2-**2**, **4**-9-**1**-1-**3**, **4**-8-**1**-3-**2**, **4**-8-**1**-2-**3**, **4**-8-**1**-1-**1**-1-**2**, **4**-7-**1**-2-**1**-1-**2**, **4**-7-**1**-1-**1**-2-**2**, **2**-1-**2**-11-**2**, **2**-1-**3**-8-**1**-1-**2**, **3**-1-**1**-11-**2**, **3**-1-**1**-9-**1**-1-**2**, **3**-1-**1**-8-**1**-2-**2**, **3**-1-**1**-7-**1**-1-**1**-1-**2**, **4**-9-**2**-1-**2**, **4**-7-**1**-3-**3**, **5**-9-**1**-1-**3**, **5**-9-**1**-2-**2**, **4**-10-**2**-1-**2**, **4**-10-**1**-1-**3**, **4**-10-**1**-2-**2**, **3**-11-**2**-1-**2**, **3**-11-**1**-1-**3**, **5**-9-**2**-1-**2**, **3**-11-**1**-2-**2**, **2**-1-**2**-9-**1**-2-**2**, **3**-1-**1**-10-**1**-1-**2**, **3**-1-**1**-9-**1**-2-**2**, **4**-9-**1**-1-**1**-1-**2**, **4**-8-**2**-1-**1**-1-**2**, **1**-1-**3**-10-**2**-1-**2**, **2**-1-**2**-10-**2**-1-**2**, **2**-1-**1**-12-**4**, **2**-2-**1**-11-**4**, **3**-1-**1**-11-**4**, **2**-1-**1**-13-**3**, **2**-1-**2**-11-**4**, **2**-2-**1**-12-**3**, **3**-11-**1**-2-**3**, **3**-1-**1**-12-**3**, **2**-1-**2**-12-**3**, **4**-11-**2**-1-**2**, **4**-10-**2**-2-**2**, **3**-2-**1**-9-**1**-1-**3**, **2**-2-**1**-1-**1**-9-**4**, **2**-2-**2**-9-**1**-1-**3**, **3**-1-**1**-9-**1**-1-**1**-1-**2**, **2**-1-**2**-9-**1**-2-**3**, **3**-1-**1**-10-**1**-1-**3**, **2**-1-**1**-2-**1**-9-**4**, **4**-9-**1**-1-**1**-2-**2**, **3**-1-**1**-9-**1**-2-**3**, **2**-1-**1**-1-**1**-10-**4**, **2**-1-**2**-10-**1**-1-**3**, **2**-1-**1**-1-**1**-9-**2**-1-**2**, **2**-2-**2**-9-**2**-1-**2**, **4**-9-**1**-2-**1**-1-**2**, **3**-2-**1**-9-**2**-1-**2**, **2**-1-**2**-9-**2**-2-**2**, **2**-1-**1**-1-**1**-9-**1**-1-**3**, **3**-1-**1**-9-**2**-2-**2**, **2**-2-**2**-10-**4**, **2**-1-**2**-9-**1**-1-**1**-1-**2**, **4**-10-**1**-2-**3**, **3**-2-**1**-10-**4**, **3**-1-**1**-10-**2**-1-**2**, **4**-10-**1**-1-**1**-1-**2**, **4**-11-**1**-1-**3**, **3**-12-**4**, **1**-2-**2**-10-**1**-1-**3**, and **2**-2-**2**-10-**1**-1-**2**; wherein the first numeral represents an number of LNA units, the next a number of DNA units, and alternating LNA and DNA regions thereafter.

In other embodiments, the ASOs of the disclosure are represented as any one of ASO numbers selected from FIGs. 1A to 1C and 2.

II.H. Internucleotide Linkages

The monomers of the ASOs described herein are coupled together via linkage groups. Suitably, each monomer is linked to the 3' adjacent monomer via a linkage group.

The person having ordinary skill in the art would understand that, in the context of the present disclosure, the 5' monomer at the end of an ASO does not comprise a 5' linkage group, although it may or may not comprise a 5' terminal group.

The terms "linkage group" and "internucleotide linkage" are intended to mean a group capable of covalently coupling together two nucleotides. Specific and preferred examples include phosphate groups and phosphorothioate groups.

The nucleotides of the ASO of the disclosure or contiguous nucleotides sequence thereof are coupled together via linkage groups. Suitably each nucleotide is linked to the 3' adjacent nucleotide via a linkage group.

Suitable internucleotide linkages include those listed within WO2007/031091, for example the internucleotide linkages listed on the first paragraph of page 34 of WO2007/031091 (hereby incorporated by reference in its entirety).

Examples of suitable internucleotide linkages that can be used with the disclosure include phosphodiester linkage (PO or subscript o), a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage (PS or subscript s), and combinations thereof.

It is, in some embodiments, preferred to modify the internucleotide linkage from its normal phosphodiester to one that is more resistant to nuclease attack, such as phosphorothioate or boranophosphate – these two, being cleavable by RNaseH, also allow that route of antisense inhibition in reducing the expression of the target gene.

Suitable sulphur (S) containing internucleotide linkages as provided herein may be preferred. Phosphorothioate internucleotide linkages are also preferred, particularly for the gap region (B) of gapmers. Phosphorothioate linkages can also be used for the flanking regions (A and C, and for linking A or C to D, and within region D, as appropriate).

Regions A, B and C, can, however, comprise internucleotide linkages other than phosphorothioate, such as phosphodiester linkages, particularly, for instance when the use of nucleotide analogues protects the internucleotide linkages within regions A and C from endo-nuclease degradation – such as when regions A and C comprise LNA nucleotides.

The internucleotide linkages in the ASO can be phosphodiester, phosphorothioate or boranophosphate so as to allow RNaseH cleavage of targeted RNA. Phosphorothioate is preferred for improved nuclease resistance and other reasons, such as ease of manufacture.

In some embodiments, the internucleotide linkages comprise one or more stereo-defined internucleotide linkages (*e.g.*, such as stereo-defined modified phosphate linkages, *e.g.*, phosphodiester, phosphorothioate, or boranophosphate linkages with a defined stereochemical structure). The term "stereo-defined internucleotide linkage" is used interchangeably with "chirally controlled internucleotide linkage" and refers to a internucleotide linkage in which the stereochemical designation of the phosphorus atom is controlled such that a specific amount of R_p or S_p of the internucleotide linkage is present within an ASO strand. The stereochemical designation of a chiral linkage can be defined (controlled) by, for example, asymmetric synthesis.

An ASO having at least one stereo-defined internucleotide linkage can be called as a stereo-defined ASO, which includes both a fully stereo-defined ASO and a partially stereo-defined ASO.

In some embodiments, an ASO is fully stereo-defined. A fully stereo-defined ASO refers to an ASO sequence having a defined chiral center (R_p or S_p) in each internucleotide linkage in the ASO. In some embodiments, an ASO is partially stereo-defined. A partially stereo-defined ASO refers to an ASO sequence having a defined chiral center (R_p or S_p) in at least one internucleotide linkage, but not in all of the internucleotide linkages. Therefore, a partially stereo-defined ASO can include linkages that are achiral or stereo-nondefined in addition to the at least one stereo-defined linkage. When an internucleotide linkage in an ASO is stereo-defined, the desired configuration, either R_p or S_p, is present in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or essentially 100% of the ASO.

In one aspect of the ASO of the disclosure, the nucleotides and/or nucleotide analogues are linked to each other by means of phosphorothioate groups. 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.

It is recognized that the inclusion of phosphodiester linkages, such as one or two linkages, into an otherwise phosphorothioate ASO, particularly between or adjacent to nucleotide analogue units (typically in region A and or C) can modify the bioavailability and/or bio-distribution of an ASO – see WO2008/113832, hereby incorporated by reference.

In some embodiments, such as the embodiments referred to above, where suitable and not specifically indicated, all remaining linkage groups are either phosphodiester or phosphorothioate, or a mixture thereof.

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 all the internucleotide linkage groups are phosphorothioate.

When referring to specific gapmer oligonucleotide sequences, such as those provided herein it will be understood that, in various embodiments, when the linkages are phosphorothioate linkages, alternative linkages, such as those disclosed herein can be used, for example phosphate (phosphodiester) linkages can be used, particularly for linkages between nucleotide analogues, such as LNA, units. Likewise, when referring to specific gapmer oligonucleotide sequences, such as those provided herein, when the C residues are annotated as 5-'methyl modified cytosine, in various embodiments, one or more of the Cs present in the ASO can be unmodified C residues.

US Publication No. 2011/0130441, which was published June 2, 2011 and is incorporated by reference herein in its entirety, refers to ASO compounds having at least one bicyclic nucleoside attached to the 3' or 5' termini by a neutral internucleoside linkage. The ASOs of the disclosure can therefore have at least one bicyclic nucleoside attached to the 3' or 5' termini by a neutral internucleoside linkage, such as one or more phosphotriester, methylphosphonate, MMI (3′-CH_2—$N(CH_3)$—O-5′), amide-3 (3′-CH_2—C(=O)—N(H)-5′), formacetal (3′-O—CH_2—O-5′) or thioformacetal (3′-S—CH_2—O-5′). The remaining linkages can be phosphorothioate.

In some embodiments, the ASOs of the disclosure have internucleotide linkages described in FIGs. 1A to 1C and 2. As used herein, *e.g.,* FIGs. 1A to 1C and 2, phosphorothioate linkages are indicated as "s", and phosphorodiester linkages are indicated by the absence of "s".

II.I. Conjugates

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 disclosure 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. WO 93/07883 and WO2013/033230 provides suitable conjugate moieties. Further suitable conjugate moieties are those capable of binding to the asialoglycoprotein receptor (ASGPr). In particular tri-valent N-acetylgalactosamine conjugate moieties are suitable for binding to the ASGPr, see for example WO 2014/076196, WO 2014/207232, and WO 2014/179620.

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.

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), and 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.

II.J. Activated ASOs

The term "activated ASO," as used herein, refers to an ASO of the disclosure that is covalently linked (*i.e.,* functionalized) to at least one functional moiety that permits covalent linkage of the ASO to one or more conjugated moieties, *i.e.,* moieties that are not themselves nucleic acids or monomers, to form the conjugates herein described. Typically, a functional moiety will comprise a chemical group that is capable of covalently bonding to the ASO via, *e.g.,* a 3'-hydroxyl group or the exocyclic NH_2 group of the adenine base, a spacer that can be hydrophilic and a terminal group that is capable of binding to a conjugated moiety (*e.g.,* an amino, sulfhydryl or hydroxyl group). In some embodiments, this terminal group is not protected, *e.g.,* is an NH_2 group. In other embodiments, the terminal group is protected, for example, by any suitable protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999).

In some embodiments, ASOs of the disclosure are functionalized at the 5' end in order to allow covalent attachment of the conjugated moiety to the 5' end of the ASO. In other embodiments, ASOs of the disclosure can be functionalized at the 3' end. In still other embodiments, ASOs of the disclosure can be functionalized along the backbone or on the heterocyclic base moiety. In yet

other embodiments, ASOs of the disclosure can be functionalized at more than one position independently selected from the 5' end, the 3' end, the backbone, and the base.

In some embodiments, activated ASOs of the disclosure are synthesized by incorporating during the synthesis one or more monomers that is covalently attached to a functional moiety. In other embodiments, activated ASOs of the disclosure are synthesized with monomers that have not been functionalized, and the ASO is functionalized upon completion of synthesis.

III. Pharmaceutical Compositions and Administration Routes

The ASO of the disclosure can be used in pharmaceutical formulations and compositions. Suitably, such compositions comprise a pharmaceutically acceptable diluent, carrier, salt, or adjuvant.

The ASO of the disclosure can be included in a unit formulation such as in a pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious side effects in the treated patient. However, in some forms of therapy, serious side effects may be acceptable in terms of ensuring a positive outcome to the therapeutic treatment.

The formulated drug may comprise pharmaceutically acceptable binding agents and adjuvants. Capsules, tablets, or pills can contain for example the following compounds: microcrystalline cellulose, gum or gelatin as binders; starch or lactose as excipients; stearates as lubricants; various sweetening or flavoring agents. For capsules the dosage unit may contain a liquid carrier like fatty oils. Likewise, coatings of sugar or enteric agents may be part of the dosage unit. The oligonucleotide formulations can also be emulsions of the active pharmaceutical ingredients and a lipid forming a micellular emulsion.

The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be (a) oral (b) pulmonary, *e.g.,* by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, (c) topical including epidermal, transdermal, ophthalmic and to mucous membranes including vaginal and rectal delivery; or (d) parenteral including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, *e.g.,* intrathecal, intra-cerebroventricular, intravitrea or intraventricular, administration. In one embodiment the ASO is administered IV, IP, orally, topically or as a bolus injection or administered directly in to the target organ. In another embodiment, the ASO is administered intrathecal or intra-cerebroventricular as a bolus injection.

Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, sprays, suppositories, liquids and powders.

Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Examples of topical formulations include those in which the ASO of the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Compositions and formulations for oral administration include but are not limited to powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Compositions and formulations for parenteral, intrathecal, intra-cerebroventricular, or intraventricular administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Delivery of drug to the target tissue can be enhanced by carrier-mediated delivery including, but not limited to, cationic liposomes, cyclodextrins, porphyrin derivatives, branched chain dendrimers, polyethylenimine polymers, nanoparticles and microspheres (Dass CR. J Pharm Pharmacol 2002; 54(I):3-27).

The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

For parenteral, subcutaneous, intradermal or topical administration the formulation can include a sterile diluent, buffers, regulators of tonicity and antibacterials. The active ASOs can be prepared with carriers that protect against degradation or immediate elimination from the body, including implants or microcapsules with controlled release properties. For intravenous administration the carriers can be physiological saline or phosphate buffered saline. International Publication No. WO2007/031091 (A2), published March 22, 2007, further provides suitable pharmaceutically acceptable diluent, carrier and adjuvants - which are hereby incorporated by reference.

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 or intra-cerebroventricular administration.

IV. Diagnostics

This disclosure further provides a diagnostic method useful during diagnosis of SNCA related diseases, *e.g.,* a synucleinopathy. Non-limiting examples of synucleinopathy include, but are not limited to, Parkinson's disease, Parkinson's Disease Dementia (PDD), dementia with Lewy bodies, and multiple system atrophy.

The ASOs of the disclosure can be used to measure expression of *SNCA* transcript in a tissue or body fluid from an individual and comparing the measured expression level with a standard *SNCA* transcript expression level in normal tissue or body fluid, whereby an increase in the expression level compared to the standard is indicative of a disorder treatable by an ASO of the disclosure.

The ASOs of the disclosure can be used to assay *SNCA* transcript levels in a biological sample using any methods known to those of skill in the art. (Touboul *et. al.*, *Anticancer Res.* (2002) 22 (6A): 3349-56; Verjout *et. al.*, *Mutat. Res.* (2000) 640: 127-38); Stowe *et. al.*, *J. Virol. Methods* (1998) 75 (1): 93-91).

By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source of cells potentially expressing *SNCA* transcript. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art.

V. Kits comprising ASOs

This disclosure further provides kits that comprise an ASO of the disclosure described herein and that can be used to perform the methods described herein. In certain embodiments, a kit comprises at least one ASO in one or more containers. In some embodiments, the kits contain all of the components necessary and/or sufficient to perform a detection assay, including all controls, directions for performing assays, and any necessary software for analysis and presentation of results. One skilled in the art will readily recognize that the disclosed ASO can be readily incorporated into one of the established kit formats which are well known in the art.

VI. Methods of Using

The ASOs of the disclosure can be utilized for therapeutics and prophylaxis.

SNCA is a 140 amino acid protein preferentially expressed in neurons at pre-synaptic terminals where it is thought to play a role in regulating synaptic transmission. It has been proposed to exist natively as both an unfolded monomer and as a stable tetramer of α-helices and has been shown to undergo several posttranslational modifications. One modification that has been extensively studied is phosphorylation of SNCA at amino acid serine 129 (S129). Normally, only a small percentage of SNCA is constitutively phosphorylated at S129 (pS129), whereas the vast majority of

SNCA found in pathological intracellular inclusions is pS129 SNCA. These pathological inclusions consist of aggregated, insoluble accumulations of misfolded SNCA proteins and are a characteristic feature of a group of neurodegenerative diseases collectively known as synucleinopathies.

In synucleinopathies, SNCA can form pathological aggregates in neurons known as Lewy bodies, which are characteristic of both Parkinson's Disease (PD), Parkinson's Disease Dementia (PDD), and dementia with Lewy bodies (DLB). The present ASOs therefore can reduce the number of the SNCA pathological aggregates or prevent formation of the SNCA pathological aggregates. Additionally, abnormal SNCA-rich lesions called glial cytoplasmic inclusions (GCIs) are found in oligodendrocytes, and represent the hallmark of a rapidly progressing, fatal synucleinopathy known as multiple systems atrophy (MSA). In some embodiments, the ASOs of the disclosure reduce the number of GCIs or prevent formation of GCIs. Reports of either undetectable or low levels of *SNCA* mRNA expression in oligodendrocytes suggest that some pathological form of SNCA is propagated from neurons, where it is highly expressed, to oligodendrocytes. In certain embodiments, the ASOs of the disclosure reduce or prevent propagation of SNCA, *e.g.,* pathological form of SNCA, from neurons.

The ASOs can be used in research, *e.g.,* to specifically inhibit the synthesis of SNCA protein (typically by degrading or inhibiting the mRNA and thereby prevent protein formation) in cells and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Further provided are methods of down-regulating the expression of *SNCA* mRNA and/or SNCA protein in cells or tissues comprising contacting the cells or tissues, *in vitro* or *in vivo*, with an effective amount of one or more of the ASOs, conjugates, or compositions of the disclosure.

For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of *SNCA* transcript and/or SNCA protein is treated by administering ASO compounds in accordance with this disclosure. Further provided are methods of treating a mammal, such as treating a human, suspected of having or being prone to a disease or condition, associated with expression of *SNCA* transcript and/or SNCA protein by administering a therapeutically or prophylactically effective amount of one or more of the ASOs or compositions of the disclosure. The ASO, a conjugate, or a pharmaceutical composition according to the disclosure is typically administered in an effective amount. In some embodiments, the ASO or conjugate of the disclosure is used in therapy.

The disclosure further provides for an ASO according to the disclosure, for use in treating one or more of the diseases referred to herein, such as a disease selected from the group consisting of

Parkinson's disease, Parkinson's Disease Dementia (PDD), dementia with Lewy bodies, multiple system atrophy, and any combinations thereof.

The disclosure further provides for a method for treating α-synucleinopathies, the method comprising administering an effective amount of one or more ASOs, conjugates, or pharmaceutical compositions thereof to an animal in need thereof (such as a patient in need thereof).

In certain embodiments, the disease, disorder, or condition is associated with overexpression of *SNCA* gene transcript and/or SNCA protein.

The disclosure also provides for methods of inhibiting (*e.g.,* by reducing) the expression of *SNCA* gene transcript and/or SNCA protein in a cell or a tissue, the method comprising contacting the cell or tissue, *in vitro* or *in vivo*, with an effective amount of one or more ASOs, conjugates, or pharmaceutical compositions thereof, of the disclosure to affect degradation of expression of *SNCA* gene transcript thereby reducing SNCA protein.

In certain embodiments, the ASOs are used to reduce the expression of *SNCA* mRNA in one or more sections of brain, *e.g.,* hippocampus, brainstem, striatum, or any combinations thereof. In other embodiments, the ASOs reduce the expression of *SNCA* mRNA, *e.g.,* in brain stem and/or striatum, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5% compared to the *SNCA* mRNA expression after administration of or exposure to a vehicle (no ASO), at day 3, day 5, day 7, day 10, day 14, day 15, day 20, day 21, or day 25. In some embodiments, the expression of *SNCA* mRNA is maintained below 70%, below 60%, below 50%, below 40%, below 30%, below 20%, below 10%, or below 5% compared to the *SNCA* mRNA expression after administration of or exposure to a vehicle (no ASO) until day 28, day 30, day 32, day 35, day 40, day 42, day 45, day 49, day 50, day 56, day 60, day 63, day 70, or day 75.

In other embodiments, the ASOs of the present disclosure reduces *SNCA* mRNA and/or SNCA protein expression in medulla, caudate putamen, pons cerebellum, lumbar spinal cord, frontal cortex, and/or any combinations thereof.

The disclosure also provides for the use of the ASO or conjugate of the disclosure as described for the manufacture of a medicament. The disclosure also provides for a composition comprising the ASO or conjugate thereof for use in treating a disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein. The present disclosure also provides ASOs or conjugates for use in therapy. The present disclosure additionally provides ASOs or conjugates for use in the treatment of synucleinopathy.

The disclosure further provides for a method for inhibiting SNCA protein in a cell which is expressing SNCA comprising administering an ASO or a conjugate according to the disclosure to the cell so as to affect the inhibition of SNCA protein in the cell.

The disclosure includes a method of reducing, ameliorating, preventing, or treating neuronal hyperexcitability in a subject in need thereof comprising administering an ASO or a conjugate according to the disclosure.

The disclosure also provides for a method for treating a disorder as referred to herein the method comprising administering an ASO or a conjugate according to the disclosure as herein described and/or a pharmaceutical composition according to the disclosure to a patient in need thereof.

The ASOs and other compositions according to the disclosure can be used for the treatment of conditions associated with over expression or expression of mutated version of SNCA protein.

The disclosure provides for the ASO or the conjugate according to disclosure, for use as a medicament, such as for the treatment of α-Synucleinopathies. In some embodiments the α-Synucleinopathy is a disease selected from the group consisting of Parkinson's disease, Parkinson's Disease Dementia (PDD), dementia with Lewy bodies, multiple system atrophy, and any combinations thereof.

The disclosure further provides use of an ASO of the disclosure in the manufacture of a medicament for the treatment of a disease, disorder or condition as referred to herein. In some embodiments, the ASO or conjugate of the disclosure is used for the manufacture of a medicament for the treatment of a α-Synucleinopathy, a seizure disorder, or a combination thereof.

Generally stated, one aspect of the disclosure is directed to a method of treating a mammal suffering from or susceptible to conditions associated with abnormal levels of SNCA *i.e.*, a α-synucleinopathy), comprising administering to the mammal and therapeutically effective amount of an ASO targeted to *SNCA* transcript that comprises one or more LNA units. The ASO, a conjugate or a pharmaceutical composition according to the disclosure is typically administered in an effective amount.

In some embodiments, the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is administered at a dose of 0.1 – 15 mg/kg, such as from 0.2 – 10 mg/kg, such as from 0.25 – 5 mg/kg. The administration can be once a week, every 2nd week, every third week or even once a month.

The disease or disorder, as referred to herein, can, in some embodiments be associated with a mutation in the *SNCA* gene or a gene whose protein product is associated with or interacts with

SNCA protein. Therefore, in some embodiments, the target mRNA is a mutated form of the *SNCA* sequence.

An interesting aspect of the disclosure is directed to the use of an ASO (compound) as defined herein or a conjugate as defined herein for the preparation of a medicament for the treatment of a disease, disorder, or condition as referred to herein.

The methods of the disclosure can be employed for treatment or prophylaxis against diseases caused by abnormal levels of SNCA protein. In some embodiments, diseases caused by abnormal levels of SNCA protein are α-synucleinopathies. In certain embodiments, α-synucleinopathies include Parkinson's disease, Parkinson's Disease Dementia (PDD), dementia with Lewy bodies, and multiple system atrophy.

Alternatively stated, in some embodiments, the disclosure is furthermore directed to a method for treating abnormal levels of SNCA protein, the method comprising administering an ASO of the disclosure, or a conjugate of the disclosure, or a pharmaceutical composition of the disclosure to a patient in need thereof.

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

The disclosure further relates to use of a compound, composition, or a conjugate as defined herein for the manufacture of a medicament for the treatment of abnormal levels of SNCA protein or expression of mutant forms of SNCA protein (such as allelic variants, such as those associated with one of the diseases referred to herein).

A patient who is in need of treatment is a patient suffering from or likely to suffer from the disease or disorder.

The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Sambrook *et al.*, ed. (1989) Molecular Cloning A Laboratory Manual (2nd ed.; Cold Spring Harbor Laboratory Press); Sambrook *et al.*, ed. (1992) Molecular Cloning: A Laboratory Manual, (Cold Springs Harbor Laboratory, NY); D. N. Glover ed., (1985) DNA Cloning, Volumes I and II; Gait, ed. (1984) Oligonucleotide Synthesis; Mullis *et al.* U.S. Pat. No. 4,683,195; Hames and Higgins, eds. (1984) Nucleic Acid Hybridization; Hames and Higgins, eds. (1984) Transcription And Translation; Freshney (1987) Culture Of Animal Cells (Alan R. Liss, Inc.); Immobilized Cells And Enzymes (IRL Press) (1986); Perbal (1984) A Practical Guide To Molecular Cloning; the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Miller and

Calos eds. (1987) Gene Transfer Vectors For Mammalian Cells, (Cold Spring Harbor Laboratory); Wu *et al*., eds., Methods In Enzymology, Vols. 154 and 155; Mayer and Walker, eds. (1987) Immunochemical Methods In Cell And Molecular Biology (Academic Press, London); Weir and Blackwell, eds., (1986) Handbook Of Experimental Immunology, Volumes I-IV; Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986);); Crooke, Antisense drug Technology: Principles, Strategies and Applications, 2nd Ed. CRC Press (2007) and in Ausubel *et al*. (1989) Current Protocols in Molecular Biology (John Wiley and Sons, Baltimore, Md.).

All of the references cited above, as well as all references cited herein, are incorporated herein by reference in their entireties.

EMODIMENTS

1. An antisense oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length that is complementary to a nucleic acid sequence within an alpha-synuclein (*SNCA*) transcript, wherein the nucleic acid sequence is selected from the group consisting of (i) nucleotides 4942 – 5343 of SEQ ID NO: 1; (ii) nucleotides 6326 – 7041 of SEQ ID NO: 1; (iia) nucleotides 6336 – 7041 of SEQ ID NO: 1; (iii) nucleotides 7329 – 7600 of SEQ ID NO: 1; (iv) nucleotides 7630 – 7783 of SEQ ID NO: 1; (iva) nucleotides 7750 – 7783 of SEQ ID NO: 1; (v) nucleotides 8277 – 8501 of SEQ ID NO: 1; (vi) nucleotides 9034 – 9526 of SEQ ID NO: 1; (vii) nucleotides 9982 – 14279 of SEQ ID NO: 1; (viii) nucleotides 15204 – 19041 of SEQ ID NO: 1; (ix) nucleotides 20351 – 29654 of SEQ ID NO: 1; (ixa) nucleotides 20351 – 20908 of SEQ ID NO: 1; (ixb) nucleotides 21052 - 29654 of SEQ ID NO: 1; (x) nucleotides 30931 – 33938 of SEQ ID NO: 1; (xi) nucleotides 34932 – 37077 of SEQ ID NO: 1; (xii) nucleotides 38081 – 42869 of SEQ ID NO: 1; (xiii) nucleotides 44640 – 44861 of SEQ ID NO: 1; (xiv) nucleotides 46173 – 46920 of SEQ ID NO: 1; (xv) nucleotides 47924 – 58752 of SEQ ID NO: 1; (xvi) nucleotides 60678 – 60905 of SEQ ID NO: 1; (xvii) nucleotides 62066 – 62397 of SEQ ID NO: 1; (xviii) nucleotides 67759 – 71625 of SEQ ID NO: 1; (xix) nucleotides 72926 – 86991 of SEQ ID NO: 1; (xx) nucleotides 88168 – 93783 of SEQ ID NO: 1; (xxi) nucleotides 94976 – 102573 of SEQ ID NO: 1; (xxii) nucleotides 104920 – 107438 of SEQ ID NO: 1; (xxiii) nucleotides 108948 – 119285 of SEQ ID NO: 1; (xxiiia) nucleotides 108948 – 114019 of SEQ ID NO: 1; (xxiib) nucleotides 114292 – 116636 of SEQ ID NO: 1; (xxiv) nucleotides 131 - 678 of SEQ ID NO: 5; (xxv) nucleotides 131-348 of SEQ ID NO: 3; (xxvi) nucleotides 1 - 162 of SEQ ID NO: 4; (xxvii) nucleotides 126 – 352 of SEQ ID NO: 2; (xxviii) nucleotides 276 – 537 of SEQ ID NO: 2; (xxix) nucleotides 461 – 681 of SEQ ID NO: 2; and (xxx) nucleotides 541 – 766 of SEQ ID NO: 2.

2. The antisense oligonucleotide of embodiment 1, wherein the nucleic acid sequence is selected from the group consisting of (i) nucleotides 4992 – 5109 of SEQ ID NO: 1; (ii) nucleotides 6376 – 6991 of SEQ ID NO: 1; (iii) nucleotides 7379 – 7600 of SEQ ID NO: 1; (iv) nucleotides 7630 – 7733 of SEQ ID NO: 1; (v) nucleotides 8327 – 8451 of SEQ ID NO: 1; (vi) nucleotides 9084 – 9476 of SEQ ID NO: 1; (vii) nucleotides 10032 – 14229 of SEQ ID NO: 1; (viii) nucleotides 15254 – 18991 of SEQ ID NO: 1; (ix) nucleotides 20401 – 29604 of SEQ ID NO: 1; (x) nucleotides 30981 – 33888 of SEQ ID NO: 1; (xi) nucleotides 34982 – 37027 of SEQ ID NO: 1; (xii) nucleotides 38131 – 42819 of SEQ ID NO: 1; (xiii) nucleotides 44690 – 44811 of SEQ ID NO: 1; (xiv) nucleotides 46223 – 46870 of SEQ ID NO: 1; (xv) nucleotides 47974 – 58702 of SEQ ID NO: 1; (xvi) nucleotides 60728 – 608555 of SEQ ID NO: 1; (xvii) nucleotides 62116 – 62347 of SEQ ID NO: 1; (xviii) nucleotides 67809 – 71575 of SEQ ID NO: 1; (xix) nucleotides 72976 – 86941 of SEQ ID NO: 1; (xx) nucleotides 88218 – 93733 of SEQ ID NO: 1; (xxi) nucleotides 95026 – 102523 of SEQ ID NO: 1; (xxii) nucleotides 104970 – 107388 of SEQ ID NO: 1; (xxiii) nucleotides 108998 – 119235 of SEQ ID NO: 1; (xxiv) nucleotides 181 – 628 of SEQ ID NO: 5; (xxv) nucleotides 181 - 298 of SEQ ID NO: 3; (xxvi) nucleotides 15 – 112 of SEQ ID NO: 4; (xxvii) nucleotides 176 – 302 of SEQ ID NO: 2; (xxviii) nucleotides 326 – 487 of SEQ ID NO: 2; (xxix) nucleotides 511 – 631 of SEQ ID NO: 2; and (xxx) nucleotides 591 – 716 of SEQ ID NO: 2.

3. The antisense oligonucleotide of embodiment 1, wherein the nucleic acid sequence is selected from the group consisting of (i) nucleotides 5042 – 5243 of SEQ ID NO: 1; (ii) nucleotides 6426 – 6941 of SEQ ID NO: 1; (iii) nucleotides 7429 – 7600 of SEQ ID NO: 1; (iv) nucleotides 7630 – 7683 of SEQ ID NO: 1; (v) nucleotides 8377– 8401 of SEQ ID NO: 1; (vi) nucleotides 9134 – 9426 of SEQ ID NO: 1; (vii) nucleotides 10082 – 14179 of SEQ ID NO: 1; (viii) nucleotides 15304 – 18941 of SEQ ID NO: 1; (ix) nucleotides 20451 – 29554 of SEQ ID NO: 1; (x) nucleotides 31031 – 33838 of SEQ ID NO: 1; (xi) nucleotides 35032 – 36977 of SEQ ID NO: 1; (xii) nucleotides 38181 – 42769 of SEQ ID NO: 1; (xiii) nucleotides 44740 – 44761 of SEQ ID NO: 1; (xiv) nucleotides 46273 – 46820 of SEQ ID NO: 1; (xv) nucleotides 48024 – 58752 of SEQ ID NO: 1; (xvi) nucleotides 60778 – 60805 of SEQ ID NO: 1; (xvii) nucleotides 62166 – 62297 of SEQ ID NO: 1; (xviii) nucleotides 67859 – 71525 of SEQ ID NO: 1; (xix) nucleotides 73026 – 86891 of SEQ ID NO: 1; (xx) nucleotides 88268 – 93683 of SEQ ID NO: 1; (xxi) nucleotides 95076 – 102473 of SEQ ID NO: 1; (xxii) nucleotides 105020 – 107338 of SEQ ID NO: 1; (xxiii) nucleotides 109048 – 119185 of SEQ ID NO: 1; (xxiv) nucleotides 231 – 248 or 563 - 578 of SEQ ID NO: 5; (xxv) nucleotides 231 – 248 of SEQ ID NO: 3; (xxvi) nucleotides 38 – 62 of SEQ ID NO: 4; (xxvii) nucleotides 226 – 252 of SEQ ID NO: 2; (xxviii) nucleotides

376 – 437 of SEQ ID NO: 2; (xxix) nucleotides 561 – 581 of SEQ ID NO: 2; and (xxx) nucleotides 641 – 666 of SEQ ID NO: 2.

4. The antisense oligonucleotide of embodiment 1, wherein the nucleic acid sequence corresponds to nucleotides nucleotides 21052 – 29654 of SEQ ID NO: 1;nucleotides 30931 – 33938 of SEQ ID NO: 1; nucleotides 44640 – 44861 of SEQ ID NO: 1; or nucleotides 47924 – 58752 of SEQ ID NO: 1.

5. The antisense oligonucleotide of embodiment 1 or 4, wherein the nucleic acid sequence corresponds to nucleotides 24483 - 28791 of SEQ ID NO: 1; nucleotides 32225 - 32245 of SEQ ID NO: 1; nucleotides 44740 - 44760 of SEQ ID NO: 1or nucleotides 48640 - 48660 of SEQ ID NO: 1.

6. The antisense oligonucleotide of embodiment 1, wherein the nucleic acid sequence corresponds to (i) nucleotides 7502 – 7600 of SEQ ID NO: 1; (ii) nucleotides 7630 – 7719 of SEQ ID NO: 1; (iii) nucleotides 116881 – 117312 of SEQ ID NO: 1; or (iv) nucleotides 118606 – 118825 of SEQ ID NO: 1.

7. The antisense oligonucleotide of embodiment 1 or 6, wherein the nucleic acid sequence is nucleotides 116881 – 117119 of SEQ ID NO: 1; nucleotides 116968 – 117198 of SEQ ID NO: 1; or nucleotides 117085 – 117312 of SEQ ID NO: 1.

8. The antisense oligonucleotide of embodiment 1, 6 or 7 wherein the nucleic acid sequence is nucleotides (i) nucleotides 7552 – 7600 of SEQ ID NO: 1; (ii) nucleotides 7630 – 7669 of SEQ ID NO: 1; (iii) nucleotides 116931 – 117262 of SEQ ID NO: 1; or (iv) nucleotides 118656 – 118775 of SEQ ID NO: 1.

9. The antisense oligonucleotide of embodiment 8, wherein the nucleic acid sequence is nucleotides 116931 – 117069 of SEQ ID NO: 1; nucleotides 117018 – 117148 of SEQ ID NO: 1; or nucleotides 117135 – 117262 of SEQ ID NO: 1.

10. The antisense oligonucleotide of embodiment 1, wherein the nucleic acid sequence is nucleotides (i) nucleotides 116981 — 117212 of SEQ ID NO: 1 or (ii) nucleotides 118706 – 118725 of SEQ ID NO: 1.

11. The antisense oligonucleotide of embodiment 10, wherein the nucleic acid sequence is nucleotides 116981 – 117019 of SEQ ID NO: 1; nucleotides 117068 – 117098 of SEQ ID NO: 1; or nucleotides 117185 – 117212 of SEQ ID NO: 1.

12. The antisense oligonucleotide of any one of embodiments 1 to 11, which has from 10 to 24 nucleotides in length or from 14 to 21 nucleotides in length.

13. The antisense oligonucleotide of any one of embodiments 1 to 12, which has 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides in length.

14. The antisense oligonucleotide of any one of embodiments 1 to 13, wherein the *SNCA* transcript comprises SEQ ID NO: 1.

15. The antisense oligonucleotide of any one of embodiments 1 to 14, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 7 to SEQ ID NO: 1878 with one, two, three, or four mismatches.

16. The antisense oligonucleotide of any one of embodiments 1 to 15, wherein the contiguous nucleotide sequence comprises SEQ ID NO: 7 to SEQ ID NO: 1878.

17. The antisense oligonucleotide of embodiment 1 or 4, wherein the contiguous nucleotide sequence comprises a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 with no more than 2 mismatches.

18. The antisense oligonucleotide of embodiment 1 or 17, wherein the contiguous nucleotide sequence consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353.

19. The antisense oligonucleotide of any one of embodiments 1, 4, 5, 11 - 18, wherein the contiguous nucleotide sequence comprises a sequence selected from the group consisting of SEQ ID NO: 276; 278; 296; 295; 325; 328; 326; 329; 330; 327; 332; 333; 331; 339; 341; 390; 522 and 559.

20. The antisense oligonucleotide of any one of embodiments 1 to 19, wherein the antisense oligonucleotide is capable of inhibiting the expression of the human *SNCA* transcript in a cell which is expressing the human *SNCA* transcript.

21. The antisense oligonucleotide of any of embodiments 1 to 20, wherein the contiguous nucleotide sequence comprises at least one nucleotide analogueue.

22. The antisense oligonucleotide of any of embodiment 21, whereinthe nucleotide analogue is a 2’ sugar modified nucleoside.

23. The method of embodiment 22, wherein the 2’ sugar modified nucleoside is an affinity enhancing sugar modified nucleoside.

24. The antisense oligonucleotide of any one of embodiments 1 to 23, which is a gapmer.

25. The antisense oligonucleotide of embodiment 24, which is an alternating flank gapmer.

26. The antisense oligonucleotide of embodiment 24 or 25, which comprises the formula of 5'-A-B-C-3', wherein

    a) region B is a contiguous sequence of at least 6 DNA units, which are capable of recruiting RNase;

    a) region A is a first wing sequence of 1 to 10 nucleotides, wherein the first wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 3' end of A; and

    a) region C is a second wing sequence of 1 to 10 nucleotides, wherein the second wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 5' end of C.

27. The antisense oligonucleotide of embodiment 26, wherein region A comprises 1-4 nucleotide analogues, region B consist of 8 to 15 DNA units and region C comprises 2 to 4 nucleotide analogues.

28. The antisense oligonucleotide of embodiment 26 or 27, wherein region A comprises a combination of nucleotide analogues and DNA unit selected from (i) 1-9 nucleotide analogues and 1 DNA unit; (ii) 1-8 nucleotide analogues and 1-2 DNA units; (iii) 1-7 nucleotide analogues and 1-3 DNA units; (iv) 1-6 nucleotide analogues and 1-4 DNA units; (v) 1-5 nucleotide analogues and 1-5 DNA units; (vi) 1-4 nucleotide analogues and 1-6 DNA units; (vii) 1-3 nucleotide analogues and 1-7 DNA units; (viii) 1-2 nucleotide analogues and 1-8 DNA units; and (ix) 1 nucleotide analogue and 1-9 DNA units.

29. The antisense oligonucleotide of embodiment 26 or 27, wherein region C comprises a combination of nucleotide analogues and DNA unit selected from (i) 1-9 nucleotide analogues and 1 DNA unit; (ii) 1-8 nucleotide analogues and 1-2 DNA units; (iii) 1-7 nucleotide analogues and 1-3 DNA units; (iv) 1-6 nucleotide analogues and 1-4 DNA units; (v) 1-5 nucleotide analogues and 1-5 DNA units; (vi) 1-4 nucleotide analogues and 1-6 DNA units; (vii) 1-3 nucleotide analogues and 1-7 DNA units; (viii) 1-2 nucleotide analogues and 1-8 DNA units; and (ix) 1 nucleotide analogue and 1-9 DNA units.

30. The antisense oligonucleotide of any one of embodiments 26 to 29, wherein region A is a first wing design selected from any ASOs in FIGs. 1A to 1C and 2, and/or region C is a second wing design selected from any ASOs in FIGs. 1A to 1C and 2, wherein the upper letter is a nucleoside analog and the lower letter is a DNA.

31. The antisense oligonucleotide of any one of embodiments 1 to 30, which comprises at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten nucleotide analogues.

32. The antisense oligonucleotide of any one of embodiments 21 to 31, wherein the nucleotide analogue or analogues are independently selected from one or more 2' sugar modified nucleosides selected from the group consisting of Locked Nucleic Acid (LNA); 2'-O-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), constrained ethyl nucleoside (cEt), 2'-O-methyl nucleic acid (2'-OMe), 2'-O-methoxyethyl nucleic acid (2'-MOE), and any combination thereof.

33. The antisense oligonucleotide of any one of embodiments 1 to 32, wherein the nucleotide analogue or analogues comprise a bicyclic sugar.

34. The antisense oligonucleotide of embodiment 33, wherein the bicyclic sugar comprises cEt, 2',4'-constrained 2′-O-methoxyethyl (cMOE), α-L-LNA, β-D-LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, oxy-LNA, or thio-LNA.

35. The antisense oligonucleotide of any one of embodiments 21 to 34, wherein the nucleotide analogue or analogues comprise a β-D-oxy-LNA.

36. The antisense oligonucleotide of any one of embodiments 21 to 35, wherein the antisense oligonucleotide comprises one or more 5'methyl cytosine nucleobases.

37. The antisense oligonucleotide of any one of embodiments 24 to 36, which comprises two to five LNAs on the 5' region of the antisense oligonucleotide.

38. The antisense oligonucleotide of any one of embodiments 24 to 37, which comprises two to five LNAs on the 3' region of the antisense oligonucleotide.

39. The antisense oligonucleotide of any one of embodiments 1 to 38, which comprises an internucleoside linkage selected from: a phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, a phosphorothioate linkage, and combinations thereof.

40. The antisense oligonucleotide of any one of embodiments 1 to 39, wherein 50% of the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

41. The antisense oligonucleotide of any one of embodiments 1 to 40, wherein the internucleoside linkage comprises one or more stereodefined, modified phosphate linkages.

42. The antisense oligonucleotide of any one of embodiments 1 to 40, wherein all the internucleoside linkages in the contiguous nucleotide sequence are phosphorothioate.

43. The antisense oligonucleotide of any one of embodiments 1 to 42, wherein the antisense oligonucleotide has an *in vivo* tolerability less than or equal to a total score of 4, wherein the total score is the sum of a unit score of five categories, which are 1) hyperactivity; 2) decreased activity and arousal; 3) motor dysfunction and/or ataxia; 4) abnormal posture and breathing; and 5) tremor and/or convulsions, and wherein the unit score for each category is measured on a scale of 0-4.

44. The antisense oligonucleotide of embodiment 43, wherein the *in vivo* tolerability is less than or equal to the total score of 3, the total score of 2, the total score of 1, or the total score of 0.

45. The antisense oligonucleotide of any one of embodiments 1 to 44, which reduces expression of *SNCA* mRNA in a cell by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a cell not exposed to the antisense oligonucleotide.

46. The antisense oligonucleotide of any one of embodiments 1 to 45, which reduces expression of SNCA protein in a cell by at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% compared to a cell not exposed to the antisense oligonucleotide.

47. The antisense oligonucleotide of any one embodiments 1 to 46, which comprises the nucleotides A, T, C, and G and at least one analogue of the nucleotides A, T, C, and G, and has a sequence score greater than or equal to 0.2, wherein the sequence score is calculated by formula I:

$$\frac{\#\text{ of C nucleotides and analogues thereof} - \#\text{ of G nucleotides and analogues thereof}}{\text{Total nucleotide length.}} \quad \text{(I)}$$

48. The antisense oligonucleotide of embodiment 1 to 47, wherein the nucleotide sequence comprises, consists essentially of, or consists of a sequence selected from the group consisting of SEQ ID NOs: 7 to 1878 with a design selected from the group consisting of the designs in Figures 1A to 1C and 2, wherein the upper case letter is a sugar modified nucleoside and the lower case letter is DNA.

49. The antisense oligonucleotide of embodiment 37, wherein the nucleotide sequence comprises, consists essentially of, or consists of SEQ ID NO: 1436 with the design of ASO-003092 and SEQ ID NO: 1547 with the design of ASO-003179. wherein the upper case letter is a nucleoside analogue and the lower case letter is DNA.

50. The antisense oligonucleotide of embodiment 1 to,48 wherein the nucleotide sequence comprises, consists essentially of, or consists of a sequence selected from the group consisting of wherein the contiguous nucleotide sequence consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 with a design selected from the group consisting of the designs in Figures 1A to 1C, wherein the upper case letter is a sugar modified nucleoside and the lower case letter is DNA.

51. The antisense oligonucleotide of embodiment 50, wherein the contiguous nucleotide sequence comprises a sequence selected from the group consisting of with a design selected from the group consisting of:
TTCtctatataacatCACT (SEQ ID NO: 276)
TTTCtctatataacaTCAC (SEQ ID NO: 278);
AACTtttacataccACAT (SEQ ID NO: 296);
AACTtttacataccaCATT (SEQ ID NO: 295);
ATTAttcatcacaatCCA (SEQ ID NO: 325);
ATTAttcatcacaATCC (SEQ ID NO:328);
CattattcatcacaaTCCA (SEQ ID NO:326);
CATtattcatcacaATCC (SEQ ID NO:329);
ACAttattcatcacaaTCC (SEQ ID NO: 330);
AcattattcatcacaaTCCA (SEQ ID NO: 327);
ACATtattcatcacAATC (SEQ ID NO: 332);
TACAttattcatcacAATC (SEQ ID NO: 333);
TAcattattcatcacaaTCC (SEQ ID NO: 331);
TTCaacatttttatttCACA (SEQ ID NO:339);
ATTCaacatttttattTCAC (SEQ ID NO: 341);
ACTAtgatacttcACTC (SEQ ID NO: 390);
ACACattaactactCATA (SEQ ID NO: 522) and
GTCAaaatattcttaCTTC (SEQ ID NO:559),
wherein the upper case letters indicate a sugar modified nucleoside analouge and the lower case letters indicate DNAs.

52. The antisense oligonucleotide of any one of embodiments 1 to 48, wherein the nucleotide sequence comprises, consists essentially of, or consists of a sequence selected from the group consisting of SEQ ID NOs: 7 to 1878 with the corresponding chemical structure in FIGs. 1A to 1C and 2.

53. The antisense oligonucleotide of any one of embodiment 1 to 52, wherein the contiguous nucleotide sequence has a the chemical structure of ASO-003092 or ASO-003179.

54. The antisense oligonucleotide of any one of claims one of embodiment 1 to 52, wherein the contiguous nucleotide sequence has a the chemical structure selected from the group consisting of ASO-008387; ASO-008388; ASO-008501; ASO-008502; ASO-008529; ASO-008530; ASO-008531; ASO-008532; ASO-008533; ASO-008534; ASO-008535; ASO-008536; ASO-008537; ASO-008543; ASO-008545; ASO-008584; ASO-008226 and ASO-008261.

55. A conjugate comprising the antisense oligonucleotide of any one of embodiments 1 to 53, wherein the antisense oligonucleotide is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

56. The conjugate of embodiment 55, wherein the non-nucleotide or non-polynucleotide moiety comprises a protein, a fatty acid chain, a sugar residue, a glycoprotein, a polymer, or any combinations thereof.

57. The conjugate of embodiment 55, wherein the conjugate is an antibody fragment which has a specific affinity for a transferrin receptor.

58. A pharmaceutical composition comprising the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, and a pharmaceutically acceptable carrier.

59. The composition of embodiment 58, which further comprises a therapeutic agent.

60. The composition of embodiment 59, wherein the therapeutic agent is an alpha-synuclein antagonist.

61. The composition of embodiment 60, wherein the alpha-synuclein antagonist is an anti-alpha-synuclein antibody or fragment thereof.

62. A kit comprising the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61, and instructions for use.

63. A diagnostic kit comprising the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61, and instructions for use.

64. A method of inhibiting or reducing SNCA protein expression in a cell, the method comprising administering the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate

of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 to the cell expressing SNCA protein, wherein the SNCA protein expression in the cell is inhibited or reduced after the administration.

65. The method of embodiment 64 wherein the antisense oligonucleotide inhibits or reduces expression of *SNCA* mRNA in the cell after the administration.

66. The method of embodiment 64 or 65, wherein the expression of *SNCA* mRNA is reduced by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% after the administration compared to a cell not exposed to the antisense oligonucleotide.

67. The method of any one of embodiments 64 to 66, wherein the antisense oligonucleotide reduces expression of SNCA protein in the cell after the administration by at least about 60%, at least about 70%, at least about 80%, or at least about 90% compared to a cell not exposed to the antisense oligonucleotide.

68. The method of any one of embodiments 64 to 67, wherein the cell is a neuron.

69. A method for treating a synucleinopathy in a subject in need thereof, comprising administering an effective amount of the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 to the subject.

70. Use of the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 for the manufacture of a medicament.

71. Use of the antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 for the manufacture of a medicament for the treatment of a synucleinopathy in a subject in need thereof.

72. The antisense oligonucleotide of any one of embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 for use in therapy.

73. The antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61 for use in therapy of a synucleinopathy in a subject in need thereof.

74. The method of embodiment 64 to 69, the use of embodiment 70 or 71, or the antisense oligonucleotide for use of embodiment 72 or 73, wherein the synucleinopathy is selected from the group consisting of Parkinson's disease, Parkinson's Disease Dementia (PDD), multiple system atrophy, dementia with Lewy bodies, and any combinations thereof.

75. The method of embodiment 64 to 69, the use of embodiment 70 or 71, or the antisense oligonucleotide for use of embodiment 72 or 73, wherein the subject is a human.

76. The method of any one of embodiments 64 to 69, the use of embodiment 70 or 71, or the antisense oligonucleotide for use of embodiment 72 or 73, wherein the antisense oligonucleotide, the conjugate, or the composition is administered orally, parenterally, intrathecally, intra-cerebroventricularly, pulmorarily, topically, or intraventricularly.

77. The antisense oligonucleotide of any one embodiments 1 to 57 or the conjugate of embodiment 55 to 57, or the composition of any one of embodiments 58 to 61, the kit of embodiment 62 or 63, the method of any one of embodiments 64 to 69, the use of embodiment 70 or 71, or the antisense oligonucleotide for use of embodiment 72 or 73, wherein the nucleotide analogue comprises a sugar modified nucleoside.

78. The method of embodiment 64, wherein the sugar modified nucleoside is an affinity enhancing sugar modified nucleoside.

EXAMPLES

The following examples are offered by way of illustration and not by way of limitation.

Example 1: Construction of ASOs

Antisense oligonucleotides described herein were designed to target various regions in the *SNCA* pre-mRNA as shown in SEQ ID NO: 1 (genomic *SNCA* sequence), or in *SNCA* cDNA as shown in SEQ ID NO: 2, 3, 4 and 5. For example, the ASOs were constructed to target the regions denoted using the pre-mRNA start site and pre-mRNA end site of NG_011851.1 (SEQ ID NO: 1) and/or mRNA start site and end site of its mRNAs. The exemplary sequences of the ASOs (*e.g.,* SEQ ID Numbers) are described in FIGs. 1A to 1C and 2. In some embodiments, the ASOs were designed to be gapmers or alternating flank gapmers. *See* DES Numbers.

FIGs. 1A to 1C and 2 show non-limiting examples of the ASO design for selected sequences. The same methods can be applied to any other sequences disclosed herein. The gapmers were constructed to contain locked nucleic acids – LNAs (upper case letters). For example, a gapmer can have Beta-D-oxy LNA at the 5' end and the 3' end and have a phosphorothioate backbone. But the LNAs can also be substituted with any other nucleotide analogues and the backbone can be

other types of backbones (*e.g.,* a phosphodiester linkage, a phosphotriester linkage, a methylphosphonate linkage, a phosphoramidate linkage, or combinations thereof).

The ASOs were synthesized using methods well known in the art. Exemplary methods of preparing such ASOs are described in Barciszewski *et al.*, Chapter 10 – " Locked Nucleic Acid Aptamers" in *Nucleic Acid and Peptide Aptamers: Methods and Protocols*, vol. 535, Gunter Mayer (ed.) (2009), the entire contents of which is hereby expressly incorporated by reference herein.

Example 2A: High Content Assay to Measure Reduction of SNCA Protein in Primary Neurons

ASOs targeting *SNCA* were tested for their ability to reduce SNCA protein expression in primary mouse neurons. The primary neuronal cultures were established from the forebrain of PAC-Tg(*SNCA*^{A53T})$^{+/+}$;*SNCA*$^{-/-}$ ("PAC-A53T") mice carrying the entire human *SNCA* gene with a A53T mutation on a mouse *SNCA* knockout background. *See* Kuo Y *et al.*, *Hum Mol Genet.*, 19: 1633-50 (2010). All procedures involving mice were conducted according to Animal Test Methods (ATM) approved by the Bristol-Myers Squibb Animal Care and Use Committee (ACUC). Primary neurons were generated by papain digestion according to manufacturer's protocol (Worthington Biochemical Corporation, LK0031050). Isolated neurons were washed and resuspended in Neurobasal medium (NBM, Invitrogen) supplemented with B27 (Gibco), 1.25 µM Glutamax (Gibco), 100 unit/ml penicillin, 100 µg/ml streptomycin, and 25 µg/ml Amphotericin B.

Cells were plated on multi-well poly D-Lysine coated plates at 5,400 cells/cm^2 (for example in 384 well plates 6,000 cells/well in 25 µl NBM). ASOs were diluted in water and added to the cells at DIV01 (*i.e.,* 1 day post plating). ASOs were added to 2X final concentration in medium then delivered to cells manually. Alternatively, ASOs in water were dispensed using a Labcyte ECHO acoustic dispenser. For ECHO dispense, 250 nl of ASO in water was added to cells in medium followed by the addition of an equal volume aliquot of fresh aliquot of NBM. For primary screening, the ASOs were added to final concentrations of 5 µM, 3.3 µM, 1 µM, 200 nM, or 40 nM. For potency determination, 8-10 point titrations of the ASOs were prepared from 0.75 mM stock then delivered to cultured cells for a final concentration range of 2.7-4000 nM or 4.5-10,000 nM. ASO-000010 (TCTgtcttggctTTG, SEQ ID NO: 1879) and ASO-000838 (AGAaataagtggtAGT, SEQ ID NO: 1404) (5 µM) were included in each plate as reference control inhibitors for tubulin and SNCA, respectively. The cells were incubated with the ASOs for 14 days to achieve steady state reduction of mRNA.

After the 14-day incubation, the cells were fixed by the addition of fixative to final concentrations of 4% formaldehyde (J.T. Baker) and 4% sucrose (Sigma) in the wells. The cells were fixed for 15

minutes, and then, the fixative aspirated from the wells. Then, the cells were permeabilized for 20 minutes with a phosphate buffered saline (PBS) solution containing 0.3% Triton-X 100 and 3% bovine serum albumin (BSA) or 3% Normal goat serum Afterwards, the permeabilization buffer was aspirated from the wells, and the cells were washed once with PBS. The primary antibodies were then diluted in PBS containing 0.1% Triton X-100 and 3% BSA. Dilutions of 1:1000 of rabbit anti-SNCA (Abcam) and 1:500 of chicken anti-tubulin (Abcam) were used. Cells were incubated with the primary antibodies between 2 hours to overnight. Following the incubation, the primary antibody staining solution was aspirated, and the cells were washed 2-times with PBS. A secondary staining solution containing 1:500 dilution of goat-anti-chicken Alexa 567 antibody, goat anti-rabbit-Alexa 488 antibody, and Hoechst (10 µg/ml) in PBS containing 0.1% Triton X-100 with 3% BSA was added to the wells, and the plates were incubated for 1 hour. Afterwards, the secondary staining solution was aspirated from the wells, and the cells were washed 3-times with PBS. After washing the cells, 60 µl of PBS was added to each well. Plates were then stored in the PBS until imaging.

For imaging, the plates were scanned on a Thermo-Fisher (Cellomics) CX5 imager using the Spot Detector bio-application (Cellomics) to quantify nuclei (Hoechst stain, Channel 1), tubulin extensions (Alexa 567, channel 2) and SNCA (Alexa 488, channel 3). Object count (nuclei) was monitored but not published to the database. The total area covered by tubulin was quantified as the feature SpotTotalAreaCh2 and total intensity of staining for SNCA quantified as SpotTotalIntenCh3. The tubulin measure was included to monitor toxicity. To determine the reduction of SNCA protein, the ratio of SNCA intensity to the tubulin staining area was calculated and results normalized as % inhibition median using the median of vehicle treated wells as total and ASO-000010 or ASO-000838 wells as maximally inhibited wells for tubulin or SNCA, respectively. The results are shown in Table 1, 2 and 3 below.

Table 1 shows the percent reduction of SNCA protein expression in both a human neuroblastoma cell line SK-N-BE(2) ("SK cells") and primary neurons isolated from A53T-PAC transgenic mice ("PAC neurons") after *in vitro* culture with various ASOs from figure 1A to 1C. The cultivation of the PAC neurons is described in Example 2A and Example 2E describes the cultivation of the the SK cells. For the SK cells, the cells were treated with 25 µM of ASO and the *SNCA* mRNA expression (normalized to GAPDH) is shown as a percent of the control. For the PAC neurons, the cells were treated with either 40 nM or 5 µM of ASO and the SNCA protein expression (normalized to tubulin)

is shown as percent inhibition. Where no value is provided, the particular ASO was not tested under the particular conditions.

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
000838			93.72	005231	34.88	44.18	
000871		76.92		005232	61.94	46.84	
000944		93.71		005233	55.00	42.98	
001215			87.53	005234	59.61	48.30	
001216			70.23	005235	48.55	54.20	
001217			78.61	005236	64.58	43.82	
001218			44.15	005237	76.10	50.85	
001219			74.23	005238	58.89	37.30	
001220			45.19	005239	53.91	50.20	
001221			88.01	005240	49.68	60.10	
001222			89.32	005241	46.30	68.14	
001223			97.25	005242	71.92	38.32	
001224			81.80	005243	60.65	72.40	
001225			87.39	005244	44.93	73.00	
001226			89.46	005245	33.95	80.83	
001227			82.60	005246	40.65	67.26	
001228			92.13	005247	51.33	57.75	
001229			38.57	005248	64.71	29.11	
001230			64.61	005249	65.49	44.92	
001231			85.90	005250	59.12	56.71	
001232			97.52	005251	46.14	52.67	
001233			92.56	005252	69.43	43.26	
001234			71.25	005253	60.92	39.22	
001235			98.36	005254	61.34	65.79	
001236			95.77	005255	50.04	70.16	
001237			63.04	005256	72.20	60.01	
001238			89.50	005257	57.82	77.12	
001239			80.33	005258	39.88	71.48	
001240			90.26	005259	45.61	77.75	
001241			82.99	005260	58.25	33.64	
001242			86.40	005261	55.88	66.66	
001243			98.53	005262	43.64	81.42	
001244			95.88	005263	45.59	58.90	
001245			93.77	005264	41.46	72.58	
001246			90.82	005265	45.89	61.52	
001247			97.48	005266	47.48	56.68	
001248			93.67	005267	43.83	78.24	
001249			47.69	005268	48.81	66.14	
001250			81.30	005269	39.65	60.97	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001251			92.94	005270	36.82	62.53	
001252			65.16	005271	41.90	64.71	
001253			78.95	005272	47.97	61.19	
001254			90.36	005273	35.28	81.48	
001256			98.12	005274	45.44	57.24	
001257			68.58	005275	40.97	68.49	
001258			98.61	005276	38.97	68.12	
001259			98.39	005277	39.51	76.52	
001260			48.29	005278	44.86	75.07	
001261			92.53	005279	50.60	62.52	
001262			11.86	005280	58.51	50.62	
001264			88.31	005281	44.45	54.63	
001265			78.33	005282	44.50	57.45	
001266			91.34	005283	34.26	65.61	
001267			55.49	005284	46.66	57.00	
001268	35.33		95.85	005285	39.59	86.23	
001269			89.81	005286	62.91	46.94	
001270			97.29	005287	34.88	87.27	
001271			86.95	005288	39.59	70.30	
001272			44.51	005289	42.84	62.23	
001273			93.30	005290	41.97	65.69	
001274			91.42	005291	32.24	70.95	
001275			88.46	005292	32.43	83.62	
001276			74.14	005293	53.70	67.64	
001277			84.41	005294	61.01	54.60	
001278			87.79	005295	51.33	62.32	
001279			97.27	005296	42.19	73.78	
001280			83.63	005297	53.58	52.99	
001281			97.32	005298	47.07	41.12	
001282			94.25	005299	50.56	65.62	
001283			31.00	005300	63.23	13.82	
001284			93.18	005301	67.38	26.21	
001285			86.10	005302	83.32	26.29	
001286			80.62	005303	50.40	58.57	
001287			23.11	005304	44.75	56.31	
001288			67.56	005305	33.34	78.10	
001289			86.74	005306	49.89	53.29	
001290			66.46	005307	55.34	41.69	
001291			85.76	005308	39.01	74.61	
001292			92.26	005309	42.98	64.78	
001293			93.32	005310	61.89	55.05	
001294			64.02	005311	62.63	30.63	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001295			94.93	005312	69.06	18.51	
001296			90.24	005313	54.58	64.77	
001297			86.81	005314	46.02	61.62	
001298			91.01	005315	53.20	48.93	
001299			65.65	005316	54.78	32.32	
001300			94.40	005317	43.46	81.73	
001301			92.02	005318	74.94	36.85	
001302			92.69	005319	49.72	50.63	
001303			95.62	005320	55.05	71.07	
001304			98.14	005321	46.98	54.91	
001305			48.41	005322	60.58	26.66	
001306			98.79	005323	51.00	35.64	
001307			84.65	005324	48.71	73.43	
001308			93.86	005325	68.99	46.68	
001309			90.91	005326	54.94	42.37	
001310			84.82	005327	55.34	56.95	
001311			84.94	005328	47.29	48.13	
001312			95.91	005329	63.45	42.36	
001313			61.41	005330	49.78	81.92	
001314			42.39	005331	62.98	27.03	
001315			91.32	005332	64.80	18.30	
001316			87.26	005333	61.42	44.54	
001317			60.85	005334	58.99	40.14	
001318			95.84	005335	53.89	52.91	
001319			8.18	005336	40.83	58.21	
001320			85.45	005337	75.32	36.80	
001321			69.37	005338	35.69	84.70	
001322			28.55	005339	48.36	48.75	
001323			87.84	005340	48.12	57.88	
001324			92.81	005341	58.15	36.60	
001325			77.19	005342	72.91	36.06	
001326			94.59	005343	53.37	67.24	
001327			82.85	005344	72.26	41.55	
001328			95.78	005345	60.26	47.54	
001329			0.00	005346	50.62	56.52	
001330			85.68	005347	70.74	34.62	
001331			86.34	005348	47.46	74.57	
001332			95.33	005349	61.95	53.47	
001333			55.39	005350	76.01	41.52	
001334			86.33	005351	56.42	49.40	
001335			92.50	005352	52.01	41.92	
001336			57.28	005353	53.53	57.32	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001337			77.14	005354	43.16	50.51	
001338			89.06	005355	53.75	46.31	
001339			91.57	005356	63.93	45.46	
001340			67.34	005357	71.88	40.82	
001341			78.26	005358	47.58	61.41	
001342			86.73	005359	82.11	21.37	
001343			83.45	005360	63.34	47.07	
001344			88.15	005361	56.11	71.64	
001345			85.47	005362	54.42	57.04	
001346			81.85	005363	97.38	-32.23	
001347			84.87	005364	66.27	48.41	
001348			84.06	005365	65.30	44.53	
001349			89.69	005366	77.81	54.19	
001350			87.68	006658		58.89	
001351			8.05	006659		35.00	
001352			73.26	006660		32.33	
001353			40.01	006661		32.92	
001354			93.23	006662		32.63	
001355			89.69	006663		67.61	
001356			91.26	006664		84.01	
001357			89.88	006665		26.12	
001358			43.68	006666		32.02	
001359			88.47	006667		42.45	
001360			94.42	006668		56.06	
001361			88.15	006669		17.96	
001362			93.42	006670		37.48	
001363			87.88	006671		31.41	
001364			68.99	006672		32.67	
001365			95.09	006673		32.06	
001366			95.58	006674		29.16	
001367			86.95	006675		18.87	
001368			96.18	006676		13.88	
001369			91.02	006677		9.75	
001370			70.67	006678		-4.00	
001371			66.13	006679		-1.04	
001372			72.71	006680		27.72	
001373			90.13	006681		9.52	
001374			92.72	006682		11.67	
001375			93.58	006683		-3.12	
001376			85.61	006684		21.49	
001377			71.01	006685		61.73	
001378			0.00	006686		68.24	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001379			27.03	006687		68.61	
001380			88.23	006688		92.89	
001381			95.05	006689		-6.54	
001382			90.04	006690		-4.19	
001383			93.92	006691		-4.72	
001384			91.73	006692		-15.84	
001385			80.17	006693		-29.61	
001386			16.10	006694		-30.74	
001387			47.37	006695		52.27	
001388			4.30	006696		38.76	
001389			82.65	006697		13.29	
001390			95.66	006698		-4.94	
001391			86.09	006699		31.60	
001392			86.25	006700		98.85	
001393			84.71	006701		19.40	
001394			85.67	006702		55.72	
001395		37.01	82.51	006703		10.08	
001396			11.64	006704		43.55	
001397			70.48	006705		-11.86	
001398			92.61	006706		73.23	
001399			87.04	006707		82.89	
001400			89.92	006708		6.26	
001401			89.29	006709		85.24	
001402			89.30	006710		10.85	
001403			83.13	006711		21.66	
001404			56.75	006712		89.98	
001405			87.46	006713		89.08	
001406			96.31	006714		88.46	
001407			83.56	006715		86.61	
001408			92.38	006716		98.14	
001409			87.22	006717		76.37	
001410			75.54	006718		54.91	
001411			0.00	006719		9.05	
001413			89.97	006720		-12.37	
001414			83.35	006721		9.42	
001415			92.07	006722		10.57	
001416			81.65	006723		-33.60	
001417			66.39	006724		-24.76	
001418			91.34	006725		-4.64	
001419			95.97	006726		-58.51	
001420			89.45	006727		2.01	
001422			26.41	006728		14.83	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001423			89.46	006729		-11.20	
001424			75.68	006730		24.05	
001425			84.24	006731		1.76	
001426			78.65	006732		1.45	
001427			86.02	006733		-33.44	
001428			87.14	006734		-19.26	
001429			79.78	006735		3.51	
001430			95.27	006736		-17.79	
001431			84.42	006737		-23.12	
001432			12.51	006738		-1.94	
001433			89.85	006739		-10.54	
001434			86.60	006740		-19.34	
001436			90.20	006741		4.52	
001437			82.67	006742		20.61	
001438			64.18	006743		49.39	
001439			84.32	006744		26.67	
001440			94.46	006745		1.67	
001441			94.20	006746		-14.69	
001442			95.66	006747		71.41	
001443			87.32	006748		-9.20	
001444			86.51	006749		-4.77	
001445			88.60	006750		36.48	
001446			90.39	006751		32.62	
001447			82.04	006752		-2.29	
001448			92.17	006753		33.15	
001449			60.30	007825	90.91	6.25	
001450			96.45	007826	98.45	19.41	
001451			84.72	007827	33.89	76.63	
001452			92.90	007828	71.22	14.19	
001453			84.30	007829	89.09	24.77	
001454			83.64	007830	69.02	45.88	
001455			89.70	007831	52.61	65.25	
001456			88.28	007832	45.77	64.13	
001457			79.27	007833	35.27	66.93	
001458			96.77	007834	55.75	69.23	
001459			85.61	007835	50.44	62.14	
001460			84.09	007836	83.57	1.61	
001461			56.21	007837	21.27	49.39	
001462			90.67	007838	38.67	29.18	
001463			90.19	007839	15.87	67.92	
001465			84.33	007840	31.14	39.74	
001466			92.61	007841	93.61	8.20	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001467			88.34	007842	33.20	39.43	
001468			89.59	007843	72.64	-3.50	
001469			87.01	007844	30.46	58.52	
001470			94.90	007845	36.50	37.25	
001471			94.17	007846	65.57	16.35	
001472			76.82	007847	54.41	9.77	
001473			86.75	007848	44.89	26.42	
001474			79.57	007849	63.62	10.09	
001475			86.00	007850	25.40	22.71	
001476			71.74	007851	72.80	3.37	
001477			89.83	007852	30.09	22.42	
001478			81.05	007853	35.11	67.33	
001479			89.33	007854	46.62	18.67	
001480			93.81	007855	28.38	81.42	
001481			95.98	007856	30.19	45.29	
001482			93.95	007857	36.65	51.05	
001483			73.67	007858	31.33	60.45	
001484			90.45	007859	9.22	58.74	
001485			83.78	007860	99.21	4.04	
001486			89.29	007861	19.20	36.21	
001487			88.97	007862	27.80	34.54	
001488			0.00	007863	35.15	50.15	
001489			95.56	007864	13.78	57.98	
001491			97.87	007865	31.57	36.37	
001492			95.49	007866	83.12	-9.69	
001493			98.56	007867	83.71	13.53	
001494			96.76	007868	81.70	33.84	
001495			97.27	007869	9.38	21.24	
001496			99.04	007870	25.74	21.96	
001497			93.76	007871	59.12	18.39	
001498			97.76	007872	81.08	14.20	
001499			96.59	007873	79.14	24.50	
001500			86.77	007874	29.03	7.04	
001501			98.74	007875	72.85	13.88	
001502			98.16	007876	89.11	-5.50	
001503			95.86	007877	71.59	34.39	
001504			93.12	007878	53.55	75.38	
001505			94.71	007879	30.00	65.89	
001506			97.09	007880	27.63	48.64	
001507			95.03	007881	18.64	55.32	
001508			98.47	007882	31.80	44.28	
001509			98.00	007883	14.24	61.01	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001510			98.78	007884	13.69	65.37	
001511			98.15	007885	7.65	83.34	
001512			97.94	007886	25.22	73.06	
001513			98.42	007887	12.83	73.68	
001514			90.13	007888	8.62	70.07	
001515			96.51	007889	23.48	54.75	
001516			86.92	007890	14.76	62.18	
001517			94.99	007891	34.07	16.50	
001518			55.55	007892	25.34	49.17	
001519			64.78	007893	41.07	21.97	
001520			89.81	007894	34.40	44.36	
001521			98.46	007895	19.12	68.86	
001522			43.77	007896	22.59	40.30	
001523			86.12	007897	27.09	30.03	
001524			88.36	007898	29.06	29.97	
001525			96.84	007899	11.40	60.32	
001526			95.91	007900	16.92	57.20	
001527			97.03	007901	18.70	48.75	
001528			98.57	007902	19.97	44.39	
001529			42.58	007903	58.49	8.26	
001530			82.22	007904	50.08	33.45	
001531			98.96	007905	89.08	1.68	
001532			97.36	007906	43.31	10.34	
001533			94.01	007907	51.83	-14.10	
001534			98.77	007908	43.19	-31.83	
001535			98.66	007909	47.18	7.85	
001536			36.22	007910	53.39	20.72	
001537			98.10	007911	21.84	50.54	
001538			14.11	007912	61.80	13.34	
001539			89.73	007913	20.16	50.15	
001540			94.65	007914	30.22	52.23	
001541			97.37	007915	17.21	57.41	
001542			46.47	007916	31.52	41.55	
001543			83.28	007917	34.69	37.70	
001544			98.35	007918	52.90	11.77	
001545			97.35	007919	88.65	12.37	
001546			93.48	007920	76.86	9.80	
001547			94.75	007921	8.59	69.61	
001548			98.94	007922	20.82	51.06	
001549			96.93	007923	43.75	24.38	
001550			40.06	007924	11.96	54.98	
001551			92.73	007925	12.70	65.01	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001552			81.48	007926	68.37	2.64	
001553			51.25	007927	7.64	48.49	
001554			95.76	007928	81.26	21.17	
001555			58.84	007929	21.74	53.63	
001556			97.54	007930	44.83	57.41	
001557			94.59	007931	24.55	58.90	
001558			95.20	007932	28.59	73.25	
001559			96.90	007933	34.94	57.41	
001560			95.72	007934	12.19	67.62	
001561			98.11	007935	13.19	73.08	
001562			99.43	007936	6.99	91.64	
001563			96.50	007937	10.02	84.05	
001564			95.13	007938	6.06	88.94	
001565			97.29	007939	5.53	88.11	
001566			7.34	007940	11.10	81.11	
001567			48.99	007941	10.93	87.49	
001568			9.48	007942	6.06	94.37	
001569			88.70	007943	8.99	83.43	
001570			45.55	007944	78.30	10.37	
001571			28.53	007945	55.03	25.03	
001572			24.38	007946	47.58	21.46	
001573			40.00	007947	82.61	-14.05	
001574			53.37	007948	62.42	16.02	
001575			82.87	007949	106.76	-18.93	
001576			0.00	007950	66.12	-21.13	
001577			4.24	007951	82.92	-3.02	
001578			88.26	007952	98.71	-15.24	
001579			89.67	007953	82.13	-22.52	
001580			4.30	007954	99.46	-9.90	
001581			68.48	007955	101.97	-22.11	
001582			97.42	007956	101.43	-25.78	
001583			89.36	007957	80.47	-0.57	
001584			88.14	007958	12.52	41.42	
001585			96.53	007959	34.82	9.60	
001586			1.70	007960	42.45	48.38	
001587			83.16	007961	11.01	68.82	
001588			97.69	007962	12.20	38.28	
001589			96.73	007963	9.45	69.16	
001590			25.31	007964	11.29	49.13	
001591			89.49	007965	42.52	14.76	
001592			92.15	007966	87.30	-13.68	
001593			98.01	007967	16.55	45.65	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001594			94.49	007968	55.58	-4.50	
001595			95.32	007969	37.76	30.76	
001596			97.53	007970	24.28	30.57	
001597			96.76	007971	14.79	62.40	
001598			99.01	007972	28.84	44.82	
001599			31.61	007973	39.65	58.60	
001600			43.20	007974	20.24	57.13	
001601			97.02	007975	31.21	20.78	
001602			97.29	007976	24.51	37.98	
001603			85.39	007977	17.80	59.12	
001604			96.88	007978	47.91	21.70	
001605		80.20	98.32	007979	72.76	4.55	
001606		81.32	96.49	007980	61.27	22.58	
001607			93.58	007981	62.59	1.68	
001608			87.86	007982	59.81	22.75	
001609			97.39	007983	87.07	12.00	
001610			97.75	007984	78.59	19.42	
001611			95.64	007985	82.91	16.85	
001612			85.04	007986	90.68	26.26	
001613			93.59	007987	39.02	41.88	
001614			97.47	007988	52.78	1.91	
001615			94.15	007989	33.16	36.14	
001616			95.26	007990	28.31	52.08	
001617			96.66	007991	68.28	9.73	
001618			99.14	007992	78.17	26.84	
001619			92.11	007993	83.36	6.25	
001620			98.32	007994	52.99	33.90	
001621			98.28	007995	90.92	11.29	
001622			65.91	007996	78.60	8.99	
001623			97.22	007997	79.65	-6.28	
001624			37.36	007998	102.82	-1.89	
001625			98.98	007999	121.19	16.07	
001626			19.81	008000	130.28	15.99	
001627			1.50	008001	84.59	16.10	
001628			96.82	008002	95.26	17.26	
001629			95.28	008003	106.06	-1.76	
001630			75.33	008004	41.49	53.55	
001631			98.61	008005	55.92	24.61	
001632			92.03	008006	42.94	60.56	
001633			96.54	008007	65.62	41.22	
001634			96.04	008008	27.91	57.41	
001635			97.03	008009	38.76	47.35	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001636			95.33	008010	42.55	51.20	
001637		69.47	98.13	008011	42.50	39.28	
001638			90.61	008012	25.60	71.89	
001639			96.14	008013	20.03	79.57	
001640			95.08	008014	13.24	77.03	
001641			94.21	008015	47.33	32.67	
001642			99.28	008016	3.93	86.61	
001643			98.97	008017	55.12	51.88	
001644			97.73	008018	41.16	55.37	
001645			98.20	008019	32.70	48.13	
001646			73.02	008020	46.11	30.25	
001647			83.71	008021	41.00	30.87	
001648			98.00	008022	40.06	50.34	
001650			97.92	008023	30.02	62.98	
001651			87.49	008024	31.84	58.58	
001652			95.29	008025	21.50	71.54	
001653			98.48	008026	36.54	60.73	
001654			68.87	008027	26.61	48.43	
001655			59.51	008028	37.71	56.71	
001656			34.27	008029	42.03	61.10	
001657			53.42	008030	66.16	48.68	
001658			38.63	008031	62.90	45.58	
001659			98.43	008032	26.91	80.00	
001660			96.93	008033	9.31	86.60	
001661			98.57	008034	36.73	64.43	
001664			21.64	008035	20.72	70.12	
001665		68.25	97.09	008036	35.45	39.31	
001666			21.20	008037	11.98	84.20	
001667			76.17	008038	68.54	25.69	
001668			23.46	008039	83.82	19.31	
001669			95.13	008040	119.54	6.64	
001670			88.70	008041	70.09	28.57	
001671			96.79	008042	96.16	23.09	
001672			86.43	008043	110.12	7.64	
001673			93.03	008044	85.13	-3.82	
001674			93.49	008045	18.20	47.29	
001675			53.18	008046	9.30	70.65	
001676			96.53	008047	19.37	74.12	
001677			89.85	008048	108.64	14.06	
001678			96.92	008049	78.36	32.38	
001679			99.01	008050	10.02	70.37	
001680			92.80	008051	14.29	77.77	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001681			46.47	008052	59.21	46.51	
001682			23.90	008053	30.41	42.57	
001683			96.76	008054	34.03	70.45	
001684			98.07	008055	100.68	25.49	
001685			88.51	008056	36.85	70.50	
001686			46.72	008057	26.69	66.36	
001687			55.48	008058	69.46	14.96	
001688			87.56	008059	76.20	17.89	
001689			96.55	008060	101.05	-42.04	
001690			91.63	008061	55.16	4.51	
001691			72.70	008062	107.80	5.19	
001692			88.15	008063	95.54	13.90	
001693			75.79	008064	111.74	0.48	
001694			97.17	008065	99.24	6.89	
001695			84.27	008066	49.03	35.04	
001696			73.76	008067	86.71	-30.43	
001697			81.28	008068	42.88	23.93	
001698			92.78	008069	17.31	59.72	
001699			87.80	008070	12.73	82.15	
001700			96.54	008071	13.36	74.35	
001701			81.50	008072	12.81	74.31	
001702			96.42	008073	14.85	78.37	
001703			99.36	008074	5.77	97.91	
001704			62.57	008075	6.60	90.35	
001705			76.93	008076	9.52	56.26	
001706			96.55	008077	29.81	65.59	
001707			97.41	008078	16.32	74.58	
001708			98.62	008079	20.19	72.81	
001709			93.57	008080	11.00	62.17	
001710			91.05	008081	43.93	18.16	
001711			78.79	008082	45.23	32.77	
001712			98.12	008083	9.93	81.06	
001713			82.95	008084	50.27	10.40	
001714			96.29	008085	17.52	38.06	
001715			84.66	008086	26.27	40.21	
001716			93.49	008087	46.71	17.50	
001717			77.89	008088	69.77	22.57	
001718			95.26	008089	82.95	7.77	
001719			78.69	008090	50.97	42.26	
001720			97.97	008091	75.98	-5.32	
001721			98.37	008092	50.82	22.12	
001722			75.87	008093	98.53	35.95	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001723			96.81	008094	58.36	32.04	
001724			92.03	008095	78.20	26.56	
001725			95.15	008096	76.52	24.98	
001726			48.65	008097	89.41	16.03	
001727			61.40	008098	56.14	26.76	
001728			68.82	008099	53.69	23.21	
001729			99.24	008100	53.79	57.71	
001730			97.45	008101	19.59	86.78	
001731			98.82	008102	16.83	92.56	
001732			78.91	008103	25.45	89.09	
001733			98.43	008104	15.10	96.32	
001734			97.45	008105	37.83	30.57	
001735			98.69	008106	12.27	81.49	
001736			95.63	008107	39.07	74.08	
001737			37.00	008108	16.37	56.89	
001738			83.19	008109	65.37	30.94	
001739			84.08	008110	84.01	21.59	
001740			63.16	008111	23.27	52.20	
001741			77.16	008112	26.26	33.34	
001742			83.19	008113	70.31	33.66	
001743			96.66	008114	24.58	32.88	
001744			99.00	008115	26.53	47.18	
001745			96.87	008116	59.72	21.30	
001746			99.50	008117	28.89	86.00	
001747			74.14	008118	22.13	88.23	
001748			86.48	008119	31.41	77.00	
001749			98.64	008120	25.55	86.25	
001750			90.50	008121	24.84	67.70	
001751			98.73	008122	39.61	65.84	
001752			97.99	008123	35.93	68.46	
001753			91.35	008124	51.95	83.26	
001754			95.51	008125	41.28	84.75	
001755			96.16	008126	24.86	85.98	
001756			98.19	008127	19.61	94.88	
001757			98.24	008128	24.70	77.51	
001758			98.79	008129	33.16	76.42	
001759			98.91	008130	36.10	74.97	
001760			99.17	008131	33.30	80.49	
001761			25.21	008132	31.82	68.74	
001762			99.25	008133	3.07	71.27	
001763			98.79	008134	5.25	70.33	
001764			94.82	008135	11.95	66.23	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
001765			97.59	008136	9.70	76.98	
001766			95.90	008137	13.17	73.27	
001767			97.68	008138	18.84	65.30	
001768			91.15	008139	17.79	77.58	
001769			97.84	008140	18.27	55.79	
001770			98.67	008141	48.99	39.55	
001771			98.38	008142	28.53	64.64	
001772			71.36	008143	37.91	29.96	
001773			94.64	008144	78.90	-1.50	
001774			98.19	008145	37.15	31.34	
001775			98.22	008146	75.86	19.37	
001776			97.56	008147	104.08	13.91	
001777			98.32	008148	13.32	76.17	
002497			96.00	008149	137.45	-5.70	
002498			73.09	008150	60.94	34.50	
002501			40.30	008151	124.55	17.51	
002502			97.11	008152	115.55	17.26	
002505			97.00	008153	34.90	27.56	
002506			89.76	008154	60.02	31.91	
002509			36.73	008155	69.99	17.34	
002510			96.60	008156	72.62	6.97	
002512			89.51	008157	84.96	12.07	
002513			97.00	008158	8.73	74.48	
002515			93.89	008159	20.63	61.75	
002516			94.05	008160	51.87	34.32	
002518			84.02	008161	32.85	57.35	
002519			93.27	008162	52.45	15.77	
002521			80.85	008163	38.43	32.49	
002522			95.25	008164	43.21	30.95	
002682		95.33		008165	49.33	30.98	
002683		1.20		008166	41.27	39.31	
002684		-9.54		008167	7.28	84.28	
002685		-14.92		008168	24.84	56.84	
002686	23.43	66.50		008169	81.47	34.33	
002687		22.28		008170	4.61	81.51	
002688		22.98		008171	87.01	3.32	
002689		21.33		008172	67.12	10.72	
002690	17.77	80.59		008173	36.71	37.49	
002691		10.92		008174	45.09	30.14	
002692	46.47	50.45		008175	28.76	30.23	
002693	25.37	73.62		008176	36.56	19.39	
002694	13.73	89.68		008177	31.67	43.28	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002695		4.33		008178	70.95	24.84	
002696		54.50		008179	38.16	-0.99	
002697		18.82		008180	40.51	8.33	
002698		78.14		008181	17.10	47.31	
002699		54.43		008182	6.84	61.68	
002700		37.56		008183	30.96	46.12	
002701		29.12		008184	62.32	30.55	
002702		61.10		008185	9.01	69.14	
002703		19.91		008186	9.92	50.59	
002704		15.92		008187	47.88	2.74	
002705	43.93	26.99		008188	18.65	31.05	
002706		63.55		008189	15.14	36.37	
002707		1.11		008190	28.38	15.26	
002708		-2.77		008191	89.01	15.35	
002709		2.59		008192	42.88	28.79	
002710		62.26		008193	90.34	3.80	
002711		15.08		008194	31.19	4.70	
002712		26.32		008195	105.33	-4.79	
002713		46.80		008196	90.57	11.53	
002714		62.81		008197	83.58	12.39	
002715		37.41		008198	96.91	-19.15	
002716		7.02		008199	86.43	-1.40	
002717		3.29		008200	7.56	65.95	
002718		71.97		008201	106.12	16.42	
002719		30.10		008202	47.01	30.68	
002720		54.17		008203	79.32	-16.59	
002721		68.28		008204	22.33	-3.98	
002722		38.34		008205	34.90	4.62	
002723		92.32		008206	49.12	3.70	
002724		54.18		008207	103.20	27.65	
002725		41.66		008208	44.64	18.07	
002726		-7.44		008209	54.40	0.01	
002727		48.69		008210	45.03	4.90	
002728		50.35		008211	18.70	-11.25	
002729		62.82		008212	23.47	23.14	
002730	19.98	71.02		008213	47.65	28.77	
002731		-9.08		008214	35.89	29.45	
002732		22.18		008215	34.78	35.62	
002733		-26.37		008216	28.59	36.29	
002734		32.00		008217	10.25	26.47	
002735		37.47		008218	11.69	26.70	
002736		51.16		008219	21.85	12.37	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002737		82.19		008220	15.12	92.25	
002738	28.50	95.49		008221	15.26	72.03	
002739	31.73	93.88		008222	18.42	33.49	
002740		-11.63		008223	13.85	48.58	
002741		75.63		008224	22.35	37.14	
002742		24.64		008225	4.69	69.70	
002743		59.33		008226	3.61	84.00	
002744		-26.74		008227	8.25	72.26	
002745		-43.83		008228	6.29	62.28	
002746		57.42		008229	30.82	40.19	
002747		28.09		008230	7.61	73.25	
002748		72.43		008231	56.26	31.85	
002749		53.95		008232	66.56	46.57	
002750		43.67		008233	54.78	15.43	
002751		74.80		008234	12.17	66.92	
002752		64.91		008235	112.23	0.09	
002753		50.58		008236	98.75	-22.49	
002754		-25.68		008237	41.06	38.16	
002756		11.92		008238	22.39	74.20	
002757		43.09		008239	23.22	74.19	
002758		63.86		008240	17.68	80.49	
002759		-25.37		008241	66.10	20.58	
002760		47.32		008242	29.17	14.26	
002761	37.76	78.45		008243	84.73	-18.67	
002762	15.98	92.30		008244	20.68	39.38	
002763	25.18	60.22		008245	12.92	53.15	
002764		2.36		008246	8.80	48.85	
002765	24.45	52.94		008247	17.59	43.71	
002766		15.20		008248	21.26	15.95	
002767		-29.58		008249	14.25	47.75	
002768		48.77		008250	7.25	79.18	
002769		45.69		008251	9.17	60.46	
002770		38.67		008252	10.00	63.76	
002771		37.54		008253	81.03	-15.99	
002772		54.79		008254	32.11	18.35	
002773		42.63		008255	83.84	-0.91	
002774		13.83		008256	58.17	3.07	
002775		-11.57		008257	6.53	60.92	
002776		0.87		008258	24.24	27.57	
002777		-14.96		008259	8.86	63.53	
002778		41.12		008260	7.43	52.54	
002779	2.88	96.07		008261	4.74	80.82	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002781		-7.21		008262	43.21	6.68	
002782		18.54		008263	37.38	18.63	
002783		-17.40		008264	51.77	-13.47	
002784		33.49		008265	73.34	-12.22	
002785	18.22	82.74		008266	74.99	-4.89	
002786		64.97		008267	96.96	5.59	
002787		48.31		008268	54.16	14.67	
002788		70.21		008269	69.52	-7.42	
002789		22.04		008270	102.07	-23.69	
002790		-35.98		008271	98.12	-2.72	
002791		82.42		008272	53.29	14.89	
002792		5.33		008273	105.43	0.23	
002793		-72.87		008274	67.65	11.74	
002794		13.30		008275	117.82	-23.52	
002795		17.01		008276	111.38	-14.08	
002796		-15.62		008277	115.30	-24.91	
002797		-11.81		008278	56.02	1.19	
002798	20.46	92.79		008279	80.79	47.99	
002799		36.69		008280	56.83	76.04	
002800		8.18		008281	70.71	18.03	
002801	24.63	78.64		008282	75.86	2.95	
002802		24.94		008283	46.04	5.69	
002803		59.45		008284	35.78	23.82	
002804	14.68	72.02		008285	45.24	8.41	
002805	5.48	101.11		008286	45.76	29.08	
002806		-51.77		008287	93.27	9.04	
002807		29.71		008288	72.46	1.81	
002808		13.64		008289	72.71	2.26	
002809		14.03		008290	24.01	18.96	
002810		7.26		008291	25.01	1.77	
002811		0.47		008292	22.67	13.43	
002812		23.34		008293	26.72	13.31	
002813		28.04		008294	91.83	-7.23	
002814		38.49		008295	15.97	41.66	
002815		48.52		008296	10.68	44.06	
002817	6.88	79.56		008297	22.31	34.51	
002818		46.21		008298	40.79	28.28	
002819		19.80		008299	15.52	61.12	
002820	30.99	59.98		008300	40.04	31.97	
002821		14.53		008301	12.72	39.45	
002822		10.38		008302	71.43	-8.15	
002823		28.46		008303	92.63	-28.14	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002824		64.36		008304	56.89	-8.90	
002825		57.18		008305	57.90	30.25	
002826		61.70		008306	82.97	53.57	
002827		80.80		008307	97.02	4.31	
002828	24.17	94.67		008308	92.71	-10.91	
002829		74.62		008309	77.69	-23.36	
002830		56.37		008310	81.48	2.06	
002831		68.47		008311	72.07	-35.71	
002832		70.03		008312	53.23	24.35	
002833	23.72	97.46		008313	62.65	1.63	
002834		77.62		008314	69.03	8.83	
002835		85.90		008315	24.45	10.47	
002836	23.08	97.91		008316	23.44	12.02	
002837	19.28	94.65		008317	34.87	16.77	
002838	18.33	104.88		008318	30.38	44.13	
002839		85.79		008319	36.15	27.49	
002840		85.59		008320	58.43	29.61	
002841		92.58		008321	54.72	34.66	
002842	18.82	95.83		008322	52.18	18.69	
002843		101.31		008323	93.13	10.44	
002844		92.28		008324	95.24	2.58	
002845		97.70		008325	83.16	8.86	
002846		92.26		008326	99.56	4.41	
002847	16.72	94.46		008327	65.57	0.34	
002848	25.33	87.32		008328	105.10	-12.65	
002849	20.05	94.91		008329	74.61	17.91	
002850	16.14	99.26		008330	108.70	-22.11	
002851		90.11		008331	83.72	-9.12	
002852	9.88	96.79		008332	79.35	-15.30	
002853		86.42		008333	58.45	-15.82	
002854		97.04		008334	60.79	40.00	
002855		82.28		008335	66.22	41.79	
002856		89.01		008336	88.87	60.12	
002857		98.68		008337	97.55	24.43	
002858	12.25	89.87		008338	84.91	10.25	
002859	10.30	94.96		008339	97.28	31.05	
002860	21.65	83.01		008340	103.42	5.22	
002861		52.61		008341	79.11	-5.51	
002862		71.58		008342	106.42	-12.19	
002863	22.64	76.10		008343	17.32	48.63	
002864	32.06	72.52		008344	102.86	-26.65	
002865		77.41		008345	77.52	24.80	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002866		90.16		008346	92.45	-17.45	
002867	25.45	68.04		008347	95.63	-8.04	
002868		84.17		008348	65.16	-6.42	
002869		96.43		008349	78.78	-15.57	
002870		96.31		008350	88.65	-15.28	
002871		84.28		008351	27.60	52.68	
002872		92.88		008352	5.62	79.17	
002873		57.41		008353	71.84	28.85	
002874		83.22		008354	13.57	60.26	
002875		76.54		008355	2.67	68.53	
002876		72.10		008356	21.07	45.91	
002877		68.45		008357	20.67	42.12	
002878		66.91		008358	6.52	84.78	
002879		49.09		008359	10.20	76.95	
002880		49.72		008360	6.76	80.77	
002881		81.79		008361	10.71	67.80	
002882		51.80		008362	5.16	67.30	
002883		74.95		008363	64.44	-23.84	
002884		69.44		008364	30.17	9.59	
002885		53.71		008365	76.68	2.17	
002886		60.10		008366	60.36	11.19	
002887		87.87		008367	45.28	40.74	
002888		57.43		008368	69.18	37.04	
002889		69.96		008369	84.30	5.53	
002890		60.39		008370	3.19	62.48	
002891		46.41		008371	22.45	12.41	
002892		72.22		008372	7.45	28.50	
002893		79.33		008373	43.39	0.89	
002894		76.86		008374	48.11	-10.71	
002895		78.35		008375	46.35	22.48	
002896		84.26		008376	11.27	81.58	
002897		90.55		008377	53.22	2.35	
002898		89.03		008378	12.41	65.59	
002899		86.63		008379	7.05	68.90	
002900		90.84		008380	12.44	64.66	
002901	17.19	93.64		008381	17.12	64.21	
002902		72.42		008382	46.94	52.68	
002903		63.04		008383	14.70	61.67	
002904	37.80	72.98		008384	6.60	77.21	
002905		57.74		008385	2.07	100.40	
002906	22.25	88.63		008386	3.23	93.44	
002907		65.67		008387	3.80	97.24	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002908	23.07	62.36		008388	2.82	97.77	
002909	25.58	73.56		008389	5.90	83.57	
002910		65.86		008390	34.56	49.25	
002911	35.41	58.77		008391	8.18	72.24	
002912		73.36		008392	69.95	25.72	
002913		31.74		008393	41.15	38.39	
002914		59.69		008394	57.07	48.37	
002915		27.75		008395	36.53	58.28	
002916		45.10		008396	69.58	19.29	
002917		60.59		008397	88.93	3.38	
002918		13.88		008398	94.58	4.35	
002919		28.74		008399	91.83	17.41	
002920		0.85		008400	94.57	10.66	
002921		51.73		008401	78.87	2.52	
002922		61.98		008402	77.69	16.13	
002923		41.41		008403	85.76	-10.19	
002924		65.74		008404	99.57	16.74	
002925		56.59		008405	52.54	22.39	
002926		46.85		008406	41.35	20.70	
002927		4.82		008407	87.19	16.92	
002928		54.34		008408	84.72	-11.70	
002929		71.20		008409	50.08	33.39	
002930		58.30		008410	43.50	2.69	
002931		71.04		008411	89.13	-40.63	
002932		69.92		008418	7.61	39.27	
002933		74.66		008419	29.46	33.86	
002934		41.68		008420	119.06	-2.42	
002935	35.29	63.18		008421	105.01	-21.43	
002936		62.82		008422	81.48	-22.75	
002937		51.06		008423	41.55	-1.35	
002938	41.44	79.88		008424	46.88	12.78	
002939		41.98		008425	49.52	45.96	
002940		27.73		008426	63.30	13.89	
002941		35.61		008427	50.14	26.28	
002942		44.94		008428	40.91	22.32	
002943		18.85		008429	53.49	2.76	
002944		48.41		008430	68.65	4.67	
002945		23.64		008431	33.62	54.21	
002946		-4.83		008432	51.46	38.70	
002947		54.67		008433	62.43	39.14	
002948		41.03		008434	31.83	40.49	
002949		4.17		008435	20.66	51.87	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002950		22.52		008436	41.54	35.26	
002951		72.99		008437	29.68	49.20	
002952		65.01		008438	38.82	24.98	
002953		49.43		008439	35.66	-5.69	
002954		14.23		008440	42.72	10.94	
002955		82.17		008441	53.95	-10.45	
002956		78.37		008442	23.72	16.38	
002957		41.97		008443	25.61	-6.29	
002958		47.59		008444	40.16	2.56	
002959		53.29		008445	41.81	7.16	
002960		63.16		008446	88.89	5.84	
002961		40.33		008447	38.91	32.29	
002962		76.96		008448	108.85	1.08	
002963		70.92		008449	79.14	7.22	
002964		58.89		008450	94.26	-25.65	
002965		82.07		008451	91.31	-32.08	
002966		81.55		008452	82.11	-39.17	
002967		94.11		008453	73.97	-29.90	
002968	27.54	81.58		008454	74.64	3.68	
002969		86.51		008455	106.24	34.24	
002970		52.77		008456	103.54	-18.60	
002971		55.04		008457	101.19	-17.45	
002972		77.75		008458	36.74	43.65	
002973		51.75		008459	40.34	38.13	
002974		44.56		008460	48.90	23.25	
002975		25.94		008461	55.67	67.84	
002976		58.69		008462	69.33	37.95	
002977		55.99		008463	20.10	78.14	
002978		38.04		008464	85.74	-27.49	
002979		74.10		008465	74.12	15.11	
002980		77.28		008466	65.57	-35.99	
002981		61.74		008467	57.61	-31.57	
002982	36.47	88.88		008468	28.73	-4.08	
002983	35.04	56.83		008469	81.82	-15.33	
002984		54.64		008470	50.25	9.74	
002985		27.53		008471	39.69	47.91	
002986		6.97		008472	67.79	2.14	
002987		69.57		008473	53.58	1.73	
002988		68.81		008474	56.28	9.80	
002989	25.80	71.60		008475	65.69	47.96	
002990	29.45	68.74		008476	54.24	39.98	
002991	28.01	65.69		008477	104.37	-3.39	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
002992	36.12	48.78		008478	95.67	20.07	
002993	27.05	39.64		008479	112.06	28.12	
002994	24.77	64.32		008480	66.46	54.30	
002995	48.48	38.31		008481	94.72	4.55	
002996		30.55		008482	110.11	8.57	
002997		33.31		008483	112.36	8.26	
002998		32.09		008484	68.41	-1.04	
002999		51.54		008485	75.62	41.62	
003000		35.18		008486	106.62	20.41	
003001		22.05		008487	88.40	55.72	
003002		55.54		008488	84.72	30.21	
003003		52.49		008489	99.75	9.47	
003004		28.96		008490	95.25	3.31	
003005		32.53		008491	71.03	20.76	
003006		52.82		008492	58.37	22.56	
003007		34.61		008493	58.13	37.50	
003008		55.33		008494	80.75	37.30	
003009		55.30		008495	95.86	24.74	
003010		23.41		008496	57.89	40.77	
003011		28.72		008497	27.16	21.81	
003012		26.69		008498	83.08	1.76	
003013		50.85		008499	87.91	6.76	
003014		25.80		008500	25.94	29.28	
003015		58.24		008501	1.72	87.42	
003016		57.76		008502	1.61	69.55	
003017		60.10		008503	34.25	52.85	
003018		55.98		008504	29.28	-7.25	
003019		37.95		008505	40.18	47.18	
003020		51.08		008506	60.75	0.04	
003021		49.22		008507	41.83	21.51	
003022		27.15		008508	34.91	37.89	
003023		45.72		008509	71.80	-14.64	
003024		21.63		008510	80.61	-6.40	
003025		10.98		008511	5.69	64.19	
003026		58.38		008512	38.68	24.76	
003027		60.66		008513	4.28	78.53	
003028		85.31		008514	50.75	7.70	
003029		90.85		008515	13.34	25.84	
003030		83.55		008516	12.16	45.28	
003031		80.99		008517	33.59	13.29	
003032		58.38		008518	11.39	49.67	
003033		88.79		008519	32.53	38.83	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003034		88.43		008520	21.77	59.27	
003035		60.36		008521	28.90	62.73	
003036		66.47		008522	31.55	46.54	
003037		75.80		008523	66.82	-21.00	
003038		62.86		008524	86.26	-62.50	
003039		53.38		008525	112.10	-16.24	
003040		68.27		008526	94.70	2.50	
003041		82.91		008527	72.96	12.66	
003042		77.35		008528	93.18	-7.03	
003043		88.89		008529	1.88	99.04	
003044		82.69		008530	2.27	91.35	
003045		91.31		008531	1.39	80.64	
003046		90.21		008532	1.04	91.15	
003047		77.62		008533	1.19	87.02	
003048		91.95		008534	3.73	82.31	
003049		70.94		008535	3.28	77.58	
003050		68.28		008536	1.11	86.48	
003051		23.34		008537	4.74	68.14	
003052		89.15		008538	21.35	59.00	
003053		79.91		008539	10.28	62.40	
003054		75.11		008540	18.97	42.59	
003055		40.65		008541	27.06	60.19	
003056		64.49		008542	28.41	44.08	
003057		46.73		008543	4.66	72.34	
003058	18.38	79.72		008544	4.73	73.86	
003059		64.89		008545	4.19	81.08	
003060		82.81		008546	6.06	62.56	
003061	35.17	77.51		008547	20.33	32.30	
003062		91.09		008548	76.10	-59.95	
003063	24.07	83.73		008549	90.60	-74.35	
003064		76.58		008550	96.18	4.99	
003065		33.05		008551	80.34	26.28	
003066		46.13		008552	27.93	25.41	
003067		55.28		008553	19.38	20.13	
003068		60.22		008554	18.12	44.27	
003069	23.24	90.99		008555	27.78	40.95	
003070		100.65		008556	19.94	51.94	
003071		100.06		008557	23.20	42.43	
003072		83.67		008558	14.23	47.73	
003073		52.68		008559	19.26	49.24	
003074		40.20		008560	15.41	48.03	
003075		46.91		008561	12.91	73.32	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003076		94.63		008562	106.19	-22.88	
003077		36.22		008563	52.52	-0.19	
003078		73.25		008564	59.22	-16.32	
003079		30.02		008565	74.50	-36.52	
003080	26.56	63.86		008566	39.32	5.59	
003081		41.53		008567	86.82	7.62	
003082		28.13		008568	62.94	4.97	
003083		29.28		008569	56.64	34.24	
003084		62.36		008570	84.80	-3.60	
003085		56.40		008571	29.00	-7.70	
003086		40.35		008572	36.07	-10.85	
003087		46.51		008573	19.27	22.46	
003088		81.62		008574	14.29	21.12	
003089		40.70		008575	22.21	43.66	
003090		16.74		008576	21.97	54.57	
003091		-31.97		008577	25.21	26.23	
003092	27.33	75.64		008578	16.70	56.13	
003093		57.04		008579	9.88	56.33	
003094		47.08		008580	14.69	21.29	
003095		50.25		008581	31.82	20.19	
003096		97.99		008582	5.37	79.00	
003097		21.77		008583	10.01	71.97	
003098		28.49		008584	1.50	94.47	
003099		28.12		008585	27.78	32.87	
003100		42.21		008586	38.37	3.21	
003101		21.21		008587	61.87	14.52	
003102		64.79		008588	39.07	21.39	
003103		38.31		008589	30.36	7.73	
003104		47.01		008590	77.32	26.31	
003105		49.06		008591	66.39	23.41	
003106		34.90		008592	83.33	-2.62	
003107		75.42		008593	87.31	-46.33	
003108		43.21		008594	91.50	-20.13	
003109		49.01		008595	84.56	10.77	
003110		36.26		008596	99.76	-24.78	
003111		23.63		008597	87.43		
003112		66.14		008598	98.73		
003113		34.90		008599	93.92	-7.14	
003114		58.51		008600	92.89	-13.36	
003115		38.73		008601	84.08	-29.91	
003116		51.08		008602	77.11	-1.29	
003117		55.85		008603	98.86	-33.69	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003118		51.05		008604	97.78	11.74	
003119		76.32		008605	89.40	15.55	
003120		38.75		008606	97.80	-24.70	
003121		41.33		008607	99.13	-23.15	
003122		26.75		008608	101.58	22.19	
003123		89.71		008609	102.61	-20.97	
003124		94.73		008610	88.07	14.66	
003125		36.37		008611	67.93	19.97	
003126		45.19		008612	96.84	39.36	
003127		48.72		008613	97.72	19.80	
003128		96.16		008614	104.96	6.65	
003129		75.36		008615	53.49	52.14	
003130		79.23		008616	72.32	16.79	
003131		32.12		008617	59.08	22.33	
003132		86.82		008618	21.11	86.06	
003133		91.23		008619	25.08	74.87	
003134		91.15		008620	20.59	56.54	
003135		61.01		008621	40.80	56.14	
003136		92.96		008622	42.87	30.93	
003137		98.16		008623	20.12	21.58	
003138		96.08		008624	36.23	62.53	
003139		85.71		008625	20.50	56.99	
003140		93.92		008626	21.85	68.58	
003141		83.10		008627	74.62	2.25	
003142		49.19		008628	24.42	54.20	
003143		68.12		008629	40.53	46.28	
003144		72.13		008630	45.97	36.97	
003145		88.75		008631	43.20	9.45	
003146		52.03		008632	30.06	60.57	
003147		85.96		008633	39.74	38.65	
003148		81.98		008634	43.72	40.50	
003149		60.54		008635	44.20	44.95	
003150		76.59		008636	46.23	19.51	
003151		88.52		008637	48.27	42.91	
003152		61.33		008638	35.60	75.46	
003153		65.84		008639	41.45	50.54	
003154		-22.95		008640	38.63	66.05	
003155		55.13		008641	48.44	66.16	
003156		55.05		008642	22.75	88.00	
003157		57.84		008643	29.02	74.22	
003158		67.08		008644	46.00	64.65	
003159		90.69		008645	59.76	51.99	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003160		72.52		008646	37.91	78.53	
003161		74.97		008647	51.76	58.99	
003162		60.08		008648	30.23	70.94	
003163		59.49		008649	33.54	83.38	
003164		59.78		008650	54.27	57.50	
003165		81.07		008651	100.27	27.28	
003166		73.40		008652	81.00	30.20	
003167		70.43		008653	72.23	15.07	
003168		66.28		008654	66.92	9.73	
003169		83.03		008655	66.26	14.18	
003170		53.53		008656	57.45	12.46	
003171		52.55		008657	74.32	17.81	
003172	35.33	85.95		008658	67.55	21.14	
003173	20.25	83.03		008659	43.67	33.40	
003174		62.18		008660	50.49	35.83	
003175		79.00		008661	45.17	42.72	
003176	30.83	77.82		008662	39.03	23.82	
003177		61.99		008663	43.03	40.46	
003178		45.26		008664	105.40	-6.50	
003179	25.35	73.05		008665	81.88	4.16	
003180		79.38		008666	92.28	6.70	
003181		70.10		008667	60.19	43.73	
003182		74.37		008668	63.66	19.92	
003183		73.15		008669	94.07	8.48	
003184		59.43		008670	48.31	43.81	
003185		44.93		008671	51.68	23.34	
003186		53.61		008672	72.23	16.98	
003187		46.54		008673	66.41	27.67	
003188		47.63		008674	28.09	51.95	
003189		48.17		008675	7.60	59.96	
003190		30.31		008676	100.11	0.57	
003191		47.32		008677	58.31	9.26	
003192		40.98		008678	49.53	6.48	
003193		49.25		008679	69.02	-8.39	
003194		42.57		008680	71.05	18.78	
003195		36.82		008681	70.42	23.46	
003196		-25.70		008682	52.80	13.96	
003197		35.92		008683	36.48	72.06	
003198	33.09	44.05		008684	30.17	78.02	
003199	32.12	69.44		008685	12.54	48.73	
003200		23.75		008686	11.09	79.37	
003201		47.15		008687	20.11	76.19	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003202		59.65		008688	14.29	79.90	
003203	35.85	67.82		008689	10.53	82.79	
003204		42.96		008690	10.98	84.56	
003205		-17.25		008691	15.05	40.07	
003206		71.37		008692	12.93	68.76	
003207		20.74		008693	22.38	66.83	
003208		66.08		008694	13.87	75.99	
003209		44.05		008695	27.81	59.48	
003210		58.38		008696	22.24	62.24	
003211		17.14		008697	82.14	1.37	
003212		56.51		008698	81.57	-8.67	
003213		27.62		008699	100.46	-11.16	
003214		27.76		008700	59.78	-5.82	
003215		42.83		008701	57.00	39.68	
003216		37.45		008702	56.80	5.60	
003217		1.28		008703	39.24	9.05	
003218		57.76		008704	64.80	-9.23	
003219		8.08		008705	76.57	15.49	
003220		38.66		008706	16.76	53.96	
003221		53.42		008707	36.03	34.26	
003222		21.62		008708	10.00		
003223		-17.26		008709	11.61	80.91	
003224		19.25		008710	8.81	88.32	
003225		58.69		008711	84.04	0.03	
003226	45.22	67.60		008712	76.06	17.37	
003227		32.63		008713	25.61	84.31	
003228		66.33		008714	12.88		
003229	32.72	91.79		008715	76.98	-2.75	
003230		84.54		008716	94.96	11.83	
003231	18.30	110.67		008717	93.91	2.40	
003232		38.03		008718	100.17	-16.30	
003233		59.42		008719	91.54	13.49	
003234		55.28		008720	97.94	7.92	
003235		69.81		008721	100.28	31.06	
003236		-8.88		008722	101.50	21.56	
003237		35.74		008723	94.78	12.67	
003238		40.93		008724	86.03	31.68	
003239		65.69		008725	93.84	28.07	
003240		61.50		008726	84.38	21.37	
003241		26.85		008727	71.50	6.72	
003242		8.46		008728	34.62	34.34	
003274		75.48		008729	62.65	16.28	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003275		81.53		008730	93.91	-1.01	
003276		86.28		008731	94.63	-3.52	
003277		89.60		008732	104.86	-21.83	
003278		98.90		008733	87.33	-0.89	
003279	31.60	86.29		008734	90.07	-6.51	
003280		30.88		008735	12.76	75.03	
003281		64.42		008736	15.68	59.26	
003282		63.62		008737	22.45	43.45	
003283		22.11		008738	15.62	76.17	
003284		30.73		008739	17.72	79.88	
003285		76.98		008740	36.15	51.83	
003286		63.56		008741	25.98	65.80	
003287		74.35		008742	40.95	23.08	
003288		78.57		008743	47.24	30.97	
003289		78.13		008744	11.85		
003290		93.20		008745	29.81	34.45	
003291		83.96		008746	102.09	51.23	
003292		70.56		008747	13.74	67.47	
003293		72.75		008748	29.79		
003294		77.67		008749	13.25	77.62	
003295		13.96		008750	30.33	65.46	
003296		38.53		008751	14.95		
003297		71.74		008752	27.50		
003298		58.27		008753	27.75	29.10	
003299		55.71		008754	26.68	65.84	
003300		71.55		008755	29.58	58.42	
003301		43.11		008756	63.80	24.58	
003302		51.44		008757	83.62	-8.59	
003303		29.31		008758	99.02	-13.63	
003304		82.51		008759	102.25	-4.26	
003305		90.20		008760	108.26	-20.36	
003306		80.15		008761	92.73	-15.24	
003307		84.71		008762	10.50		
003308		76.87		008763	20.08	80.81	
003309		22.92		008764	37.65	76.43	
003310		19.40		008765	7.18	85.46	
003311		70.95		008766	10.48	77.25	
003312		71.27		008767	19.59	64.53	
003313		72.19		008768	10.37	86.37	
003314		66.48		008769	18.43	-42.72	
003315		71.96		008770	24.87	67.85	
003316		42.88		008771	12.63	80.76	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
003317		75.76		008772	11.47		
003318		40.39		008773	61.58	-2.84	
003319		23.04		008774	13.87	63.48	
003320		63.14		008775	71.43	-50.77	
003321		37.14		008776	47.25	-15.93	
003322		25.13		008777	96.37	16.36	
003323		87.00		008778	73.74	61.94	
003324		58.90		008779	68.14	41.00	
003325		55.25		008780	100.54	18.68	
003326		3.60		008781	43.90	49.68	
003327		33.45		008782	61.07	-7.51	
003328		56.37		008783	61.91	19.67	
003329		60.49		008784	70.96	-0.06	
003330		81.29		008785	51.11	11.89	
003331		76.22		008786	45.57	41.46	
003332		74.15		008787	27.87		
003333		44.44		008788	36.19	78.55	
003334		-19.13		008789	37.25	58.80	
003335		42.85		008790	18.90	59.50	
003336		69.34		008791	39.68	42.57	
003337		74.87		008792	35.77	53.91	
003338		77.48		008793	25.24	58.97	
003339		73.78		008794	23.12	77.38	
003340		52.89		008795	44.61	11.30	
003341		41.75		008796	21.41	76.54	
003342		77.95		008797	83.94	-9.77	
003343		50.80		008798	50.21	50.37	
003344		57.59		008799	37.25	75.62	
003345	26.98	74.35		008800	37.42	-36.80	
003346		-21.50		008801	20.94	56.21	
003347		63.11		008802	96.86	-0.99	
003348		61.47		008803	106.01		
003349		86.85		008804	90.76	8.55	
003350		14.40		008805	97.38	3.92	
003351		61.89		008806	54.14	44.43	
003352		70.61		008807	97.46	9.01	
003353		73.88		008808	102.33	-8.76	
003354		55.78		008809	87.28	25.67	
003355		24.37		008810	56.16	60.39	
003356		65.30		008811	82.15	27.77	
003357		69.87		008812	47.52	56.66	
004842	66.43	60.01		008813	83.92	30.12	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
004843	78.67	6.69		008814	94.04	17.42	
004844	106.29	32.11		008815	77.58	12.66	
004845	89.51	1.14		008816	58.92	19.47	
004846	106.28	14.57		008817	45.37	21.46	
004847	38.71	43.24		008818	55.98	43.35	
004848	55.61	32.35		008819	54.03	53.98	
004849	75.08	16.35		008820	64.33	58.54	
004850	76.30	58.79		008821	52.50	55.12	
004851	83.17	34.11		008822	74.80	22.86	
004852	42.61	51.86		008823	95.21		
004853	60.12	47.34		008824	36.13	63.15	
004854	90.33	0.16		008825	32.09	64.49	
004855	94.95	16.20		008826	81.11	45.29	
004856	31.66	57.54		008827	76.18	36.36	
004857	31.76	73.09		008828	83.63	21.20	
004858	68.75	41.66		008829	87.88	38.64	
004859	73.63	49.78		008830	82.31	47.66	
004860	66.87	36.74		008831	72.16	81.78	
004861	16.75	93.47		008832	71.96	84.78	
004862	28.88	75.56		008833	98.60	32.15	
004863	55.59	31.89		008834	101.20	7.29	
004864	41.42	56.48		008835	95.58	15.90	
004865	48.89	41.88		008836	27.69	78.30	
004866	22.93	86.43		008837	22.36	92.45	
004867	23.55	83.72		008838	30.05	87.30	
004868	37.28	42.41		008839	59.59	38.83	
004869	56.13	73.75		008840	66.41		
004870	65.76	62.33		008841	65.78	4.01	
004871	22.71	97.66		008842	48.10	40.87	
004872	36.75	43.17		008843	56.40		
004873	58.22	30.67		008844	48.84	21.62	
004874	51.16	60.26		008845	45.77	53.83	
004875	72.81	40.30		008846	38.79	59.81	
004876	33.85	71.57		008847	61.46	33.64	
004877	47.33	46.70		008848	78.28	-11.96	
004878	68.08	20.64		008849	83.14	18.21	
004879	68.60	34.25		008850	35.26	22.50	
004880	66.72	45.90		008851	21.04	76.97	
004881	13.43	100.98		008852	64.79	22.08	
004882	23.94	97.34		008853	52.82	28.91	
004883	27.38	55.94		008854	78.28	40.47	
004884	28.69	42.19		008855	108.07	14.72	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
004885	37.72	89.15		008856	96.40		
004886	20.94	85.41		008857	64.70	46.14	
004887	28.41	86.07		008858	79.46	43.07	
004888	31.68	60.85		008859	75.71		
004889	26.57	92.62		008860	42.15	61.77	
004890	56.87	83.42		008861	51.48	69.41	
004891	22.53	97.52		008862	119.59	9.36	
004892	27.44	97.04		008863	99.49	1.99	
004893	39.21	65.29		008864	57.74	36.42	
004894	29.74	93.37		008865	58.09	27.89	
004895	54.33	66.52		008866	74.09	9.96	
004896	29.02	42.73		008867	56.76	25.23	
004897	92.43	91.36		008868	94.07	16.49	
004898	53.08	74.59		008869	114.08	-6.54	
004899	55.34	91.21		008870	66.64	43.95	
004900	64.11	74.38		008871	36.94	45.83	
004901	23.34	67.79		008872	60.83	0.98	
004902	21.57	91.34		008873	99.17	11.28	
004903	17.33	92.92		008874	111.48	15.50	
004904	38.63	82.17		008875	104.32	19.90	
004905	53.40	82.51		008876	105.53	25.85	
004906	56.36	86.11		008877	88.62	8.29	
004907	71.44	63.30		008878	95.77	9.11	
004908	45.27	74.84		008879	89.72	7.56	
004909	34.39	72.69		008880	44.12	29.47	
004910	36.45	85.01		008881	65.38	-70.54	
004911	39.02	62.84		008882	79.98	46.28	
004912	31.57	65.97		008883	61.35	36.83	
004913	35.70	86.56		008884	62.50	25.09	
004914	36.92	74.59		008885	58.54	20.30	
004915	30.83	91.77		008886	95.93	51.85	
004916	41.11	72.85		008887	40.76	31.60	
004917	34.83	83.73		008888	44.84	9.24	
004918	50.68	42.52		008889	69.14	39.04	
004919	48.45	28.74		008890	80.68		
004920	76.97	-1.98		008891	96.58	27.91	
004921	40.45	78.05		008892	80.78	7.95	
004922	36.28	45.00		008893	51.17	24.19	
004923	52.79	49.31		008894	44.82	27.33	
004924	45.10	52.15		008895	114.09		
004925	43.67	45.03		008896	134.80		
004926	50.14	54.69		008897	99.70	17.68	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
004927	56.64	64.52		008898	89.07	16.71	
004928	65.48	66.42		008899	38.29	44.32	
004929	62.59	43.66		008900	55.27	-3.26	
004930	72.38	60.75		008901	100.02	17.95	
004931	39.55	75.60		008902	73.53	18.18	
004932	26.83	90.35		008903	104.88	-0.27	
004933	31.40	76.43		008904	27.88	56.68	
004934	43.52	80.52		008905	26.15	51.25	
004935	39.38	43.83		008906	29.06	52.77	
004936	47.32	82.57		008907	23.23	60.57	
005008		29.20		008908	16.53	78.72	
005009		63.57		008909	16.13	88.43	
005010		60.83		008910	34.17	52.80	
005011		59.08		008911	76.84	-6.26	
005012		47.35		008912	83.79	-4.78	
005013		30.27		008913	102.22	7.25	
005014		65.35		008914	99.50	-3.97	
005015		70.87		008915	104.15	0.84	
005016		60.67		008916	96.05	10.83	
005017		55.88		008917	76.54	12.60	
005018		24.75		008918	83.94	2.69	
005019		7.46		008919	101.02	-19.99	
005020		23.06		008920	91.71	-0.01	
005021		60.79		008921	72.06	-6.88	
005022		70.44		008922	76.87	22.49	
005023		69.98		008923	103.01	-13.97	
005024		68.10		008924	70.79	6.49	
005025		66.38		008925	55.25	48.18	
005026		31.66		008926	56.49	19.86	
005027		57.57		008927	35.19	50.78	
005028		65.54		008928	35.19	36.86	
005029		66.90		008929	48.70	46.97	
005030		68.43		008930	29.86	88.58	
005031		58.90		008931	47.83	63.73	
005032		41.55		008932	51.51	69.14	
005033		28.77		008933	70.03	38.53	
005034		73.61		008934	58.98	63.66	
005035		71.12		008935	61.55	35.30	
005036		73.98		008936	58.07	30.95	
005037		72.64		008937	46.88	46.47	
005038		79.28		008938	54.92	61.08	
005039		59.37		008939	123.45	-5.94	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
005040		29.99		008940	116.82	-47.46	
005041		30.56		008941	28.62	30.27	
005042		65.98		008942	65.62	-16.74	
005043		63.95		008943	39.33	31.95	
005044		64.87		008944	63.48	30.41	
005045		70.95		008945	67.14	16.25	
005046		69.64		008946	49.01	-34.12	
005047		57.93		008947	49.79	61.47	
005048		44.19		008948	41.01	71.95	
005049		54.45		008949	48.76	45.13	
005050		80.99		008950	44.72	18.21	
005051		86.49		008951	47.66	-11.32	
005052		88.12		008952	59.87	-7.73	
005053		84.16		008953	78.68	12.14	
005054		83.94		008954	69.52	18.01	
005055		55.45		008955	86.22	-6.78	
005056		37.48		008956	103.89	-9.37	
005057		41.74		008957	100.69	10.97	
005058		77.41		008958	105.40	26.92	
005059		75.79		008959	104.13	-8.60	
005060		73.97		008960	77.53	7.28	
005061		74.08		008961	43.55	28.47	
005062		26.45		008962	22.43	55.20	
005063		24.24		008963	32.26	53.94	
005064		20.10		008964	54.49	36.16	
005065		25.22		008965	61.14	-2.80	
005066		59.16		008966	30.18	70.44	
005067		52.52		008967	23.66	71.89	
005068		84.87		008968	34.22	63.68	
005069		79.78		008969	28.27	67.70	
005070		54.26		008970	30.27	73.92	
005071		63.79		008971	31.82	35.74	
005072		42.21		008972	41.65	58.44	
005073		69.43		008973	39.29	57.97	
005074		57.10		008974	33.31	60.39	
005075		79.53		008975	42.66	66.78	
005076		70.39		008976	53.86	65.19	
005077		69.15		008977	112.73	-11.73	
005078		48.26		008978	112.79	-16.95	
005163	47.38	77.83		008979	107.98	-17.22	
005164	45.78	48.54		008980	107.97	-21.91	
005165	48.64	52.03		008981	101.56	-3.76	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
005166	36.99	67.67		008982	94.98	-7.28	
005167	64.21	52.50		008983	101.95	-42.77	
005168	94.18	11.02		008984	117.87	-10.50	
005169	47.39	76.00		008985	50.93	21.86	
005170	62.02	52.88		008986	69.30		
005171	42.23	81.86		008987	40.92	51.72	
005172	63.80	54.69		008988	86.03	11.94	
005173	60.15	73.83		008989	98.73		
005174	66.79	45.84		008990	93.40	-26.23	
005175	67.35	21.60		008991	114.15	-29.70	
005176	61.49	20.26		008992	112.79	-29.20	
005177	58.17	33.03		008993	83.04	10.48	
005178	59.94	31.08		008994	51.80	40.10	
005179	55.09	34.81		008995	88.85	-0.20	
005180	34.06	40.31		008996	63.75	9.43	
005181	39.61	31.91		008997	27.60	45.22	
005182	45.49	67.69		008998	41.05	15.40	
005183	33.60	70.61		008999	64.39	15.78	
005184	36.09	60.64		009000	32.63	32.17	
005185	36.13	53.42		009001	36.47	44.02	
005186	34.30	42.37		009002	73.22	25.36	
005187	37.78	30.28		009003	87.01	12.32	
005188	36.77	26.58		009004	91.06	15.83	
005189	51.51	24.87		009005	72.69	9.83	
005190	33.26	59.30		009006	70.86	37.49	
005191	34.56	25.68		009007	60.31	33.13	
005192	48.09	14.48		009008	92.31	3.32	
005193	39.51	29.52		009009	80.63	24.95	
005194	34.64	39.93		009010	86.33	6.03	
005195	29.47	23.19		009011	86.70	33.64	
005196	27.53	46.58		009012	82.69	1.71	
005197	48.02	21.35		009013	31.56	45.26	
005198	31.40	53.62		009014	101.02	12.09	
005199	34.70	32.21		009015	93.66	7.25	
005200	38.66	47.06		009016	99.43	31.26	
005201	35.74	53.03		009017	70.91	-0.98	
005202	39.83	25.31		009018	41.24	53.60	
005203	61.60	3.69		009019	34.57	55.30	
005204	36.95	39.92		009020	52.43	61.69	
005205	54.06	26.87		009021	59.98	51.39	
005206	36.52	47.82		009022	74.14	33.58	
005207	30.21	61.54		009023	72.14	-0.71	

ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM	ASO_NO	SK cells asyn/GAPDH %inhb @25 uM	PAC neuron asyn/tub %inh @40nM	PAC neuron aysn/tub % Inh @5 uM
005208	27.68	37.86		009024	72.66	4.00	
005209	37.91	32.22		009025	77.57	-6.84	
005210	41.54	59.06		009026	94.95	17.73	
005211	36.16	40.08		009027	36.59	69.55	
005212	46.29	46.75		009028	22.91	60.53	
005213	42.59	14.86		009029	32.75	75.07	
005214	43.10	35.43		009030	99.82	2.17	
005215	50.21	10.22		009031	46.18	46.27	
005216	40.03	32.74		009032	72.06	22.16	
005217	40.25	30.60		009033	32.71	59.98	
005218	38.34	32.13		009034	32.30	65.60	
005219	51.90	34.55		009035	29.11	49.79	
005220	44.35	57.77		009036	43.80	59.17	
005221	41.32	59.38		009037	62.94	27.78	
005222	39.96	30.87		009038	41.07	78.41	
005223	50.33	16.11		009039	41.74	59.76	
005224	34.89	34.61		009040	79.46	22.12	
005225	41.18	9.75		009041	73.58	39.76	
005226	33.90	37.60		009042	74.10	48.08	
005227	44.80	-5.95		009043	90.10	15.32	
005228	35.86	24.66		009044	79.40	27.06	
005229	45.12	6.62		009045	70.14	32.33	
005230	59.74			009046	61.17	26.16	

Table 2 shows the potency of the various ASOs in reducing SNCA protein expression in primary neurons isolated from A53T-PAC transgenic mice *in vitro*. The PAC neurons were cultured *in vitro* with the 10-point titration (indicates above) of the different ASOs and the potency (IC_{50}) of the ASOs is shown as a ratio of SNCA to tubulin expression (µM).

ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)
ASO-000838	0.03	ASO-002521	1.95	ASO-003199	0.01
ASO-001233	1.52	ASO-002522	0.002	ASO-003202	0.02
ASO-001268	0.04	ASO-002686	0.03	ASO-003203	0.05
ASO-001281	0.19	ASO-002690	0.03	ASO-003206	0.02
ASO-001282	0.07	ASO-002692	0.11	ASO-003229	0.03
ASO-001308	0.02	ASO-002693	0.01	ASO-003279	0.01
ASO-001310	0.21	ASO-002694	0.01	ASO-003323	0.01
ASO-001328	0.003	ASO-002705	0.06	ASO-003330	0.01
ASO-001334	0.16	ASO-002730	0.06	ASO-003345	0.02
ASO-001344	0.03	ASO-002738	0.05	ASO-003349	0.01

ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)
ASO-001357	0.03	ASO-002739	0.09	ASO-004871	0.05
ASO-001363	0.03	ASO-002761	0.05	ASO-004881	0.02
ASO-001365	0.01	ASO-002762	0.01	ASO-004885	0.16
ASO-001367	0.22	ASO-002763	0.05	ASO-004901	0.13
ASO-001384	0.10	ASO-002765	0.04	ASO-004902	0.03
ASO-001395	0.03	ASO-002779	0.04	ASO-004903	0.02
ASO-001398	0.02	ASO-002785	0.01	ASO-004910	0.02
ASO-001434	0.15	ASO-002798	0.02	ASO-004913	0.07
ASO-001453	0.46	ASO-002801	0.01	ASO-004917	0.03
ASO-001459	0.28	ASO-002804	0.03	ASO-004932	0.06
ASO-001463	0.11	ASO-002805	0.01	ASO-004934	0.08
ASO-001467	0.30	ASO-002817	0.03	ASO-004936	0.11
ASO-001468	0.12	ASO-002820	0.04	ASO-005273	0.05
ASO-001471	0.03	ASO-002825	0.02	ASO-005276	0.04
ASO-001481	0.05	ASO-002828	0.02	ASO-005281	0.09
ASO-001484	0.25	ASO-002832	0.01	ASO-005289	0.11
ASO-001486	0.06	ASO-002833	0.01	ASO-005292	0.02
ASO-001532	0.06	ASO-002836	0.04	ASO-005304	0.05
ASO-001537	0.02	ASO-002837	0.02	ASO-005305	0.02
ASO-001549	0.01	ASO-002838	0.01	ASO-005308	0.05
ASO-001554	0.15	ASO-002842	0.13	ASO-005309	0.02
ASO-001560	0.06	ASO-002843	0.01	ASO-005317	0.03
ASO-001561	0.01	ASO-002844	0.01	ASO-005319	0.07
ASO-001582	0.07	ASO-002847	0.01	ASO-005330	0.02
ASO-001585	0.03	ASO-002848	0.01	ASO-005336	0.08
ASO-001605	0.01	ASO-002849	0.01	ASO-005348	0.02
ASO-001606	0.01	ASO-002850	0.005	ASO-006712	0.01
ASO-001638	0.05	ASO-002852	0.01	ASO-008226	0.01
ASO-001639	0.10	ASO-002858	0.01	ASO-008261	0.01
ASO-001665	0.02	ASO-002860	0.01	ASO-008387	0.01
ASO-001669	0.10	ASO-002863	0.01	ASO-008388	0.01
ASO-001671	0.01	ASO-002864	0.01	ASO-008501	0.004
ASO-001673	0.08	ASO-002867	0.02	ASO-008502	0.01
ASO-001677	0.52	ASO-002901	0.02	ASO-008529	0.004
ASO-001694	0.24	ASO-002908	0.08	ASO-008530	0.01
ASO-001702	0.18	ASO-002935	0.02	ASO-008531	0.01
ASO-001730	0.22	ASO-002968	0.01	ASO-008532	0.004
ASO-001755	0.32	ASO-002983	0.04	ASO-008533	0.01
ASO-001757	0.29	ASO-002990	0.04	ASO-008534	0.01
ASO-001774	0.19	ASO-002992	0.35	ASO-008535	0.01
ASO-002041	0.04	ASO-002994	0.04	ASO-008536	0.003
ASO-002497	10.08	ASO-002995	0.11	ASO-008537	0.01
ASO-002498	6.00	ASO-003058	0.02	ASO-008543	0.01

ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)	ASO_NO	LE PAC ASyn/Tub IC50 (uM)
ASO-002501	6.00	ASO-003061	0.03	ASO-008545	0.01
ASO-002502	0.04	ASO-003063	0.05	ASO-008584	0.003
ASO-002505	17.45	ASO-003069	0.03	ASO-286762	0.03
ASO-002506	2,165.47	ASO-003072	0.09	ASO-286785	0.12
ASO-002509	10,000.00	ASO-003092	0.04	ASO-287033	0.03
ASO-002510	560.94	ASO-003172	0.01	ASO-287041	0.57
ASO-002512	1.47	ASO-003173	0.01	ASO-287053	4.00
ASO-002513	55.07	ASO-003175	0.01	ASO-287965	0.06
ASO-002515	19.89	ASO-003176	0.02	ASO-288902	0.11
ASO-002516	1.01	ASO-003177	0.02	ASO-288903	0.27
ASO-002518	2.71	ASO-003179	0.02	ASO-288905	0.04
ASO-002519	10.56	ASO-003181	0.01	ASO-290315	0.02
				ASO-292378	0.07

Table 3 shows the effect of additional exemplary ASOs from figure 1A to 1C on SNCA protein expression in PAC neurons when cultured *in vitro* with 5 µM of the ASO. The SNCA protein expression was normalized to tubulin expression and is shown as a percent of the control.

ASO_NO	"PAC neurons aysn/tub % Ctrl@5 uM"	ASO_NO	"PAC neurons aysn/tub % Ctrl@5 uM"	ASO_NO	"PAC neurons aysn/tub % Ctrl@5 uM"
ASO-000875	17.41	ASO-000885	43.42	ASO-000862	117.31
ASO-000873	29.15	ASO-000882	20.58	ASO-000840	8.82
ASO-000872	26.91	ASO-000880	88.38	ASO-000847	12.14
ASO-000874	4.94	ASO-000884	105.54	ASO-000850	15.52
ASO-000878	11.16	ASO-000883	55.93	ASO-000842	15.68
ASO-000879	5.54	ASO-000837	43.76	ASO-000865	18.84
ASO-000835	12.81	ASO-000836	19.21	ASO-000866	20.29
ASO-000876	36.99	ASO-000839	37.85	ASO-000843	20.39
ASO-000877	7.82	ASO-000855	48.04	ASO-000853	21.49
ASO-000867	170.64	ASO-000856	103.49	ASO-000852	25.01
ASO-000869	71.40	ASO-000857	118.02	ASO-000851	27.66
ASO-000864	146.16	ASO-000858	141.21	ASO-000845	30.91
ASO-000863	205.30	ASO-000859	60.26	ASO-000846	32.06
ASO-000870	71.03	ASO-000860	62.01	ASO-000841	37.83
ASO-000881	6.19	ASO-000861	111.60	ASO-000844	58.08

Example 2B: Spontaneous Calcium Oscillation Measurement

Reduced oscillations in intracellular free calcium concentration (calcium oscillation) corresponds to increased neurotoxicity and therefore, can indicate reduced tolerability *in vivo*. To measure primary cortical neuron spontaneous calcium oscillation, rat primary cortical neurons were prepared from Sprague-Dawley rat embryos (E19). Briefly, the brain cortex was dissected and incubated at 37°C for 30-45 minutes in papain/DNase/Earle's balanced salt solution (EBSS) solution. After trituration and centrifugation of the cell pellet, the reaction was stopped by incubation with EBSS containing protease inhibitors, bovine serum albumin (BSA), and DNase. The cells were then triturated and washed with Neurobasal (NB, Invitrogen) supplemented with 2% B-27, 100 µg/ml penicillin, 85 µg/ml streptomycin, and 0.5 mM glutamine.

The cells were plated at a concentration of 25,000 cells/well onto 384-well poly-D-lysine coated fluorescent imaging plates (BD Biosciences) in 25 µl/well supplemented Neurobasal (NB) media (containing B27 supplement and 2 mM glutamine). The cells were grown for 12 days at 37ºC in 5% CO_2 and fed with 25 µl of additional media on DIV04 (*i.e.,* 4 days after plating) and DIV08 (*i.e.,* 8 days after plating) for use on DIV12 (*i.e.,* 12 days after plating).

On the day of the experiment, the NB media was removed from the plate and the cells were washed once with 50 µl/well of 37ºC assay buffer (Hank's Balanced Salt Solution, containing 2 mM $CaCl_2$ and 10 mM Hopes pH 7.4). Oscillations were tested both in the presence and in the absence of 1mM $MgCl_2$. The cells were loaded with a cell permanent fluorescent calcium dye, Fluo-4-AM (Invitrogen, Molecular Probes F14201). Fluo-4-AM was prepared at 2.5 mM in DMSO containing 10% pluronic F-127 and then diluted 1:1000 in the assay buffer for a final concentration of 2.5 µM. The cells were incubated for 1 hr with 20 µl of 2.5 µM Fluo-4-AM at 37ºC in 5% CO_2. After the incubation, an additional 20 µl of room temperature assay buffer was added, and the cells were allowed to equilibrate to room temperature in the dark for 10 minutes.

The plates were read on a FDSS 7000 fluorescent plate reader (Hamamatsu) at an excitation wavelength of 485 nm and emission wavelength of 525 nm. The total fluorescence recording time was 600 seconds at 1Hz acquisition rate for all 384 wells. An initial baseline signal (measurement of intracellular calcium) was established for 99 seconds before the addition of the ASOs. ASOs were added with a 384 well head in the FLIPR in 20 µl of assay buffer at 75 µM for a final concentration of 25 µM. In some instances an ASO targeting *tau* such as ASO-000013 (OxyAs OxyTs OxyTs DNAts DNAcs DNAcs DNAas DNAas DNAas DNAts DNAts DNAcs DNAas OxyMCs OxyTs OxyT; ATTtccaaattcaCTT, SEQ ID NO: 1880) or ASO-000010 (TCTgtcttggctTTG, SEQ ID NO: 1879) was included as controls.

Fluorescence time sequence intensity measurements (described above) were exported from the Hamamatsu reader, and transferred to an in-house proprietary application in IDBS E-Workbook

suite for data reduction and normalization. In each 384 well screening plate, up to a maximum of 48 individual ASOs were tested in quadruplicate wells. 12 wells were exposed to a positive control (ASO-000010), which significantly inhibits the calcium oscillations counted during the 300 sec acquisition time frame and 12 wells were exposed to an negative control inactive ASO (ASO-000013) which does not inhibit the observation of calcium oscillations. Finally, 24 wells were dedicated to a vehicle control consisting of RNase-DNase-free water at the same concentration used to dilute the test ASOs. The effects of test ASOs in individual wells on calcium oscillation frequency (over the 300sec period) were expressed as a % control of the median number of calcium oscillations counted in the 24 vehicle control wells. Individual 384 well assay plates passed QC standards if the positive and negative ASO controls (ASO-000010 and ASO-000013) exhibited well characterized pharmacology in the Ca assay, and if the vehicle and pharmacological control wells generated a minimum of ~20 calcium oscillations over the 300 sec experimental time period.

Example 2C: QUANTIGENE® Analysis (96-well assay) to Measure mRNA Reduction in Human Neurons

The ability of ASOs to reduce human *SNCA* mRNA and/or possible human off target mRNA species was measured *in vitro* by QUANTIGENE® analysis. Human neurons (Cellular Dynamics Inc., "iNeurons"), were thawed, plated, and cultured per manufacturer's specifications. These iNeurons are highly pure population of human neurons derived from induced pluripotent stem (iPS) cells using Cellular Dynamic's proprietary differentiation and purification protocols.

Lysis: Cells were plated on poly-L-ornithine/laminin coated 96-well plates at 50,000 to 100,000 cells per well (dependent on the expression of the off target being investigated) and maintained in Neurobasal media supplemented with B27, glutamax, and Penicillin-Streptomycin. The ASOs were diluted in water and added to cells at DIV01 (*i.e.,* 1 day post plating). For single point measurements, a final ASO concentration of 0.5 µM was typically used. For IC_{50} determinations, the neurons were treated with a seven-point concentration response dilution of 1:4, with the highest concentration as 5 µM to define the IC_{50}. The cells were then incubated at 37ºC and 5% CO_2 for 6 days to achieve steady state reduction of mRNA.

After the incubation, the media was removed and cells were washed 1X in DPBS and lysed as follows. 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 working cell lysis buffer solution was made by adding 50 µl proteinase K to 5ml of pre-warmed (37ºC) Lysis mix and diluted in dH_2O to a 1:4 final dilution. The working lysis buffer was added to the plates (100 to 150 µl/ well, depending on the expression of the off target being investigated), triturated 10 times,

sealed and incubated for 30 min at 55ºC. Following the lysis, the wells were triturated 10 more times, and the plates were stored at -80ºC or assayed immediately.

Assay: Depending on the specific capture probe used (*i.e., SNCA*, *PROS1*, or tubulin), the lysates were diluted (or not diluted) in the lysis mix. Then, the lysates were added to the capture plates (96-well polystyrene plate coated with capture probes) at a total volume of 80 µl/well. Working probe sets reagents were generated by combining nuclease-free water (12.1 µl), lysis mixture (6.6 µl), blocking reagent (1 µl), and specific 2.0 probe set (0.3 µl) (human *SNCA* catalogue #SA-50528, human PROS1 catalogue #SA-10542, or human beta 3 tubulin catalogue #SA-15628) per manufacturer's instructions (QUANTIGENE® 2.0 AFFYMETRIX®). Next, 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 at 240g for 20 seconds and then incubated for 16-20 hours at 55ºC to hybridize (target RNA capture).

Signal amplification and detection of target RNA began by washing plates with buffer 3 times (300 µl/well) to remove any unbound material. Next, the 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 step 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 step was repeated as described previously. The plates were again centrifuged at 240g for 20 seconds to remove any excess wash buffer and then, the 2.0 Substrate was added (100 µl/well) to the plates. Plates were incubated for 5 minutes at room temperature and then, the 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 were then normalized to the background-subtracted average signal for the housekeeping tubulin RNA. The percent inhibition for the treated sample was calculated relative to the control treated sample lysate.

Example 2D: QUANTIGENE® Analysis (96-well assay) to Measure mRNA Reduction in Ramos Cells

To measure possible human off target IKZF3 (IKAROS family zinc finger 3) mRNA reduction, Ramos cells (a human lymphocytic cell line) were used. Since Ramos cells do not express *SNCA*, *RB1* (RB transcriptional corepressor 1), which is expressed in Ramos cells, was used as a positive control for assessing ASO-mediated knockdown IKZF3 mRNA expression. Two ASOs were

synthesized to bind to and knockdown human RB1 mRNA expression. Beta-2 microglobulin (β2M) was used as a housekeeping gene control. The Ramos cells were grown in suspension in RPMI media supplemented with FBS, glutamine, and Pen/Strep.

Lysis: Cells were plated on poly-L-ornithine/laminin coated 96 well plates at 20,000 cells per well and maintained in Neurobasal media containing B27, glutamax and Penicillin-Streptomycin. ASOs were diluted in water and added to cells at 1 day post plating (DIV01) to a final concentration of 1 μM. Following ASO treatment, the cells were incubated at 37ºC for 4 days to achieve steady state reduction of mRNA. After the incubation, the 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. Lysis mix (QuantiGene 2.0 Affymetrix) was pre-warmed in an incubator at 37ºC for 30 minutes. For lysing cells in suspension, 100 μl of 3X Lysis Buffer (with 10 μl/ml proteinase K) was added to 200 μl of cells in suspension. The cells were then triturated 10 times to lyse, and the plate sealed and incubated for 30 min at 55ºC. Afterwards, the lysates were stored at -80ºC or assayed immediately.

Assay: Depending on the specific capture probe used (*i.e.,* IKZF3, RB1, and β2M), the lysates were diluted (or not diluted) in the lysis mix. Then, the lysates were added to the capture plate (96 well polystyrene plate coated with capture probes) at a total volume of 80 μl/well. 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 IKZF3 catalogue #SA-17027, human RB1 catalogue #SA-10550, or human beta-2 microglobulin catalogue #SA-10012) 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 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 (300 μl/well) to remove any unbound material. Next, the 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 step 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 step again was repeated as described previously. The plates were again centrifuged at 240g for 20 seconds to remove any excess wash buffer and then, the 2.0 Substrate was added (100 μl/well) to the plates. Plates were incubated for 5 minutes at room temperature, and then, the

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 (*i.e.,* no lysate, just 1X lysis buffer) was subtracted from the average signal of each technical replicate. The background-subtracted, average signals for the gene of interest were then normalized to the background-subtracted average signal for the housekeeping mRNA (for Ramos cells, it was beta-2-microglobulin). The percent inhibition for the treated sample was calculated relative to the average of the untreated sample lysate.

Example 2E: qPCR assay to measure reduction of *SNCA* mRNA in SK-N-BE(2) cells

ASOs targeting *SNCA* were tested for its ability to reduce *SNCA* mRNA expression in human SK-N-BE(2) neuroblastoma cell acquired from ATCC (CRL-2271).

SK-N-BE(2) cells were grown in cell culturing media (MEM [Sigma, cat.no M2279] supplemented with 10% Fetal Bovine Serum [Sigma, cat.no F7524], 1x GlutamaxTM [Sigma, cat.no 3050-038] 1x MEM Non-essential amino acid solution [Sigma, cat.no M7145] and 0.025mg/ml Gentamycin [Sigma, cat.no G1397]). Cells were trypsinized every 5 days, by washing with Phosphate Buffered Saline (PBS), [Sigma cat.no 14190-094] followed by addition of 0.25% Trypsin-EDTA solution (Sigma, T3924), 2-3 minutes incubation at 37°C, and trituration before cell seeding. Cells were maintained in culture for up to 15 passages.

For experimental use, 12,500 cells per well were seeded in 96 well plates (Nunc cat.no 167008) in 100µL growth media. Oligonucleotides were prepared from a 750µM stock. ASO dissolved in PBS was added approximately 24 hours after the cells were seeded to a final concentration of 25µM for single point studies. Cells were incubated for 4 days without any media change. For potency determination, 8 concentrations of ASO were prepared for a final concentration range of 16-50,000 nM. ASO-004316 (CcAAAtcttataataACtAC, SEQ ID NO: 1881) and ASO-002816 (TTCctttacaccACAC, SEQ ID NO: 1882) were included as controls.

After incubation, cells were harvested by removal of media followed by addition of 125µL PureLink©Pro 96 Lysis buffer (Invitrogen 12173.001A) and 125µL 70% ethanol. RNA was purified according to the manufacture's instruction and eluted in a final volume of 50µL water resulting in an RNA concentration of 10-20ng/µl. RNA was diluted 10 fold in water prior to the one-step qPCR reaction. For one-step qPCR reaction qPCR-mix (qScript TMXLE 1-step RT-qPCR TOUGHMIX®Low ROX from QauntaBio, cat.no 95134-500) was mixed with two Taqman probes in a ratio 10:1:1 (qPCR mix: probe1:probe2) to generate the mastermix. Taqman probes were acquired from LifeTechnologies: SNCA: Hs01103383_m1; PROS1: Hs00165590_m1: TBP:

4325803; GAPDH 4325792. Mastermix (6µL) and RNA (4µL, 1-2 ng/µL) were then mixed in a qPCR plate (MICROAMP®optical 384 well, 4309849). After sealing, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a ViiaTM 7 system (Applied Biosystems, Thermo), and the following PCR conditions 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 results are shown in Table 1 under Example 2A.

Example 3: *In vitro* Analysis of ASO-003092 and ASO-003179 on the Reduction of Human *SNCA* mRNA

ASO-:1436003092 (20-base SEQ ID NO) and ASO-003179 (19-base SEQ ID NO:1547) are LNA-modified ASOs that target the exon6 region of human SNCA pre-mRNA (SEQ ID NO:1).

Potency of ASO-003092 and ASO-003179 in Mouse Neurons

Using the methods described above in Example 2A, ASO-003092 and ASO-003179 were tested for their ability to reduce SNCA protein expression as a downstream result of reduction in *SNCA* mRNA. Briefly, primary neurons derived from PAC-A53T mice were treated with ASO-003092, ASO-003179, or control ASOs for 14 days. Cells were then fixed and the levels of SNCA protein and tubulin protein were measured by high content imaging. Tubulin levels were measured to monitor toxicity and to normalize SNCA protein reduction.

As shown in Table 4 below and Table 1 in Example 2A, incubation of cells with 40 nM of ASO-003092 or ASO-003179 resulted in 76% and 73% reduction in SNCA protein expression, respectively. In contrast, both ASOs had minimal to no effect on the level of tubulin protein expression.

Table 4: ASO-003092 and ASO-003179 activity in A53T-PAC neurons

ASO	ASO concentration	aSyn/tub %inh	SD	N	Tub %inh	SD	N
ASO-003092	40 nM	75.64	13.81	3	-11.29	18.70	4
ASO-003179	40 nM	73.05	9.54	4	-9.51	19.17	4

SD = standard deviation

N = number of tests

The above results demonstrate that ASO-003092 and ASO-003179 effectively reduce *SNCA* mRNA, which in turn mediates the reduction of SNCA protein levels. These ASOs were well tolerated both in mouse and in human neurons. These findings support the continued development of SNCA-specific ASOs (*e.g.*, ASO-003092 and ASO-003179) as a disease-modifying therapeutic for the treatment of synucleinopathies.

Example 4: *In Vivo* Tolerability and *In Vivo SNCA* mRNA Reduction

The *in vivo* tolerability of selected ASOs was tested to see how the ASOs were tolerated when injected into different animal models (*i.e.,* mice and cynomolgous monkeys):

Mice

Subjects: Male and female (2-3 months old) PAC-Tg($SNCA^{A53T}$)$^{+/+}$;$SNCA^{-/-}$ ("PAC-A53T") mice carrying the entire human *SNCA* gene with a A53T mutation on a mouse *SNCA* knockout background were used for acute, long term, and PK/PD *in vivo* efficacy studies. In some cases wild-type (WT) C57B/6 mice were used for long term (*i.e.,* 4 weeks) health assessment. Mice were housed in groups of 4 or 5 in a temperature controlled housing room with food and water available *ad libitum*. All procedures involving mice were conducted according to Animal Test Methods (ATM) approved by the Bristol-Myers Squibb Animal Care and Use Committee (ACUC).

ASO Dosing Solution Preparation: Sterile saline (1 mL) syringes fitted with 0.2 µm Whatman filters and nuclease free centrifuge tubes were used to prepare dosing solutions. Indicated volume of water or saline was added to an ASO powder and was vortexed (~1 min) to dissolve the ASO powder. The solution was then allowed to sit for 10 min and was vortexed again for ~1 min. The tubes were briefly centrifuged to return all of the liquid to the bottom of the tube, and then, the solution was filtered through a 0.2 µm sterile filter into a 2nd RNase free tube. A small aliquot of the primary stock was diluted to 1 mg/ml for analysis of the concentration using Nanodrop. The analytical sample was vortexed three times with manual inversion to mix thoroughly. Then, the UV absorbance of the sample was measured twice at 260 nm with Nanodrop (the pedestal was rinsed and wiped three times before applying the sample). The test sample was discarded once the analysis was complete. The sample was considered ready for dosing if UV absorbance was between 90 and 110% of the sample. If UV absorbance exceeded 110% of the sample, a secondary dilution was prepared; if the absorbance was < 90%, the sample was prepared at a higher initial concentration and similar steps were followed as described above. Samples were stored at 4°C until use.

Freehand Intracerebroventricular (ICV) Injection: 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 2.5-3 mm from the tip in order to limit its penetration into the brain. Mice were anesthetized using isoflurane anesthetic (1-4%). Once sufficiently anesthetized, the mice were 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. Dosing was conducted using 10 µl

Hamilton syringes fitted with a 27 ½ g needle. The needle tip was then inserted through the scalp and the skull, about 1 mm lateral and 1 mm caudal to bregma (*i.e.,* right of the midline, about 3mm back as measured from the eye line). Once the needle was positioned, the ASO was given in a volume of 5 µl in saline vehicle and injected over ~30 seconds. The needle was left in place for 5-10 seconds before removal. The mice were returned to their home cage and allowed to recover for ~2-4 min. Mice were observed continuously for 30 minutes immediately after dosing for adverse behavioral effects of drug and/or dosing. During this time, any mouse that convulsed more than 3 separate times was immediately euthanized and given an automatic score of 20. Drug tolerability was scored 1 hr ± 15min post dosing. Animals dosed with non-tolerated compounds (tolerability score > 4) were euthanized immediately following the 1 hr evaluation.

ASO Tolerability Assessment: Animals dosed with the ASOs were evaluated right after the dosing and monitored for 2 hours for any adverse effects. For acute tolerability (AT) studies, mice were evaluated at the time of dosing and again at the takedown, *i.e.,* 3 days post ASO injection. For long term health assessment, the mice were weighed weekly and monitored for any health and behavioral issues until the completion of the experiment. Mice that had weight losses of greater than 15% of their initial body weight or exhibited tolerability issues were removed from the studies and euthanized. Health and tolerability assessments were conducted according to the following chart:

Table 5: Tolerability scoring system[a]

Category	Score 1	Score 2	Score 3	Score 4
Hyperactivity, stereotypies, home cage behavior	•Very slightly increased home cage exploration or rearing compared to controls	•Increased home cage exploration (*e.g.* digging, burying, etc.) •Increased grooming	•Moderately increased home cage activity •Detectable stereotypies (*e.g.* circling, repetitive behaviors, etc.)	•Marked hyperactivity •Marked stereotypies
Decreased vigilance, exploration and responsiveness	•Some reduction in exploratory activity •Responds normally to stimulation	•Drowsiness •Slightly reduced response to touch or handling	•Stupor (reduced responsiveness, decreased corneal reflex)	•Coma (does not respond to stimulation, *e.g.* pinch), no corneal reflex
Motor coordination and strength	•Mild change to gait or grip strength (falls between 5-10sec) •No falls, normal righting response	•Reduced grip strength (falls in less than 5sec) •Mild ataxia (*e.g.* slow righting response, swaying)	•Highly reduced grip strength (falls in less than 2sec) •Ataxia (*e.g.* staggering, falling impaired walking)	•Severe ataxia (*e.g.* crawling, fails to grip bar) •No ability to right

Category	Score 1	Score 2	Score 3	Score 4
Posture, appearance, breathing	•Very slight abnormal posture (subtle)	•Slight abnormal posture (*e.g.* hunched, extended, low posture, tail position, straub tail) •Piloerection or ptosis •unkempt coat	•Moderately abnormal posture (*e.g.* ventral recumbency) •Shallow breathing	•Markedly abnormal posture (*e.g.* lateral recumbency) •Facial paralysis (*e.g.* drooling, protruding tongue) •Labored breathing
Tremor, hyper-activity, convulsion	•Detectable tremor	•Hyper-responsive to stimuli (*e.g.* noise) •Marked tremors	•Few or partial seizures, rearing and falling as part of convulsing	•Repeated or continuous seizure (running, bouncing, clonic and/or tonic)

[a] Normal is scored as "0". Animals are scored on an individual basis at successive time points post dosing. Observations are rated at 1 h ± 15 min, then 24 h ± 2 h, then 7 days (if appropriate). Convulsions count for the 1 hr timepoint, even if they occur prior to the observation window. A total tolerability score is calculated based on the sum of the individual category scores, with a maximum possible score of 20.

Tissue Collection: Following final behavioral and health assessments, mice were decapitated on a guillotine and the brains were quickly removed. Each brain was split into two hemispheres and a) hippocampus was dissected for mRNA measurements in the 3-day acute tolerability studies; b) hippocampus, brain stem, and striatum from one hemisphere were dissected for mRNA measurements, whereas the same regions were dissected from the second hemisphere for protein/PK measurements in the dose-response time course PK/PD studies.

In some of the studies, the blood and the cerebrospinal fluid (CSF) were also collected for PK (blood) and PK/protein (CSF) measurements. To collect the blood and the CSF, the mice were deeply anesthetized with Isoflurane (4%). Blood was collected via cardiac puncture using 23G needle. Once removed, the blood was transferred into 2 ml BD Microtainer (K2EDTA BD #365974) tubes and placed on ice until processing. To process the blood, the tubes were centrifuged at 4500xg for 10 min at 4ºC. Then, the plasma was removed and placed into 0.5 ml Eppendorf tubes and stored at -80ºC until use. To collect the CSF, the thoracic cavity was opened exposing the heart, and as much of the blood was drained to avoid contamination of the CSF. The CSF samples were collected via Cisterna magna using micropipettes and placed into lo-bind protein Eppendorf tubes. Then, the tubes were centrifuged at 4500xg for 15min at 4ºC. The CSF was carefully transferred to clean lo-bind 0.5ml Eppendorf tubes and stored at -80ºC until further use.

Cyno Data

Subject: Male cynomolgous monkeys weighing 3.5-10.0 kg at the start of the study were used. Each was implanted with an intrathecal cerebrospinal fluid (CSF) catheter entering at the L3 or L4 vertebrae. The distal tip of the polyurethane catheter extended within the intrathecal space to approximately the L1 vertebrae. The proximal end was connected to a subcutaneous access port located on the animal's lower back. Animals were allowed to heal for at least two weeks prior to the start of the study. Laboratory animal care was according to Public Health Service Policy on the Humane Care and Use of Laboratory Animals and the Guide for the Care and use of Laboratory Animals NRC (2011) (National Research Council: Guide for the Care and Use of Laboratory Animals (The National Academies Collection: Reports funded by National Institutes of Health). National Academies Press (US), Washington (DC)). The protocol was approved by the Wallingford Animal Care and Use Committee of the Bristol-Myers Squibb Company.

CSF & Blood Sampling: The CSF port was accessed subcutaneously using aseptic techniques, and CSF was sampled from awake animals sitting upright in a primate restraint chair. Approximately 0.1 ml of CSF was discarded at the start of collection to clear dead space in the catheter and port. CSF was collected by gravity flow to a maximum of 0.5 ml CSF per sample. CSF was spun at 2,000 g at 4° C for 10 min. The supernatant was frozen on dry ice or in liquid nitrogen and kept at -90° C until analyzed.

Blood was sampled from an available vein, typically the saphenous vein. Blood samples were prepared in a number of procedures depending upon the particular measure in question. For plasma, blood was collected into EDTA-treated tubes. For serum, blood was collected into serum-separator tubes and allowed to clot for at least 30 min prior to centrifugation. For measures of clotting and clotting factors, blood was collected into citrated tubes, and for analysis of RNA, blood was collected into tubes containing RNA later. After processing, samples were frozen on dry ice or in liquid nitrogen and kept frozen until analyzed.

Intrathecal Dosing: Animals were trained to be dosed while awake and using modified commercially-available restraint chairs, animals were maintained in a prone position. *SNCA*-targeted anti-sense oligonucleotides (ASOs) were dissolved in saline, sterilized by filtration, and administered at 0.33 ml/min in a 1.0 ml volume followed by a 0.5 ml sterile water flush. Total infusion time was 4.5 min. Animals remained in the prone position for 30 min post infusion.

Necropsy: Cynomolgus monkeys were administered the appropriate volume of a commercially available euthanasia solution while anesthetized with ketamine and/or isoflurane. Necropsy tissues were obtained immediately thereafter and the brain was transferred to wet ice for dissection. Areas of interest were dissected using 4-6 mm slices in an ASI Cyno Brain Matrix as well as free handed techniques. Samples were placed fresh in RNAlater, or frozen on dry ice for later analysis. CNS

tissue was rapidly dissected form cynomolgus monkeys and pieces no longer than 4 mm on any axis were collected and placed in 5mLs of RNA later. Samples were stored at 4ºC overnight then transferred to -20ºC for storage until analyzed.

Brain regions analyzed included medulla, pons, midbrain, cerebellum, caudate-putamen (left and right), hippocampus (left and right), frontal cortex (left and right), temporal cortex (left and right), parietal cortex (left and right), occipital cortex (left and right) and cortical white matter. Additionally, spinal cord was sampled at the cervical, thoracic and lumbar regions. Samples were also collected from liver, kidney and heart. On some occasions, samples of trigeminal nuclei, tibial nerve and the aorta were collected to examine off-target pharmacology in those areas.

ELISA quantitation of ASO concentration in mouse or monkey tissue, plasma, and CSF:

Tissue was homogenized with plasma and water in a 1:1 ratio. Standard curve was generated by 2-fold serial dilution from 5000 to 4.9 nM in plasma (for plasma and CSF) and in plasma:water (for tissues samples) and then further diluted to 5000-fold total with 5xSSCT (750 mM NaCl, and 75 mM sodium citrate, pH 7.0, containing 0.05 % (v/v) Tween-20) alone and in 5x SSCT containing 35 nM capture and 35 nM detection reagents to obtain a standard range of 1–1000 pM. The dilution factor used varied depending on the expected sample concentration range. The capture probe was AAAGGAA with a 3' Biotin (Exiqon) and the detection probe was 5' DigN-isopropyl 18 linker--GTGTGGT (Exiqon).

Experimental samples and standards were added to Clarity lysis buffer (Phenomenex, cat#AL0-8579) in a 1:1 ratio prior to dilution with capture and detection buffer and before transferring to the ELISA plate. CSF samples were diluted with plasma (2-fold) prior to addition of lysis buffer. A streptavidin-coated plate (Thermo 15119) was washed 3 times with 5X SSCT buffer. 100 µl samples were added and incubated for 60 min at room temperature. The detection probe, 100 µl anti-Dig-AP Fab fragment diluted 1:4000 in PBS containing 0.05% Tween-20 (Roche Applied Science, Cat. No. 11 093 274 910), was added and incubated for 60 min at room temperature. After washing the plate with 2X SSCT buffer, 100 µl Tropix CDP-star Sapphire II substrate (Applied Biosystems) was added for 30 min at room temperature. Antisense oligonucleotide concentrations were measured by luminescence (Enspire-PerkinElmer).

Alpha-synuclein protein measurements:

Brain tissue samples were homogenized at 10 ml/g tissue in RIPA buffer (50 mM Tris HCl, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate) using bead homogenizer Qiagen Tissuelyser II for 25 cycles/sec, with a 5 mm stainless steel bead for 2 min total. Homogenized samples were incubated 30 min on ice. 50 µl aliquot of each sample was

retained for PK analysis. The remaining samples were centrifuged 20,800g, for 60 min, 4°C. The supernatant was retained and used for analysis. Total protein was measured using Pierce BCA protein assay kit (23227).

Brain tissue extracts: SNCA protein was measured using the MJFR1+4B12 ELISA. Briefly, ELISA plates (Costar) were coated with 100 µl of the anti-SNCA antibody MJFR1 (Abcam) at a concentration of 0.1 µg/ml diluted in BupH carbonate-bicarbonate buffer, pH 9.4 (Thermo Scientific) overnight (O/N) at 4°C. The next day plates were washed 4-times with Dulbecco's PBS (Life Technologies) and blocked with 3% BSA (bovine serum albumin, protease free, Fraction V, Roche Diagnostic) in PBS for 2~3h at room temperature (RT) or overnight at 4°C. Both the standards and the brain samples were diluted with 1% BSA/0.05% Tween/PBS containing Roche protease inhibitor (Roche 11836145001, 1 pellet/25 ml) and Phosphatase Inhibitor 2&3 (Sigma, 1:100). SNCA wild-type (rPeptide) was used as a standard. Samples were loaded in duplicate (50 µl/well) and incubated for O/N at 4°C. After plates were equilibrated to RT, 50 µl of the detection antibody 4B12 (Biolegend) (diluted 1:4000 in 1% BSA/0.1% Tween/DPBS) was added to each well and co-incubated with the samples at RT for ~2 hours. Detection antibody was pre-conjugated with alkaline phosphatase (AP kit from Novus Biologicals). Plates were then washed 4-times with 0.05% Tween/PBS and developed with 100 µl of alkaline phosphatase substrate (Tropix CDP Star Ready-to-Use with Sapphire II, T-2214, Life Technologies) for 30 minutes. Luminescence counts were measured with Perkin Elmer EnVision (2102 Multilabel Reader). The plates were kept constant shaking (Titer plate shaker, speed 3) during the assay. Data was analyzed using GraphPad Prism. Total protein in brain tissue was measured using a Micro protein assay kit (Thermofisher #23235) according to manufacturer's instructions.

Cerebral spinal fluid (CSF): SNCA protein was measured using the U-PLEX Human SNCA Kit: (cat# K151WKK-2, Meso Scale Discovery) according to manufacturer's instructions. CSF samples were diluted 10-fold. Hemoglobin was measured in CSF samples using the Abcam mouse Hemoglobin ELISA kit (ab157715). CSF samples were diluted 40-fold for the hemoglobin measurements.

mRNA measurements by qRT-PCR

Brain regions were harvested and placed in 1.5 ml RNA-later Tissue Protect tubes (Qiagen cat#76514) that were prefilled with RNA-later, a RNA stabilization solution. Tissue in RNA-later solution can be stored at 4ºC for 1 month, or at -20ºC or -80ºC indefinitely.

RNA Isolation*: RNeasy Plus Mini Kit*: RNA from mouse hippocampus and cortex and was isolated using the RNeasy Plus Mini Kit (Qiagen cat#74134). Tissue samples were homogenized in a

volume of 600 µL or 1200 µL RLT Plus buffer containing 10 µl/ml of 2-mercaptoethanol and 0.5% Reagent Dx. 600 µL lysis buffer was used if the tissue sample was <20 mg, 1200 µl lysis buffer was used for tissue samples >20 mg. For homogenization, tissue sample was transferred to a 2.0 mL round-bottom Eppendorf Safe-Lock tube (Eppendorf cat#022600044) containing 600 µL RLT Plus Buffer (plus 10ul/ml of 2-mercaptoethanol and 0.5% Reagent Dx), and a 5 mm stainless steel Bead (Qiagen cat#69989) Samples were homogenized, using a Qiagen's TissueLyser II instrument. Samples were processed for 2.0 min at 20 Hz, samples rotated 180° and processed for another 2.0 min at 20Hz. Samples were then processed 2.0 min at 30 Hz, samples rotated 180° and processed for another 2.0 min at 30Hz. Longer and/or at higher frequency homogenization used if processing not complete. A 600 µL of the tissue lysate was then transferred into a gDNA Eliminator spin column in a 2.0 mL collection tube and samples centrifuged for 30 secs at 10,000g. All centrifugation steps were performed at RT. The flow-through was collected and an equal volume of 70% ethanol added and mixed. 600 µL was transferred to RNeasy spin column placed in a 2.0 mL collection tube and samples centrifuged for 15 secs at 10,000g. The flow-through was discarded and the remaining 600 ul sample added to the spin column. The spin columns were centrifuged and the flow-through discarded. Columns were washed with 700 µl of Wash Buffer RW1, centrifuged for 15 secs at 10,000g, and the flow-through discarded The columns were then washed 2-times with 500 µL of Buffer RPE containing 4 volumes of ethanol as described in kit protocol. Columns were first centrifuged for 15 secs at 10,000g for first wash and then for 2.0 min at 10,000g for the second wash.. After second wash, columns were centrifuged once for 1.0 min at 10,000g to dry the membranes. Columns were then transferred to a new 1.5 mL collection tube and 30 µl of RNase-free water was added directly to the center of the membrane. The membranes were allowed to incubate for 10 min at RT. Then, the columns were centrifuged for 1.0 min at 10,000g to elute the RNA. The elution, containing the RNA, was collected and stored on ice until the RNA concentrations could be determined by UV absorbance using a NanoDrop Spectrophotometer (Thermo). RNA samples were stored at -80°C.

RNA Isolation: RNEASY® Plus Universal Mini Kit: RNA from all other Cyno, Mouse, and Rat tissue samples was isolated using RNEASY® Plus Universal Mini Kit (Qiagen cat#73404). For homogenization, 50 µg or less of tissue sample was transferred to a 2.0 mL round-bottom Eppendorf Safe-Lock tube (Eppendorf cat#022600044) containing 900 µL QIAZOL® Lysis Reagent, and a 5 mm stainless steel Bead (Qiagen cat#69989) Samples were homogenized, using a Qiagen's TissueLyser II instrument. Samples were processed for 2.0 min at 20 Hz, samples rotated 180° and processed for another 2.0 min at 20 Hz. Samples were then processed 2.0 min at 30 Hz, samples rotated 180° and processed for another 2.0 min at 30 Hz. Longer and/or at higher frequency homogenization used if processing not complete. Homogenized tissue lysate was then

transferred into a new 2.0 mL round-bottom Eppendorf Safe-Lock tube and left at RT for 5.0 min. 100 µL of gDNA Eliminator Solution was added to each tube and tubes were vigorously shaken for 30 secs. 180 µL of Chloroform (Sigma cat#496189) was added to each tube and tubes were vigorously shaken for 30 secs. Tubes were left at RT for 3 min. Centrifuge tubes at 12,000g for 15 min at 4ºC. After centrifugation the upper aqueous phase was transferred to a new 2.0 mL round-bottom Eppendorf Safe-Lock tube ~500 µL. An equal volume of 70% ethanol added and mixed. All future centrifugation steps were performed at RT. 500 µL was transferred to RNeasy spin column placed in a 2.0 mL collection tube and samples centrifuged for 15 secs at 10,000g. The flow-through was discarded and the remaining 500 µl sample added to the spin column. The spin columns were centrifuged and the flow-through discarded and the columns washed with 700 µl of Wash Buffer RWT containing 2 volumes of ethanol. Columns were centrifuged for 15 secs at 10,000g, the flow-through discarded. The columns were then washed twice with 500 µL of Buffer RPE containing 4-volumes of ethanol as described in kit protocol. Columns were first centrifuged for 15 secs at 10,000g for first wash and then for 2.0 min at 10,000g for the second wash.. After second wash, columns were centrifuged once for 1.0 min at 10,000g to dry the membranes. Columns were then transferred to a new 1.5 mL collection tube and 30 µl of RNase-free water added directly to the center of the membrane. Membranes were allowed to incubate for 10 min at RT. Columns were centrifuged for 1.0 min at 10,000g to elute the RNA. The elutions, containing the RNA, were collected and stored on ice until RNA concentration determined by UV absorbance using a NanoDrop Spectrophotometer (Thermo). RNA samples were stored at -80°C.

cDNA Synthesis by Reverse Transcription*:* 300 ng of RNA was diluted to a final volume of 10.8 µL using nuclease-free water (Invitrogen cat#10977-015) in a PCR-96-AB-C microplate (Axygen cat#321-65-051). Added 6.0 µL to each well of reaction mix 1 containing the following: 2.0 µL of 50 µM random decamers (Ambion cat#AM5722G) and 4.0 µL of a 1X dNTP mix (Invitrogen cat#10297-018). The plate was sealed with optical sealing tape (Applied Biosystems cat# 4360954) and centrifuged for 1.0 min at 1,000 x g at RT. Next, the plate was heated for 3.0 min at 70ºC using a 96-well Thermal Cycler GeneAmp PCR System 9700 (Applied Biosystems). The plate was then cooled completely on ice. Next, 3.25 µL of the reaction mix 2 (containing 2 µL of 10X strand buffer, 1.0 µL of MMLV-RT 200U/µL reverse transcriptase enzyme (Ambion cat#2044), and 0.25 µL of RNase inhibitor 40U/µL (Ambion cat#AM2682)) were added to each of the wells. Plate was sealed with optical sealing tape and centrifuged for 1.0 min at 1,000 x g at RT. Using a 96-well Thermal Cycler, the plate was heated at 42ºC for 60 min proceeded by 95ºC for 10min. Then, the plates were cooled on ice. The cDNA plates were stored at -20ºC until ready to use for PCR analysis.

qPCR for amplification and quantification of alpha synuclein and GAPDH mRNA expression: cDNA was diluted 5-fold in nuclease free water in a PCR-96-AB-C microplate. 16 µL of Master Mix solution consisting of the following: 10 µL of 2X Taqman Gene Expression Master Mix (Applied Biosystems cat#4369016), 1.0 µL of 20X Taqman primer-probe set (Applied Biosystems), and 5.0 µL of nuclease-free water, was added to each well of a 384-well optical PCR plate (Applied Biosystems cat#4483315). 4.0 µL of diluted cDNA was added to each well of the 384-well optical PCR plate. Plate was sealed with optical sealing tape and centrifuged for 1.0 min at 1,000 x g at RT. PCR was performed on the Applied Biosystems 700 HT Fast Real-Time PCR System using the following parameters in standard mode: 50ºC for 2.0 min, 95ºC for 10 min, followed by 40 cycles of 95ºC for 15 secs and 60ºC for 1.0 min.

qRT-PCR primer-probe sets: Primer-probes sets from Applied Biosystems (Thermo Fisher) included the following:
Human alpha synuclein (cat#Hs01103383_m1) FAM labelled
Human PROS1 (cat#HS00165590_m1) FAM labelled
Cyno alpha synuclein (cat#Mf02793033_m1) FAM labelled
Cyno GAPDH (cat#Mf04392546_g1) FAM labelled
Cyno GAPDH (cat#Mf04392546_g1) VIC labelled Primer Limited
Rat alpha synuclein (cat#Rn01425141_m1) FAM labelled
Rat GAPDH (cat#Rn01775763-g1) FAM labelled
Rat GAPDH (cat#4352338E) VIC labelled Primer Limited
Mouse GAPDH (cat#Mm99999915-g1) FAM labelled
Mouse GAPDH (cat#4352339E) VIC labelled Primer Limited.

The results are shown in Table 6 below.

Table 6 shows the tolerability score ("Tox Score") and the percent reduction (or knockdown, "KD") of both the *SNCA* mRNA and SNCA protein expression in ASO-treated A53T-PAC transgenic or WT (wild-type) mice. The tolerability scores are provided for days 1 (1D) and 28 (28D) post ASO administration. The percent reduction in *SNCA* mRNA and SNCA protein expression is shown for days 3 (3D) and 28 (28D) post ASO administration in the hippocampus (Hippo), brain stem (BS), and striatum (Str).

ASO_NO	Tox Score @1D	3D mRNA %KD	Tox Score @28D	Tox Score WT @28D	28D mRNA %KD Hippo	28D mRNA %KD BS	28D mRNA %KD Str	28D protein %KD Hippo	28D protein %KD BS	28D protein %KD Str
001221	1.17									
001233	4.67									
001268	3.33	40.44	1.11		46.53			6	18	28

ASO_NO	Tox Score @1D	3D mRNA %KD	Tox Score @28D	Tox Score WT @28D	28D mRNA %KD Hippo	28D mRNA %KD BS	28D mRNA %KD Str	28D protein %KD Hippo	28D protein %KD BS	28D protein %KD Str
001281	2									
001282	0.17									
001308	1									
001310	8.67									
001318	2.4									
001328	1.33		3.7		76.07					
001334	6.67									
001344	5.17									
001357	1.83									
001363	1.67									
001365	3									
001367	0.5									
001384	0									
001395	0.33									
001467	7									
001468	2		1		44.52					
001471	0									
001481	0									
001484	0									
001486	9									
001532	2.4									
001537	2.5									
001549	4									
001554	0.67									
001560	0									
001561	3.67									
001582	3.33									
001585	1.83									
001605	2.67		0.9		68.71					
001606	1.17		0.38		35.19					
001638	0.17									
001639	1.8		3.22		45.2					
001665	1.83	48.79	0.85		42.43	37.6	29.78	40	39	23
001669	6									
001671	8.5									
001673	2.33									
001677	14.67									
001694	4.33									
001702	1.2		3.11		40.84					
001730	1.33									
001755	1.83									
001757	3.17									

ASO_NO	Tox Score @1D	3D mRNA %KD	Tox Score @28D	Tox Score WT @28D	28D mRNA %KD Hippo	28D mRNA %KD BS	28D mRNA %KD Str	28D protein %KD Hippo	28D protein %KD BS	28D protein %KD Str
001774	5.83									
002041	10.33									
002686	6									
002690	4.67									
002692	10.17									
002693	4.67									
002694	2.92	68.84	20							
002705	13									
002730	7									
002738	0.5	61.37	0.14		21.86					
002739	2.45	54.89	0		56.01	39.56	31.85			
002761	0.2	56.99	0.78		43.68					
002762	0	66.77	0		56.42	44.29	36.57			
002763	0	30.72								
002765	9.33									
002779	5.33	73.12								
002785	1.06	55.86	20							
002798	5.17									
002801	15.67									
002804	0.75	49.67	20							
002805	11.67									
002817	7.83									
002820	0.17	33.91								
002825	3.67	38.94								
002828	3.83	34.63								
002832	3.33	52.91								
002833	2.95	68.25	0.67		36.09	31.75	34.77	32	33	32
002836	3.5	43.36								
002837	6.72	70.55	0		49.92	40.11	32.79			
002838	1.17	39.98								
002842	8.2	67.24	20							
002843	1.67	61.22								
002844	3.33	36.06								
002847	0.17	49.42								
002848	1.25	55.38	1.78							
002849	3.83	30.6								
002850	4.67	49.15								
002852	1	41.36								
002858	3.67	48.1								
002859	9.33	64.97								
002860	6.83	57.18								
002863	1.67	46.96								

ASO_NO	Tox Score @1D	3D mRNA %KD	Tox Score @28D	Tox Score WT @28D	28D mRNA %KD Hippo	28D mRNA %KD BS	28D mRNA %KD Str	28D protein %KD Hippo	28D protein %KD BS	28D protein %KD Str
002864	1.33	48.12								
002867	10.5									
002901	10									
002904	1.12	59.49	1.25							
002906	4.33									
002908	2.5	32.81								
002909	16.33									
002911	2.33	28.97								
002912	1	48.24								
002935	6.33									
002938	4.43	46.49								
002968	3.05	65.11	20							
002982	4.67									
002983	12									
002989	12.67									
002990	10.67									
002991	9									
002992	14									
002993	7.71									
002994	9.33									
002995	2	42.3								
003058	8.67									
003061	4.33	49.84								
003063	0.67	48.41								
003069	0.6	46.48								
003072	9.6									
003080	15.33									
003092	1.78	60.45	0.13		58.79	41.16	42.86			
003172	4.5	49.72								
003173	0.5	58.71	0.8		57.56	34.34	32.72	43	41	51
003175	0.33	60.31			61.03	40.44	43.33			
003176	0.1	64.56	0.13		45.9	23.89	35.99	42	27	27
003177	0	43.64								
003179	0	63.6	1.3		56.07	36.86	-9.84	54	35	56
003181	0.67	44.36								
003198	0.67	46.33								
003199	1.33	43.74								
003202	0	49.56								
003203	7.5									
003206	4	47								
003226	9.67									
003229	1.17	64.32			48.4	37.47	37.26			

ASO_NO	Tox Score @1D	3D mRNA %KD	Tox Score @28D	Tox Score WT @28D	28D mRNA %KD Hippo	28D mRNA %KD BS	28D mRNA %KD Str	28D protein %KD Hippo	28D protein %KD BS	28D protein %KD Str
003231	10									
003279	8.33									
003323	6.67	65.91								
003330	6.83	54.69								
003345	2.52	68.56	0		53.82	34.6	34.81			
003349	0.83	55.42								
004871	7.00	65.13			51.22	45.50	43.72			
004881	16.00									
004885	6.00	58.31			49.31	41.08	52.78			
004901	4.40	63.12			61.97	43.13	44.91			
004902	0.00	59.68			41.82	24.44	19.42			
004903	4.00	46.00								
004910	0.40	45.27								
004913	4.80	48.56								
004917	1.00	32.38								
004932	8.00	49.21								
004934	6.40	44.30								
004936	4.00	33.89								

Example 5: Analysis of *in vivo* Activity and Tolerability of *SNCA*-Targeted Antisense Oligonucleotides (ASOs) in Cynomolgous Monkeys

To evaluate the ASO activity and tolerability *in vivo*, an intrathecal ported Cynomolgus monkey model (Cyno IT) was developed. This model enables the evaluation of ASO-003092- or ASO-003179-mediated knockdown of *SNCA* and alpha-synuclein protein SNCA.

As described above in Example 3, each animal was implanted with an intrathecal cerebrospinal fluid (CSF) catheter entering at the L3 or L4 vertebrae. ASO-003179 and ASO-003092 were dissolved in saline and administered to the animals, infused over 4.5 min using the IT port (2 animals per dose group). Each of the animals received one of the following: (i) ASO-003179 (8 or 16 mg total) and (ii) ASO-003092 (4 or 8 mg total). Animals were then euthanized at various time points post dosing, when the tissues were harvested for analysis of the ASO exposure and activity. Brain regions analyzed included medulla (Med), pons (V-Pons), midbrain (V-MB), cerebellum (CBL), caudate-putamen (left and right) (CauP), hippocampus (left and right) (Hip), frontal cortex (left and right) (FrC), temporal cortex (left and right) (TeC), parietal cortex (left and right) (PaC), occipital cortex (left and right) (Occ), and cortical white matter (WM). Additionally, spinal cord was sampled at the cervical (CSC), thoracic (TSC), and lumbar (LSC) regions. Samples were also

collected from liver, kidney, heart, trigeminal nuclei, tibial nerve, and aorta to examine off-target pharmacology in those areas.

The ASOs were well tolerated in cyno with no adverse effects being observed (data not shown). And as shown in Figures. 3 and 4 and Table 7 below, the administration of ASO-003179 resulted in the reduction of *SNCA* mRNA expression in all brain tissues analyzed at 2 weeks post dosing at a dose of both 8 mg and 16 mg. (Figure 3). For ASO-003092, reduction was observed in the frontal cortex and the lumbar spinal cord but not in other tissues at 2 weeks post dosing (Figure 4).

Table 7: Effect of ASOs on brain *SNCA* mRNA levels in cyno brain

ASO No.	Dose (mg)	Time point (weeks)	Med	CBL	FrC	PaC	CauP	TeC	Occ	Hip	V-MB	V-Pons	CSC	TSC	LSC	WM
003092	4	2	87	132	61	78	111	54	90	58	82	105	70	59	29	65
	8	2	93	102	69	95	94	38	71	61	77	86	60	33	23	57
003179	4	2	132	110	66	121	126	56	95	101	143	133	100	119	34	123
	8	2	44	44	24	39	57	18	34	43	46	58	57	35	19	60
	8	2	49	72	45	71	106	46	63	79	107	73	48	42	7	80
	16	2	70	85	38	55	70	29	41	51	61	58	20	21	12	56

The results presented here demonstrate that the SNCA-specific ASOs disclosed herein (*e.g.*, ASO-003092 and ASO-003179) effectively reduce *SNCA* mRNA and are well tolerated in neurons and studies in preclinical species *in vivo*. Moreover, results from the A53T-PAC neurons confirm that ASO-003092- and ASO-003179-mediated reductions of mRNA result in reductions of SNCA protein levels *in vitro* and *in vivo*. Taken together, these findings support the continued development of SNCA-specific ASOs as a disease-modifying therapeutic for the treatment of synucleinopathies.

SEQUENCE LISTING

<110> Roche Innovation Center Copenhagen A/S

<120> ALPHA-SYNUCLEIN ANTISENSE OLIGONUCLEOTIDES AND USES THEREOF

<130> P34685-WO

<150> US 62/616,944
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Asn Val Gly Gly Ala Val Val Thr Gly Val Thr Ala Val Ala Gln Lys
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<210> 1878
<211> 18
<212> DNA
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<220>
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<210> 1879
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<220>
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<220>
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<220>
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<210> 1882
<211> 16
<212> DNA
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<220>
<223> Antisense Oligonucleotide

<400> 1882
ttcctttaca ccacac 16

CLAIMS

1. An antisense oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is at least 90% complementary to an intron region within an alpha-synuclein (*SNCA*) transcript.

2. The antisense oligonucleotide of claim 1, wherein the intron region is selected from intron 1 corresponding to nucleotides 6336 - 7604 of SEQ ID NO: 1; intron 2 corresponding to nucleotides 7751 - 15112 of SEQ ID NO: 1; intron 3 corresponding to nucleotides 15155 - 20908 of SEQ ID NO: 1 or intron 4 corresponding to nucleotides 21052 - 114019 of SEQ ID NO: 1.

3. the antisense oligonucleotide of claim 1, wherein the contiguous nucleotide sequence is at least 90% complementary to a nucleic acid sequence within an alpha-synuclein (*SNCA*) transcript, wherein the nucleic acid sequence is selected from the group consisting of
   i) nucleotides 21052 - 29654 of SEQ ID NO: 1;
   ii) nucleotides 30931 – 33938 of SEQ ID NO: 1;
   iii) nucleotides 44640 – 44861 of SEQ ID NO: 1;
   iv) nucleotides 47924 – 58752 of SEQ ID NO: 1;
   v) nucleotides 4942 – 5343 of SEQ ID NO: 1;
   vi) nucleotides 6336 – 7041 of SEQ ID NO: 1;
   vii) nucleotides 7329 – 7600 of SEQ ID NO: 1;
   viii) nucleotides 7751 – 7783 of SEQ ID NO: 1;
   ix) nucleotides 8277 – 8501 of SEQ ID NO: 1;
   x) nucleotides 9034 – 9526 of SEQ ID NO: 1;
   xi) nucleotides 9982 – 14279 of SEQ ID NO: 1;
   xii) nucleotides 15204 – 19041 of SEQ ID NO: 1;
   xiii) nucleotides 20351 – 20908 of SEQ ID NO: 1
   xiv) nucleotides 34932 – 37077 of SEQ ID NO: 1;
   xv) nucleotides 38081 – 42869 of SEQ ID NO: 1;
   xvi) nucleotides 38081 – 38303 of SEQ ID NO: 1
   xvii) nucleotides 40218 – 42869 of SEQ ID NO: 1
   xviii) nucleotides 46173 – 46920 of SEQ ID NO: 1;
   xix) nucleotides 60678 – 60905 of SEQ ID NO: 1;
   xx) nucleotides 62066 – 62397 of SEQ ID NO: 1;
   xxi) nucleotides 67759 – 71625 of SEQ ID NO: 1;
   xxii) nucleotides 72926 – 86991 of SEQ ID NO: 1;
   xxiii) nucleotides 88168 – 93783 of SEQ ID NO: 1;
   xxiv) nucleotides 94976 – 102573 of SEQ ID NO: 1;

xxv) nucleotides 104920 – 107438 of SEQ ID NO: 1;
xxvi) nucleotides 106378 – 106755 of SEQ ID NO: 1;
xxvii) nucleotides 106700 – 106755 of SEQ ID NO: 1;
xxviii) nucleotides 108948 – 114019 of SEQ ID NO: 1; and
xxix) nucleotides 114292 – 116636 of SEQ ID NO: 1.

4. The antisense oligonucleotide of any one of claims 1 to 3, wherein the nucleic acid sequence corresponds to nucleotides 24483 - 28791 of SEQ ID NO: 1; nucleotides 32226 - 32242 of SEQ ID NO: 1; nucleotides 44741 - 44758 of SEQ ID NO: 1or nucleotides 48641 - 48659 of SEQ ID NO: 1.

5. The antisense oligonucleotide of any one of claims 1 to 4, wherein the contiguous nucleotide sequence comprises a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 with no more than 2 mismatches.

6. The antisense oligonucleotide of any one of claims 1 to 5, wherein the contiguous nucleotide sequence consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353.

7. The antisense oligonucleotide of any one of claims 1 to 6, wherein the contiguous nucleotide sequence comprises a sequence selected from the group consisting of SEQ ID NO: 276; 278; 296; 295; 325; 328; 326; 329; 330; 327; 332; 333; 331; 339; 341; 390; 522 and 559.

8. The antisense oligonucleotide of any one of claims 1 to 7, which is a gapmer with at least two nucleotide analogs.

9. The antisense oligonucleotide of any one of claims 1 to 8, which comprises the formula of 5'-A-B-C-3', wherein
   a) region B is a contiguous sequence of at least 6 DNA units, which are capable of recruiting RNase;
   b) region A is a first wing sequence of 1 to 10 nucleotides, wherein the first wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 3' end of A; and
   c) region C is a second wing sequence of 1 to 10 nucleotides, wherein the second wing sequence comprises one or more nucleotide analogues and optionally one or more DNA units and wherein at least one of the nucleotide analogues is located at the 5' end of C.

10. The antisense oligonucleotide of claim 9, wherein region A comprises 1-4 nucleotide analogues, region B consist of 8 to 15 DNA units and region C comprises 2 to 4 nucleotide analogues.

11. The antisense oligonucleotide of any one of claims 8 to 27, wherein the nucleotide analogues are 2’ sugar modified nucleosides independently selected from the group consisting of Locked

Nucleic Acid (LNA); 2'-O-alkyl-RNA; 2'-amino-DNA; 2'-fluoro-DNA; arabino nucleic acid (ANA); 2'-fluoro-ANA, hexitol nucleic acid (HNA), intercalating nucleic acid (INA), 2'-O-methyl nucleic acid (2'-OMe), 2'-O-methoxyethyl nucleic acid (2'-MOE), and any combination thereof.

12. The antisense oligonucleotide of claim 11, wherein the LNA is independently selected from the group consisting of cEt, 2',4'-constrained 2′-O-methoxyethyl (cMOE), oxy-LNA, alpha-L-oxy-LNA, beta-D-oxy LNA, 2'-O,4'-C-ethylene-bridged nucleic acids (ENA), amino-LNA, , or thio-LNA.

13. The antisense oligonucleotide of any one of claims 1 to 12, wherein the contiguous nucleotide sequence comprise one or more beta-D-oxy-LNA units.

14. The antisense oligonucleotide of any one of claims 1 to 13, wherein at least 50% the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

15. The antisense oligonucleotide of any one of claims 1 to 40, wherein the antisense oligonucleotide has an *in vivo* tolerability less than or equal to a total score of 4, wherein the total score is the sum of a unit score of five categories, which are 1) hyperactivity; 2) decreased activity and arousal; 3) motor dysfunction and/or ataxia; 4) abnormal posture and breathing; and 5) tremor and/or convulsions, and wherein the unit score for each category is measured on a scale of 0-4.

16. The antisense oligonucleotide of any one of claims 1 to 15, which reduces expression of *SNCA* mRNA in a cell by at least 60%, compared to a cell not exposed to the antisense oligonucleotide.

17. The antisense oligonucleotide of claim 1 to 16, wherein the nucleotide sequence comprises, consists essentially of, or consists of a sequence selected from the group consisting of wherein the contiguous nucleotide sequence consists of a sequence selected from SEQ ID NO: 7 to SEQ ID NO: 1302 or SEQ ID NO: 1309-1353 with a design selected from the group consisting of the designs in Figures 1A to 1C, wherein the upper case letter is a sugar modified nucleoside and the lower case letter is DNA.

18. The antisense oligonucleotide of any one of claims 1 to 50, wherein the contiguous nucleotide sequence comprises a sequence and a design selected from the group consisting of:
TTCtctatataacatCACT (SEQ ID NO: 276)
TTTCtctatataacaTCAC (SEQ ID NO: 278);
AACTtttacataccACAT (SEQ ID NO: 296);
AACTtttacataccaCATT (SEQ ID NO: 295);
ATTAttcatcacaatCCA (SEQ ID NO: 325);

ATTAttcatcacaATCC (SEQ ID NO:328);
CattattcatcacaaTCCA (SEQ ID NO:326);
CATtattcatcacaATCC (SEQ ID NO:329);
ACAttattcatcacaaTCC (SEQ ID NO: 330);
AcattattcatcacaaTCCA (SEQ ID NO: 327);
ACATtattcatcacAATC (SEQ ID NO: 332);
TACAttattcatcacAATC (SEQ ID NO: 333);
TAcattattcatcacaaTCC (SEQ ID NO: 331);
TTCaacatttttatttCACA (SEQ ID NO:339);
ATTCaacatttttattTCAC (SEQ ID NO: 341);
ACTAtgatacttcACTC (SEQ ID NO: 390);
ACACattaactactCATA (SEQ ID NO: 522) and
GTCAaaatattcttaCTTC (SEQ ID NO:559),
wherein the upper case letters indicate a 2' sugar modified nucleoside analogue and the lower case letters indicate DNAs.

19. The antisense oligonucleotide of any one of claims 1 to 18, wherein the contiguous nucleotide sequence has a the chemical structure selected from the group consisting of ASO-008387; ASO-008388; ASO-008501; ASO-008502; ASO-008529; ASO-008530; ASO-008531; ASO-008532; ASO-008533; ASO-008534; ASO-008535; ASO-008536; ASO-008537; ASO-008543; ASO-008545; ASO-008584; ASO-008226 and ASO-008261.

20. A conjugate comprising the antisense oligonucleotide of any one of claims 1 to 19, wherein the antisense oligonucleotide is covalently attached to at least one non-nucleotide or non-polynucleotide moiety.

21. The conjugate of claim 20, wherein the conjugate is an antibody fragment which has a specific affinity for a transferrin receptor.

22. A pharmaceutical composition comprising the antisense oligonucleotide of any one claims 1 to 19 or the conjugate of claim 20 or 21, and a pharmaceutically acceptable carrier.

23. Use of the antisense oligonucleotide of any one claims 1 to 19, or the conjugate of claim 20 or 21, or the composition of claim 22 for the manufacture of a medicament.

24. Use of the antisense oligonucleotide of any one claims 1 to 19, or the conjugate of claim 20 or 21, or the composition of claim 22 for the manufacture of a medicament for the treatment of a synucleinopathy in a subject in need thereof.

25. The antisense oligonucleotide of any one of claims 1 to 19, or the conjugate of claim 20 or 21, or the composition of claim 22 for use in medicine.

26. The antisense oligonucleotide of any one claims 1 to 19, or the conjugate of claim 20 or 21, or the composition of claim 22 for use in the treatment of a synucleinopathy.

27. The antisense oligonucleotide for use in treatment of claim 26, wherein the synucleinopathy is selected from the group consisting of Parkinson’s disease, Parkinson's Disease Dementia (PDD), multiple system atrophy, dementia with Lewy bodies, and any combinations thereof.