

**AGENTS THAT BIND NUCLEIC ACIDS ENCODING ELAVL3 CRYPTIC EXONS,  
PHARMACEUTICAL COMPOSITIONS, AND USES IN MANAGING  
NEUROLOGICAL DISEASES**

5                                   **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of U.S. Provisional Application No. 63/541,983 filed October 2, 2023. The entirety of this application is hereby incorporated by reference for all purposes.

10                   **INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED AS AN XML FILE  
VIA THE OFFICE ELECTRONIC FILING SYSTEM**

The Sequence Listing associated with this application is provided in XML format and is hereby incorporated by reference into the specification. The name of the XML file containing the Sequence Listing is 23005PCT.xml. The XML file is 12,444 bytes, was created on October 1,  
15   2024, and is being submitted electronically via the USPTO patent electronic filing system.

**BACKGROUND**

Alzheimer's disease is a progressive neurodegenerative disease, typically observed as people age, beginning with mild memory loss leading to declining memory and dementia. There  
20   is currently no known cure for Alzheimer's disease. Thus, there is a need to identify therapeutic methods for managing Alzheimer's disease, dementia, and other neurodegenerative diseases.

Tar DNA-binding protein 43 (TDP-43) (encoded by the gene TARDBP) binds nuclear RNA involved in mRNA splicing. Mutations in the TARDBP gene cause familial amyotrophic lateral sclerosis-frontotemporal dementia (ALS-FTD). Ling et al. report TDP-43 repression of  
25   nonconserved cryptic exons is compromised in amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD). Science, 2015, 349(6248): 650–655. TDP-43 is also implicated in other major forms of neurodegenerative disorders such as Alzheimer's disease (AD), chronic traumatic encephalopathy, and multiple system atrophy. Abnormal accumulation of TDP-43 into  
30   cytoplasmic or nuclear inclusions with accompanying nuclear clearance is a common pathology identified in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer' disease (AD). Sun et al. report cryptic exon incorporation occurs in Alzheimer's brain lacking

TDP-43 inclusions but exhibiting nuclear clearance of TDP-43 indicating nuclear depletion of TDP-43 as determined by cryptic exon incorporation. *Acta Neuropathol*, 2017, 133:923–931.

Ogawa et al. report ELAVL3 is highly expressed in the adult brain and ELAVL3 is essential for the maintenance of Purkinje neuron axons indicating that neuronal Elav-like proteins are crucial for the maintenance of axonal homeostasis in mature neurons. *Sci Rep*, 2018, 8, 2722.

Diaz-Garcia report nuclear depletion of RNA-binding protein ELAVL3 (HuC) in sporadic and familial amyotrophic lateral sclerosis. *Acta Neuropathol*, 2021, 142, 985–1001.

Kim et al. report ALS-implicated protein TDP-43 sustains levels of STMN2, a mediator of motor neuron growth and repair. *Nature Neuroscience*, 2019, 22, 167–179 (2019). See also WO2021195446.

References cited herein are not an admission of prior art.

### SUMMARY

This disclosure relates to agents such as antisense oligonucleotides which bind nucleic acids encoding cryptic exons suppressing or preventing cryptic splicing of ELAVL3 RNA and uses in treating or preventing TDP-43 related neurodegenerative or neurological diseases or conditions relates thereto. In certain embodiments, the antisense oligonucleotide is a nucleobase polymer capable of decreasing cellular levels of or expression of ELAVL3 cryptic exon nucleic acids and increasing or restoring functional ELAVL3 protein expression excluding cryptic exon peptide sequences.

In certain embodiments, this disclosure relates to antisense oligonucleotides that specifically bind ELAVL3 RNA or DNA sequence(s) coding for a cryptic exon, thereby suppressing or preventing inclusion of a cryptic exon in ELAVL3 RNA expression. In certain embodiments, this disclosure relates to antisense oligonucleotides in the form of nucleobase polymers that specifically bind ELAVL3 cryptic exon mRNA, pre-mRNA, or nascent RNA sequences, thereby suppressing or preventing inclusion of an abortive or altered ELAVL3 sequence. In certain embodiments, disclosed herein are antisense oligonucleotides that specifically bind an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence, wherein the antisense oligonucleotide increases normal ELAVL3 protein expression.

In certain embodiments, the sequences to modulate ELAVL3 can be potentially delivered as a siRNA or via viral mediated delivery. In certain embodiments, sequences disclosed herein are

contained in one or more recombinant vectors encoding the sequences in operable combination with a heterologous promoter.

In certain embodiments, the antisense oligonucleotide is a nucleobase polymer designed to hybridized with ELAVL3 cryptic exon RNA encoding pre-mRNA or mRNA or expressed pre-mRNA, mRNA, or nascent RNA or DNA. In certain embodiments, the nucleobase polymer specifically binds/hybridizes with the RNA or DNA of ELAVL3 cryptic exon having the following sequence

GTGCATGTGACACTGTGACTCCGGCTGTGACCTGATGGGGCCTCAGGGATGCGTCTG  
GCTCTGGCAGGATGTTTGTGTGTACCGCGATGTTGTGTGGGTGTGTCTACCTGTGCC  
10 CTGCTCTGAGGGATTGAGTGTGATATCGTGTGTTTGTGCTGCGCTGTGATGG (SEQ ID NO: 1).

In certain embodiments, the nucleobase polymer comprises the reverse complement, for example, SEQ ID NO: 1 which is AGTCACAGTGTACATGCAC (SEQ ID NO: 2) or fragment thereof. In certain embodiments, the nucleobase polymer comprises  
15 GTCACATGCACCTGTCAAAT (SEQ ID NO: 3) or fragment thereof. In certain embodiments, the nucleobase polymer comprises GTCACATGCAC (SEQ ID NO: 4) or fragment thereof. In certain embodiments, the nucleobase polymer comprises ACCACATACCCATCACAGCG (SEQ ID NO: 5) or fragment thereof. In certain embodiments, the nucleobase polymer comprises ACAGCCGGAGTCACAGTGTCA (SEQ ID NO: 6) or fragment thereof. In certain embodiments,  
20 the nucleobase polymer comprises CCATCAGGTCACAGCCGGAGTCA (SEQ ID NO: 7) or fragment thereof. In certain embodiments, the nucleobase polymer comprises CCAGACGCATCCCTGAGGCC (SEQ ID NO: 8) or fragment thereof. In certain embodiments, the nucleobase polymer comprises CGCGGTGACACACAAACATC (SEQ ID NO: 9) or fragment thereof.

25 In certain embodiments, the nucleobase polymer comprises monomers of 1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (LNA), ribose, deoxyribose, 2'-O-methyl ribose, 2'-O-methoxyethyl ribose, 2'-fluororibose, phosphodiester, phosphorothioate, methylphosphonate, phosphorodiamidate, piperazine phosphorodiamidate, P-(2-(hydroxymethyl)morpholino)-N,N-dimethylphosphoramidate, morpholin-2-ylmethanol, (2-  
30 (hydroxymethyl)morpholino) (piperazin-1-yl)phosphinate, or *N*-(2-aminoethyl) glycine (peptide nucleic acids) or combinations thereof.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof an effective amount of a nucleobase polymer, or pharmaceutical composition containing the same, that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA as reported  
5 herein. In certain embodiments, this disclosure relates to methods for treating a disease or condition associated with a TDP-pathology or a decline in TDP-43 functionality in neuronal cells in a subject.

In certain embodiments, this disclosure relates to pharmaceutical compositions comprising one or more antisense oligonucleotides or nucleobase polymers disclosed herein, e.g., comprising  
10 or consisting of a sequence as disclosed herein, e.g., SEQ ID NOs. 1-9 or fragments thereof.

#### **BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS**

Figure 1 shows a volcano plot on differentially expressed genes associated with the knockdown of TDP-43 in induced pluripotent motor neurons (iPS-MNs). ELAVL3 is significantly  
15 reduced when TDP-43 is reduced in iPS-MNs.

Figure 2 shows a Shashimi plot of ELAVL3 that indicates the inclusion of a cryptic exon when TDP-43 is knocked down in samples.

Figure 3 illustrates that STMN2 and ELAVL3 have cryptic exons in iPS-MSs which is confirmed by RT-PCR.

Figure 4 shows Sanger sequencing of gel extracted RT-PCR product confirming inclusion of cryptic exon: RNA sequence ATCAAGGTGCATGTGACACTGTGACT (SEQ ID NO: 10) (bold SEQ ID NO: 13 segment of SEQ ID NO: 1) and protein sequence IKVHVTL (SEQ ID NO: 11) (bold start of cryptic exon protein expression (SEQ ID NO: 12)).  
20

Figure 5 shows data from a custom Nanostring<sup>TM</sup> panel used to detect the inclusion of a cryptic exon - assess ELAV3 cryptic exon inclusion as percent spliced in (PSI) for control or  
25 FTLD-TDP samples.

Figure 6 shows a schematic overview of the design of antisense oligonucleotides (ASOs) for targeting ELAVL3 cryptic exon. SSOs reduce cryptic exon inclusion and normalize ELAVL3 expression. SSOs designed targeting either predicted ESE sequences or splice acceptor/donor  
30 junctions. qPCR reveals SSOs occupying predicted ESE sequences reduce inclusion of ELAVL3 cryptic exons (Left) and normalize total ELAVL3 expression (Right) in SH-SY5Y cells.

Figure 7 shows data indicating one can correct ELAVL3 cryptic exon splicing using the antisense oligonucleotides, having SEQ ID NO: 2-9, and other cryptic splicing events, including STMN2 (Stathmin 2) are also corrected.

5

## DETAILED DISCUSSION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. An “embodiment” refers to an example, and this disclosure is not necessarily intended to be limited to such example. It is also to be understood that the terminology used herein is for the purpose of  
10 describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

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 belongs. Although any methods and materials similar or equivalent to those described herein can  
15 also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the  
20 methods and/or materials in connection with which the publications are cited.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited  
25 method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, organic chemistry, biochemistry, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

30 It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. In

this specification and in the claims that follow reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

As used in this disclosure and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "including" (and any form of including, such as  
5 "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") have the meaning ascribed to them in U.S. Patent law in that they are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

"Consisting essentially of" or "consists of" or the like, when applied to methods and compositions encompassed by the present disclosure refers to compositions like those disclosed  
10 herein that exclude certain prior art elements to provide an inventive feature of a claim, but which may contain additional composition components or method steps, etc., that do not materially affect the basic and novel characteristic(s) of the compositions or methods.

The term "comprising" in reference to a nucleic acid having a nucleotide sequence refers to a nucleotide that may contain additional 5'-end or 3'-end nucleotides, i.e., the term is intended to  
15 include the nucleic acid sequence within a larger sequence. The term "consisting of" in reference to a nucleic acid having a nucleotide sequence refers to a nucleic acid having the exact number of nucleotides in the sequence and not more or having not more than a range of nucleotides expressly specified in the claim. In certain embodiments, the disclosure contemplates that the "5'-end" of a nucleic acid may consist of a nucleotide sequence," which refers to the 5'-end of the nucleic acid  
20 having the exact number of nucleotides in the sequence and not more or having not more than a range of nucleotides specified in the claim; however, the 3'-end may be connected to additional nucleotides, e.g., as part of a larger nucleic acid. In certain embodiments, the disclosure contemplates that the "3'-end" of a nucleic acid may consist of a nucleotide sequence," which refers to the 3'-end of the nucleic acid having the exact number of nucleotides in the sequence and  
25 not more or having not more than a range of nucleotides specified in the claim; however, the 5'-end may be connected to additional nucleotides, e.g., as part of a larger nucleic acid.

A "subject" refers to any animal, preferably a human patient, livestock, rodent, monkey, or domestic pet.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject  
30 (e.g., patient) is cured and the disease is eradicated. Rather, embodiments of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "in combination with," when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to a subject or human patient prior to, concurrent with, or subsequent to each other such that they are contained/circulating in the patient at the same time, e.g., considering half-lives of the agents.

"Neurodegenerative disorder" refers to a disease condition involving neural loss mediated or characterized at least partially by deterioration of a neural cell, neural stem cell and/or neural progenitor cell. Non-limiting examples of neurodegenerative disorders include polyglutamine expansion disorders (e.g., HD, Kennedy's disease (also referred to as spinobulbar muscular atrophy), and spinocerebellar ataxia (e.g., type 1, type 2, type 3 (also referred to as Machado-Joseph disease), type 6, type 7, and type 17)), other trinucleotide repeat expansion disorders (e.g., fragile X syndrome, fragile XE mental retardation, Friedreich's ataxia, myotonic dystrophy, spinocerebellar ataxia type 8, and spinocerebellar ataxia type 12), Alexander disease, Alper's disease, Alzheimer disease, amyotrophic lateral sclerosis (ALS), ataxia telangiectasia, Batten disease, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt- Jakob disease, Guillain-Barre syndrome, ischemia stroke, Krabbe disease, kuru, Lewy body dementia, multiple sclerosis, multiple system atrophy, Chorea, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, progressive supranuclear palsy, spinal cord injury, spinal muscular atrophy (SMA), and frontotemporal dementia (FTD) and other neurological disorder which cause memory or cognitive dysfunction such as memory loss, speech impediments, autism, etc. In some contexts, neurodegenerative disorders encompass neurological injuries or damages to the CNS or PNS associated with physical injury (e.g., head trauma, concussions, mild to severe traumatic brain injury (TBI), diffuse axonal injury, cerebral contusion, acute brain swelling, and the like).

The term "specific binding agent" refers to a molecule, such as a protein, antibody, or nucleic acid, that binds a target molecule with a greater affinity than other random molecules, proteins, or nucleic acids. Examples of specific binding agents include antibodies that bind an epitope of an antigen or a receptor which binds a ligand. "Specifically binds" refers to the ability of a specific binding agent (such as an ligand, receptor, enzyme, nucleic acid, antibody or binding region/fragment thereof) to recognize and bind a target molecule such that its affinity (as determined by, e.g., affinity ELISA or other assays) is at least 10 times as great, but optionally 50

times as great, 100, 250 or 500 times as great, or even at least 1000 times as great or more as the affinity of the same for any other random molecule, nucleic acid, or polypeptide.

As used herein, the term "conjugated" refers to linking molecular entities through covalent bonds, or by other specific binding interactions, such as due to hydrogen bonding and other van der Waals forces. The force to break a covalent bond is high, e.g., about 1500 pN for a carbon-to-carbon bond. The force to break a combination of strong protein interactions is typically a magnitude less, e.g., biotin to streptavidin is about 150 pN. Thus, a skilled artisan would understand that conjugation must be strong enough to bind molecular entities in order to implement the intended results.

A "linking group" refers to any variety of covalent molecular arrangements that can be used to bridge to molecular moieties together. An example formula may be  $-R_n-$  wherein R is selected individually and independently at each occurrence as:  $-CR_nR_n-$ ,  $-CHR_n-$ ,  $-CH-$ ,  $-C-$ ,  $-CH_2-$ ,  $-C(OH)R_n$ ,  $-C(OH)(OH)-$ ,  $-C(OH)H$ ,  $-C(Hal)R_n-$ ,  $-C(Hal)(Hal)-$ ,  $-C(Hal)H-$ ,  $-C(N_3)R_n-$ ,  $-C(CN)R_n-$ ,  $-C(CN)(CN)-$ ,  $-C(CN)H-$ ,  $-C(N_3)(N_3)-$ ,  $-C(N_3)H-$ ,  $-O-$ ,  $-S-$ ,  $-N-$ ,  $-NH-$ ,  $-NR_n-$ ,  $-(C=O)-$ ,  $-(C=NH)-$ ,  $-(C=S)-$ ,  $-(C=CH_2)-$ , which may contain single, double, or triple bonds individually and independently between the R groups. If an R is branched with an  $R_n$  it may be terminated with a group such as  $-CH_3$ ,  $-H$ ,  $-CH=CH_2$ ,  $-CCH$ ,  $-OH$ ,  $-SH$ ,  $-NH_2$ ,  $-N_3$ ,  $-CN$ , or  $-Hal$ , or two branched Rs may form an aromatic or non-aromatic cyclic structure. It is contemplated that in certain instances, the total Rs or "n" may be less than 100 or 50 or 25 or 10. Examples of linking groups include bridging alkyl groups and alkoxyalkyl groups.

A "label" refers to a detectable compound or composition that is conjugated directly or indirectly to another molecule, such as an antibody or a protein, to facilitate detection of that molecule. Specific, non-limiting examples of labels include fluorescent tags, enzymatic linkages, and radioactive isotopes. In one example, a peptide "label" refers to incorporation of a heterologous polypeptide in the peptide, wherein the heterologous sequence can be identified by a specific binding agent, antibody. Specific binding agents and metals can be conjugated to solid surfaces to facilitate purification methods. A label includes the incorporation of a radiolabeled amino acid or the covalent attachment of biotinyl moieties that can be detected by marked avidin (for example, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the

following: radioisotopes or radionucleotides (such as  $^{35}\text{S}$  or  $^{131}\text{I}$ ), fluorescent labels (such as fluorescein isothiocyanate (FITC), rhodamine, lanthanide phosphors), enzymatic labels (such as horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase), chemiluminescent markers, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter  
5 (such as a leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), or magnetic agents, such as gadolinium chelates. In some embodiments, labels may be attached by spacer arms of various lengths to reduce potential steric hindrance.

A “fluorescent tag” or “fluorescent dye” refers to a compound that can re-emit electromagnetic radiation upon excitation with electromagnetic radiation (e.g., ultraviolet light) of  
10 a different wavelength. Typically, the emitted light has a longer wavelength (e.g., in visible spectrum) than the absorbed radiation. As the emitted light typically occurs almost simultaneously, i.e., in less than one second, when the absorbed radiation is in the invisible ultraviolet region of the spectrum, the emitted light may be in the visible region resulting in a distinctive identifiable color signal. Small molecule fluorescent tags typically contain several combined aromatic groups,  
15 or planar or cyclic molecules with multiple interconnected double bonds. Chen et al. report a variety of fluorescent tags that can be viewed across the visible spectrum. *Nature Biotechnology*, 2019, 37, 1287-1293. The term “fluorescent tag” is intended to include compounds of larger molecular weight such as natural fluorescent proteins, e.g., green fluorescent protein (GFP) and phycobiliproteins (PE, APC), and fluorescence particles such as quantum dots, e.g., preferably  
20 having 2-10 nm diameter.

As used herein, the term “small molecule” refers to any variety of covalently bound molecules with a molecular weight of less than 900 or 1000. Typically, the majority of atoms include carbon, hydrogen, oxygen, nitrogen, and to a lesser extent sulfur and/or a halogen. Examples include steroids, short peptides, mono or polycyclic aromatic or non-aromatic,  
25 heterocyclic compounds.

The term “nucleobase polymer” refers to a polymer comprising nitrogen containing aromatic or heterocyclic bases that bind to naturally occurring nucleic acids through hydrogen bonding otherwise known as base pairing containing at least one chemical modification such that it is not naturally occurring. A typical nucleobase polymer is a nucleic acid, RNA, DNA, or  
30 chemically modified form thereof. A nucleobase polymer may contain DNA or RNA or a combination of DNA or RNA nucleotides or may be single or double stranded or both, e.g., they

may contain overhangs, hairpins, bends, etc. Nucleobase polymers may contain naturally occurring or synthetically modified bases and backbones.

With regard to the nucleobases, it is contemplated that the term encompasses isobases, otherwise known as modified bases, e.g., are isoelectronic or have other substitutes configured to mimic naturally occurring hydrogen bonding base-pairs. Examples of nucleotides with modified adenosine or guanosine include, but are not limited to, hypoxanthine, xanthine, 7-methylguanine. Examples of nucleotides with modified cytidine, thymidine, or uridine include 5,6-dihydrouracil, 5-methylcytosine, 5-hydroxymethylcytosine. Contemplated isobases include 2'-deoxy-5-methylisocytidine (iC) and 2'-deoxy-isoguanosine (iG) (see U.S. Pat. No. 6,001,983; No. 10 6,037,120; No. 6,617,106; and No. 6,977,161).

Within any of the nucleotide sequences disclosed herein U may be substituted for T, or T may be substituted for U. U is one of the four nucleobases in the nucleic acid RNA. In DNA, the uracil (U) nucleobase is replaced by thymine (T). Uracil is a demethylated form of thymine. Thus, from a structural standpoint natural RNA is distinct from DNA due to the presence of a 2' hydroxy 15 on the ribose unit and demethylated thymine bases.

Nucleobase polymers may be chemically modified, e.g., within the sugar backbone or on the 5' or 3' ends. The nucleobase polymers can be modified, for example, with 2'-amino, 2'-O-allyl, 2'-fluoro, 2'-O-methyl, 2'-methyl, 2'-H of the ribose ring, or a locked nucleic acid. Locked nucleic acid (LNA) refers to oligonucleotides that contain one or more nucleobases in which an extra methylene bridge fixes the conformation sugar moiety, e.g., in the C3'-endo (beta-D-LNA) or C2'-endo (alpha-L-LNA) conformation of ribose. Using locked nucleic acids within a nucleobase polymer typically increases the specific binding between a double stranded complex. In certain embodiments, the nucleobase polymer comprises locked monomers of 1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol or phosphorodiamidate morpholino 25 oligomers (PMO).

The term "nucleobase polymer that hybridizes" refers to a molecule capable of hybridizing to a single-stranded nucleic acid target. The nucleobase polymer may target, e.g., comprise a sequence that is, or is the reverse complement of, more than 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, or more nucleotides or nucleobases or continuous nucleotide nucleobases of nucleic acids associated with an ELAVL3 cryptic exon, e.g., SEQ ID NO: 1-9. The nucleobase polymer may be a single 30 stranded nucleic acid or analog containing a sufficiently small number of mismatches, additions,

or deletions as long as the probe retains the ability to bind to the target. The nucleobase polymer may be the single stranded tail of a double stranded nucleic acid. The nucleobase polymer may be a part of a loop structure or single stranded tail of a hairpin structure. In certain embodiments, the nucleobase polymer may be less than 500, 200, 100, 50, or 25 nucleotides or nucleobases. In  
 5 certain embodiments, the fragment is greater than 5, 10, 15, or 20 nucleotides or nucleobases but less than 100, 50, or 25.

#### **Antisense oligonucleotides that bind ELAVL3 cryptic exon sites**

This disclosure relates to antisense oligonucleotides and nucleobase polymers which bind  
 10 a nucleic acid of ELAVL3 cryptic exons, e.g., pre-mRNA, mRNA, or DNA, suppressing or preventing cryptic splicing of ELAVL3 and uses in treating or preventing TDP-43 related neurodegenerative disease. In certain embodiments the nucleobase polymer is capable of decreasing cellular levels of or expression of ELAVL3 cryptic exon protein sequences and increasing or restoring functional ELAVL3 protein expression.

15 In order to prevent in vivo breakdown, nucleobase polymers are chemically modified, e.g., within the sugar backbone or on the 5' or 3' ends. In certain embodiments, nucleobase polymers disclosed herein may contain monomers of phosphodiester, phosphorothioate, methylphosphonate, phosphorodiamidate, piperazine phosphorodiamidate, ribose, 2'-O-methyl ribose, 2'-O-methoxyethyl ribose, 2'-fluororibose, deoxyribose, 1-(hydroxymethyl)-2,5-  
 20 dioxabicyclo[2.2.1]heptan-7-ol, P-(2-(hydroxymethyl)morpholino)-N,N-dimethylphosphoramidate, morpholin-2-ylmethanol, (2-(hydroxymethyl)morpholino) (piperazin-1-yl)phosphinate, or peptide nucleic acids (e.g., N-(2-aminoethyl) glycine wherein nucleobases are attached through a methyl carbonyl linker) or combinations thereof.

In certain embodiments, this disclosure contemplates nucleobase polymers with monomers  
 25 having base modifications, e.g., 5-methyl-cytosine, uracil and 5-(1-propynyl)uracil as parts of 2'-deoxynucleotides, sugar modifications, e.g., 2'-deoxy-2'-fluororibocytidine, 2'-arabincytidine, 2'-deoxy-2'-fluoroarabincytidine (2'-F-araC), locked nucleic acids (LNA), e.g., 1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol monomer backbone, unlocked nucleic acids (UNA), e.g., 2-(2-hydroxyethoxy)propane-1,3-diol monomer backbone, and phosphate modifications, e.g.,  
 30 phosphoramidate, methylphosphonate and phosphorothioate.

In certain embodiments, nucleobase polymers include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2',4'-C methylene bicyclo nucleotide e.g., 1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol monomer backbone.

5 In certain embodiments, nucleobase polymers include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp is a tricyclic aminoethyl-phenoxazine 2'-deoxycytidine such as G-clamp: [9-(2-aminoethoxy)-3H-benzo[b]pyrimido[4,5-e][1,4]oxazin-2(10H)-one] nucleobase, guanidino-G-clamp: 1-(2-((2-oxo-2,10-dihydro-3H-benzo[b]pyrimido [4,5-e][1,4]oxazin-9-yl)oxy)ethyl)guanidine nucleobase, i-clamp: 8-(3-aminopropoxy)-3H-benzo  
10 [b]pyrimido[4,5-e][1,4]oxazin-2(10H)-one nucleobase or analogues.

In certain embodiments, nucleobase polymers comprise one or more 5' and/or a 3'-cap structure. A "cap structure" refers to chemical modifications, which have been incorporated at either terminus of the oligonucleotide. See, for example, Adamic et al., U.S. Patent No. 5,998,203. These terminal modifications protect the nucleic acid molecule from exonuclease degradation. The  
15 cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide; carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; modified base nucleotide; phosphorodithioate linkage; threo-pentofuransyl nucleotide; acyclic 3',4'-seco  
20 nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

25 In certain embodiments, the nucleobase polymer has phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions.

In certain embodiments, the nucleobase polymer can be modified to contain a 3' end thiol  
30 group for direct absorption on conjugated to metal, gold, or silver surfaces and particles.

One synthesizes oligonucleotides (e.g., certain modified oligonucleotides or portions of oligonucleotides) using protocols known in the art as, for example, described in U.S. Patent No. 6,001,311. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end and phosphoramidites at the 3'-end.

5 In certain embodiments, the nucleobase polymer is single or double stranded RNA or DNA. In certain embodiments, the nucleotide base polymer is 3' end capped with one, two, or more thymidine nucleotides and/or is 5' end polyphosphorylated, e.g., di-phosphate, tri-phosphate.

In certain embodiments, the nucleobase polymer is modified to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H ribose groups. Constructs can be purified by gel electrophoresis using general  
10 methods or can be purified by high pressure liquid chromatography and re-suspended in water.

In certain embodiments, this disclosure relates to antisense oligonucleotides which bind cryptic exon sequences of ELAVL3 pre-mRNA, mRNA, or DNA suppressing or preventing cryptic splicing of ELAVL3 and uses in treating or preventing TDP-43 related neurodegenerative  
15 disease. In certain embodiments, the antisense oligonucleotide is a nucleobase polymer capable of decreasing cellular levels of or expression of ELAVL3 cryptic exon RNA and increasing or restoring functional ELAVL3 protein expression substantially excluding cryptic exon RNA peptide sequences.

In certain embodiments, this disclosed disclosure relates to antisense oligonucleotides that  
20 specifically bind an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence, thereby suppressing or preventing inclusion of an abortive or altered ELAVL3 RNA sequence. In certain embodiments, the abortive or altered ELAVL3 RNA sequence occurs and increases in abundance when TDP-43 function declines or TDP-pathology occurs.

In certain embodiments, disclosed herein are antisense oligonucleotides that specifically  
25 bind an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence coding for a cryptic exon, thereby suppressing or preventing inclusion of a cryptic exon in ELAVL3 RNA. In certain embodiments, disclosed herein are antisense oligonucleotides that specifically bind an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence, wherein the antisense oligonucleotide increases ELAVL3 protein expression.

30 In certain embodiments, the antisense oligonucleotide is a nucleobase polymer designed to hybridized with ELAVL3 cryptic exon DNA encoding pre-mRNA or mRNA or nascent RNA or

expressed pre-mRNA or mRNA. Within any of the sequences disclosed herein, wherein U may be T or T may be U.

In certain embodiments, the nucleobase polymer specifically binds/hybridizes with the 5' end of the ELAVL3 RNA or DNA having (SEQ ID NO: 1)

5 GTGCATGTGACACTGTGACTCCGGCTGTGACCTGATGGGGCCTCAGGGATGC  
GTCTGGCTCTGGCAGGATGTTTGTGTGTACCGCGATGTTGTGTGGGTGTGTCTACCT  
GTGCCCTGCTCTGAGGGATTGAGTGTGATATCGTGTGTTTGTGCTGCGCTGTGATGG.

In certain embodiments, the nucleobase polymer comprises the reverse complement of SEQ ID NO: 1 which is (SEQ ID NO: 2) AGTCACAGTGTACATGCAC or fragment thereof. In

10 certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 3) **GTCACATGCAC**CTGTCAAAT or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 4) **GTCACATGCAC**. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 5) ACCACATACCCATCACAGCG or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 6)  
15 ACAGCCGGAGTCACAGTGTCA or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 7) CCATCAGGTCACAGCCGGAGTCA or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 8) CCAGACGCATCCCTGAGGCC or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 9) CGCGGTGACACACAAACATC or fragment thereof.

20 In certain embodiments, the nucleobase polymer is a single stranded and designed to hybridized with ELAVL3 cryptic exon DNA encoding pre-mRNA or mRNA or expressed pre-mRNA or mRNA. In certain embodiments, the nucleobase polymer specifically binds/hybridizes with the 5' end of the ELAVL3 having (SEQ ID NO: 1)  
GTGCATGTGACACTGTGACTCCGGCTGTGACCTGATGGGGCCTCAGGGATGCGTCTG  
25 GCTCTGGCAGGATGTTTGTGTGTACCGCGATGTTGTGTGGGTGTGTCTACCTGTGCC  
CTGCTCTGAGGGATTGAGTGTGATATCGTGTGTTTGTGCTGCGCTGTGATGG. In

certain embodiments, the nucleobase polymer comprises the reverse complement of SEQ ID NO: 1 which is (SEQ ID NO: 2) AGTCACAGTGTACATGCAC or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 3)  
30 **GTCACATGCAC**CTGTCAAAT or fragment thereof. In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 4) **GTCACATGCAC**. In certain embodiments, the nucleobase

polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 5)  
10 ACCACATACCCATCACAGCG or fragment thereof. In certain embodiments, the nucleobase polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 6)  
20 ACAGCCGGAGTCACAGTGTC or fragment thereof. In certain embodiments, the nucleobase polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 7)  
30 CCATCAGGTCACAGCCGGAGTCA or fragment thereof. In certain embodiments, the nucleobase polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain

embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 8) CCAGACGCATCCCTGAGGCC or fragment thereof. In certain embodiments, the nucleobase polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the nucleobase polymer comprises (SEQ ID NO: 9) CGCGGTGACACACAAACATC or fragment thereof. In certain embodiments, the nucleobase polymer is a fragment between 5 nucleotides and 10 nucleotides in length. In certain embodiments, the nucleobase polymer is between 6 nucleotides and 11 nucleotides in length. In certain embodiments, the nucleobase polymer is between 7 nucleotides and 12 nucleotides in length. In certain embodiments, the nucleobase polymer is between 8 nucleotides and 13 nucleotides in length. In certain embodiments, the nucleobase polymer is between 9 nucleotides and 14 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 15 nucleotides in length. In certain embodiments, the nucleobase polymer is between 10 nucleotides and 20 nucleotides in length.

In certain embodiments, the antisense oligonucleotides are small sequences of DNA (e.g., about 5-50 base pairs in length) able to target RNA transcripts by Watson-Crick base pairing, resulting in reduced or modified protein expression. Oligonucleotides are composed of a phosphate backbone and sugar rings. In some embodiments oligonucleotides are unmodified. In other

embodiments oligonucleotides include one or more modifications, e.g., to improve solubility, binding, potency, and/or stability of the antisense oligonucleotide. Modified oligonucleotides may comprise at least one modification relative to unmodified RNA or DNA. In some embodiments, oligonucleotides are modified to include linkage modifications, sugar modifications, and/or  
5 nucleobase modifications. Examples of such modifications are known to those of skill in the art.

In certain embodiments, the antisense oligonucleotide is modified by the substitution of at least one nucleotide with a modified nucleotide, such that in vivo stability is enhanced as compared to a corresponding unmodified oligonucleotide. In certain embodiments, the modified nucleotide is a sugar-modified nucleotide. In certain embodiments, the modified nucleotide is a nucleobase-  
10 modified nucleotide.

In certain embodiments, antisense oligonucleotides may contain at least one modified nucleotide analogue. The nucleotide analogues may be located at positions where the target-specific activity, e.g., the splice site selection modulating activity is not substantially affected, e.g., in a region at the 5'-end and/or the 3'-end of the oligonucleotide molecule. In certain embodiments,  
15 the ends may be stabilized by incorporating modified nucleotide analogues.

In certain embodiments, antisense oligonucleotides include sugar- and/or backbone-modified ribonucleotides (i.e., include modifications to the phosphate-sugar backbone). For example, the phosphodiester linkages of a ribonucleotide may be modified to include at least one nitrogen or sulfur heteroatom. In certain embodiments, the phosphoester group connecting to  
20 adjacent ribonucleotides is replaced by a modified group, e.g., of phosphorothioate group. In certain embodiments (in the sugar-modified ribonucleotides) the 2' OH-group is replaced by a group selected from H, OR, R, halo, SH, SR, NH<sub>2</sub>, NHR, NR<sup>2</sup> or ON, wherein R is C<sub>1</sub>-C<sub>6</sub> alkyl, alkenyl or alkynyl and halo is F, Cl, Br, or I.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties.  
25 In certain embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of other types of modified sugar moieties.

In some embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms  
30 of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions.

In certain embodiments, one or more non-bridging substituent of non-bicyclic modified sugar moieties is branched.

In certain embodiments, modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. In certain  
5 embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and 2' furanose ring atoms.

In certain embodiments, an antisense oligonucleotide modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene  
10  $(-\text{CH}_2-)_n$  group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2.

In certain embodiments, modified sugar moieties comprise one or more non bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars). Modified oligonucleotides may comprise one or more nucleosides comprising an unmodified nucleobase. In some embodiments modified oligonucleotides comprise one or more  
15 nucleosides comprising a modified nucleobase.

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-  
20 aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl-uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-  
25 aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-  
30 aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include

those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone.

Also preferred are nucleobase-modified ribonucleotides, i.e., ribonucleotides, containing at least one non-naturally occurring nucleobase instead of a naturally occurring nucleobase.

5 Examples of modified nucleobases include, but are not limited to, uridine and/or cytidine modifications at the 5-position, e.g., 5-(2-amino)propyl uridine, 5-bromo uridine; adenosine and/or guanosines modified at the 8 position, e.g., 8-bromo guanosine; deaza nucleotides, e.g., 7-deaza-adenosine; O- and N-alkylated nucleotides, e.g., N<sup>6</sup>-methyl adenosine.

10 In certain embodiments, antisense oligonucleotides are linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorous atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring linkages), phosphotriesters, methylphosphonates, phosphoramidates, and phosphorothioates ("P=S"), and phosphorodithioates  
15 ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH<sub>2</sub>-N(CH<sub>3</sub>)-O-CH<sub>2</sub>-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH-O-); and N,N'-dimethylhydrazine (-CH<sub>2</sub>-N(CH<sub>3</sub>)-N(CH<sub>3</sub>)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In  
20 certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers.

Antisense oligonucleotides may be of any size and/or chemical composition sufficient to target the ELAVL3 cryptic exon nucleic acids. In certain embodiments, an oligonucleotide is between about 5-300 nucleotides or modified nucleotides. In certain embodiments, an  
25 oligonucleotide is between about 5-8, 5-10, 5-15, 8-20, 8-25, 10-100, 15-85, 20-70, 25-55, or 30-40 nucleotides or modified nucleotides. In certain embodiments, an oligonucleotide is between about 15-35, 15-20, 20-25, 25-30, or 30-35 nucleotides or modified nucleotides.

In certain embodiments, the nucleic acid can be any form of interfering RNA that targets ELAVL3 cryptic exon sequences or expressing, e.g., short interfering double stranded RNA or  
30 DNA, 15-23 or 10-25 nucleobases in length, or hairpins 20-50 nucleobases in length, wherein the double stranded portion of the hairpin comprises a cryptic exon sequence. In certain embodiments,

this disclosure relates to recombinant vectors comprising a nucleic acid encoding ELAVL3 cryptic exon sequences as reported herein in operable combination with heterologous promoters.

In certain embodiments, this disclosure relates to pharmaceutical composition comprising a nucleobase polymer as reported herein or recombinant vector encoding a nucleobase polymer as reported herein and or lipid particle as reported herein and a pharmaceutically acceptable excipient.

In certain embodiments, a binding oligonucleotide and the target RNA sequence (e.g., the abortive or altered ELAVL3 cryptic exon RNA) have 100% sequence complementarity. In certain embodiments, a binding oligonucleotide may comprise sequence variations, e.g., insertions, deletions, and single point mutations, relative to the target sequence. In certain embodiments, a binding oligonucleotide has at least 70% sequence identity or complementarity to the target RNA (e.g., ELAVL3 mRNA, pre-mRNA, or nascent RNA). In certain embodiments, a binding oligonucleotide has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 100% sequence identity to the target sequence.

In certain embodiments, term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. In certain embodiments, sequence "identity" refers to the number of exactly matching amino acids (expressed as a percentage) in a sequence alignment between two sequences of the alignment calculated using the number of identical positions divided by the greater of the shortest sequence or the number of equivalent positions excluding overhangs wherein internal gaps are counted as an equivalent position.

## Methods of Use

In certain embodiments, this disclosure relates to methods of managing a TDP-43 related neurodegenerative disease, neurological disease, or condition comprising administering to a subject in need thereof an effective amount of an agent, antisense oligonucleotide, nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA or mRNA as reported therein. In certain embodiments, this disclosure relates to methods for treating a disease or

condition associated with a TDP-pathology or a decline in TDP-43 functionality in neuronal cells in a subject.

In certain embodiments, this disclosure contemplates agents (e.g., small molecules, antisense oligonucleotides, or nucleobase polymers) that specifically bind an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence that occurs and increases in abundance when TDP-43 function declines or TDP-pathology occurs, thereby suppressing or preventing inclusion of an abortive or altered ELAVL3 RNA sequence. In certain embodiments, these agents prevent degradation of ELAVL3 protein. In certain embodiment, agents restore ELAVL3 protein levels. In certain embodiments, an agent suppresses or prevents inclusion of a cryptic exon in ELAVL3 RNA. In certain embodiments, an agent specifically binds an ELAVL3 mRNA, pre-mRNA, or nascent RNA sequence coding for a cryptic exon.

In certain embodiments, this disclosure contemplates methods for suppressing or preventing the inclusion of a cryptic exon in ELAVL3 mRNA. The inclusion of a cryptic exon in ELAVL3 mRNA may lead to a truncated transcript and protein. ELAVL3 expression may be restored through suppression of a cryptic splicing form of ELAVL3 that occurs when TDP-43 becomes sequestered or is reduced in functionality, such as by blocking the occurrence or accumulation of the cryptic form and converting it back to or restoring functional ELAVL3 RNA (e.g., by administration of an antisense oligonucleotide). Thus, this disclosure contemplates methods for increasing protein synthesis of ELAVL3 lacking cryptic exon sequences increasing full length ELAVL3 protein expression.

In certain embodiments, this disclosure relates to methods of treating, preventing, or reducing the likelihood of a disease or condition associated with a decline in TAR DNA-binding protein 43 (TDP-43) functionality in neuronal cells in a subject in need thereof. The methods may include contacting the neuronal cells with an antisense oligonucleotide that corrects reduced levels of ELAVL3 protein.

In certain embodiments, this disclosure relates to methods of treating, preventing, or reducing the likelihood of a disease or condition associated with a decline in TAR DNA-binding protein 43 (TDP-43) functionality in neuronal cells in a subject in need thereof comprising administering an effective amount of a nucleobase polymer as disclosed herein or recombinant vector encoding a nucleobase polymer as disclosed herien or pharmaceutical composition comprising the same to a subject in need thereof.

In certain embodiments, this disclosure relates to methods of improving memory or preventing memory loss comprising administering an effective amount of a nucleobase polymer as disclosed herein, a recombinant vector encoding a nucleobase polymer as disclosed herein or pharmaceutical composition comprising the same to a subject in need thereof.

- 5 In certain embodiments, the subject exhibits improved neuronal outgrowth and repair. In certain embodiments, the disease or condition is a neurodegenerative disease, neurological disorder, or condition related thereto, e.g., amyotrophic lateral sclerosis (ALS), autism, autism spectrum disorder (ADS), frontotemporal dementia (FTD), inclusion body myositis (IBM), Parkinson's disease, movement disorders, stroke, Traumatic brain injury, or Alzheimer's disease.
- 10 In certain embodiments, the disease or condition is a traumatic brain injury. In certain embodiments, the disease or condition is a proteasome-inhibitor induced neuropathy. In some embodiments, the disease or condition is associated with mutant or reduced levels of TDP-43 in neuronal cells.

- In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, speech disorder, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), Limbic-predominant Age-Related TDP-43 Encephalopathy (LATE), and Guamanian parkinsonism-dementia complex (G-PDC).
- 15

- 20 In certain embodiments, the TDP-43 related neurodegenerative disease or condition is Parkinson's diseases or traumatic brain injury.

- In certain embodiments, this disclosure relates to method of treating or preventing a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA as reported therein. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or concussion, other diseases or conditions reported herein.
- 25
- 30

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding DNA, RNA, pre-mRNA, mRNA such as

- 5 GTGCATGTGACACTGTGACTCCGGCTGTGACCTGATGGGGCCTCAGGGATGC  
 GTCTGGCTCTGGCAGGATGTTTGTGTGTACCGCGATGTTGTGTGGGTGTGTCTACCT  
 GTGCCCTGCTCTGAGGGATTGAGTGTGATATCGTGTGTTTGTGCTGCGCTGTGATGG(SEQ ID NO: 1). In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD),  
 10 Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

- In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having AGTCACAGTGTACATGCAC (SEQ ID NO: 2) or fragment thereof. In certain  
 15 embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem  
 20 Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

- In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent  
 25 RNA having (SEQ ID NO: 3) GTCACATGCACCTGTCAAAT or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem  
 30 Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having (SEQ ID NO: 4) **GTCACATGCAC**. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having **ACCACATACCCATCACAGCG** (SEQ ID NO: 5) or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease or neurological disorder comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having (SEQ ID NO: 6) **ACAGCCGGAGTCACAGTGTCA** or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent

RNA having (SEQ ID NO: 7) CCATCAGGTCACAGCCGGAGTCA or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having (SEQ ID NO: 8) CCAGACGCATCCCTGAGGCC or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

In certain embodiments, this disclosure relates to method of treating a TDP-43 related neurodegenerative disease comprising administering to a subject in need thereof a nucleobase polymer that hybridizes with ELAVL3 cryptic exon encoding pre-mRNA, mRNA, or nascent RNA having (SEQ ID NO: 9) CGCGGTGACACACAAACATC or fragment thereof. In certain embodiments, the TDP-43 related neurodegenerative disease or condition is memory loss, declining memory, dementia, declining speech, Alzheimer's (AD), Amyotrophic Lateral Sclerosis (ALS), autism, autism spectrum disorder (ADS), Frontotemporal Dementia (FTD), Multisystem Proteinopathy (MSP), Perry's Disease, Chronic Traumatic Encephalopathy (CTE), and Guamanian parkinsonism-dementia complex (G-PDC) or other diseases or conditions reported herein.

### Pharmaceutical Compositions

In certain embodiments, this disclosure relates to pharmaceutical compositions comprising an agent, antisense oligonucleotide, or nucleobase polymer as reported herein, e.g., comprising a sequence as disclosed herein, e.g., SEQ ID NOs. 1-9. In certain embodiments, this disclosure relates to the production of a medicament comprising an agent, antisense oligonucleotide, or nucleobase polymer as reported herein for therapeutic uses reported herein.

In certain embodiments, this disclosure relates to pharmaceutical compositions comprising an agent, antisense oligonucleotide, or nucleobase polymers as reported herein and a pharmaceutically acceptable excipient. These pharmaceutically acceptable compositions comprise a therapeutically effective amount of one or more of the agents, formulated together with one or more pharmaceutically acceptable carriers (additives), agents, and/or diluents.

In certain embodiments, the pharmaceutical compositions comprising an agent, antisense oligonucleotide, or nucleobase polymer as reported herein may be in a lipid formulation. For example, calcium phosphate and diethylaminoethyl (DEAE)-dextran and cationic lipid-based reagents are able to coat nucleic acids, enabling the formation of lipid complexes for integrating and/or crossing cell membranes. These complexes may be integrated into lipid formations/artificial liposomes. Cationic lipids are typically mixed with neutral lipids such as L-alpha dioleoyl phosphatidylethanolamine to enhance fusion with lipid bilayers. In certain embodiments, the pharmaceutical composition comprising a nucleobase polymer can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. U.S. Patent No. 6,395,713 and U.S. Patent No. 5,616,490 further describe general methods for delivery of nucleic acid molecules.

Formulating nucleobase polymers within polymeric or lipid nanoparticles (LNPs) is a strategy to prevent degradation. In certain embodiments, nucleobase polymers disclosed herein are containing in a particle comprising an ionizable lipid, a neutral helper lipid, cholesterol, and a diffusible polyethylene glycol (PEG)-lipid. See Semple et al., Nature Biotech, 2010, 28(2), 172-6. In another example, nucleobase polymers disclosed herein are containing in a particle comprising a cyclodextrin polymer. See Zuckerman et al., J Invest Dermatol, 2011, 131, 453-60.

In certain embodiments, nucleobase polymers disclosed herein are encapsulated in liposomes, e.g., by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example U.S. Patent No. 7,141,540 and U.S. Patent No. 7,060,498), poly(lactic-co-glycolic)acid (PLGA) and PLGA microspheres (see for example U.S. Patent No. 6,447,796), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (U.S. Patent No. 7,067,632).

In certain embodiments, nucleobase polymers disclosed herein are formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-

polyethylene glycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethylene glycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

The pharmaceutical compositions can be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, 5 drenches (aqueous or non-aqueous solutions or suspensions), gavages, lozenges, dragees, capsules, pills, tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intrathecal, intercranial, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, 10 for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) transmucosally; or (9) nasally. Additionally, agents can be implanted into a patient or injected using a drug delivery system.

In certain embodiments, the pharmaceutical composition optionally comprises a 15 pharmaceutical carrier, and that the pharmaceutical composition optionally comprises further therapeutic agents, respiratory agents, anti-inflammatory agents, etc.

In certain embodiments, a pharmaceutical composition is in the form of a liquid comprising pH buffering agents and optionally salts and/or saccharide or polysaccharide.

As used herein, the term “pharmaceutically acceptable” refers to those agents, materials, 20 compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

In certain embodiments, the pharmaceutically acceptable excipient is selected from lactose, 25 sucrose, mannitol, triethyl citrate, dextrose, cellulose, methyl cellulose, ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, croscarmellose sodium, polyvinyl N-pyrrolidone, crospovidone, ethyl cellulose, povidone, methyl and ethyl acrylate copolymer, polyethylene glycol, fatty acid esters of sorbitol, lauryl sulfate, gelatin, glycerin, glyceryl monooleate, silicon dioxide, titanium dioxide, talc, corn starch, carnauba wax, 30 stearic acid, sorbic acid, magnesium stearate, calcium stearate, castor oil, mineral oil, calcium

phosphate, starch, carboxymethyl ether of starch, iron oxide, triacetin, acacia gum, esters, or salts thereof.

Compositions may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents  
5 solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable (such as olive oil, sesame oil) and injectable organic esters such as ethyl oleate.

These compositions may also contain preserving, emulsifying, and dispensing agents.  
10 Prevention of the action of microorganisms may be controlled by addition of any of various antibacterial, antiviral, and antifungal agents, example, parabens, chlorobutanol, phenol, sorbic acid, and the like.

Liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, for example, ethyl alcohol, isopropyl alcohol,  
15 ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

In certain embodiments, a pharmaceutical composition comprises a single or two or more antisense oligonucleotides, and in certain embodiments comprises three or more antisense  
20 oligonucleotides. In certain embodiments, the two or more antisense oligonucleotides are covalently linked. In certain embodiments, the one or more antisense oligonucleotides increase ELAVL3 protein expression.

In certain embodiments, the pharmaceutical compositions comprise a multimeric  
25 oligonucleotide. The multimeric oligonucleotide comprises one or more sequences. In some embodiments, the multimeric oligonucleotide comprises two or more sequences. The multimeric oligonucleotide may comprise multiple copies of a sequence, or alternatively may comprise single copies of multiple sequences.

In certain embodiments, a pharmaceutical composition further comprises an agent for  
30 treating a neurodegenerative disease, an agent for treating a traumatic brain injury, or an agent for

treating a proteasome-inhibitor induced neuropathy. In some embodiments, a pharmaceutical composition further comprises a JNK inhibitor.

In certain embodiments, a pharmaceutical composition comprises an effective amount of an agent (e.g., an antisense oligonucleotide) that binds an ELAVL3 mRNA, pre-mRNA, or nascent  
5 RNA or DNA sequence coding for a cryptic exon, and optionally an effective amount of another active agent, and a pharmaceutically acceptable carrier, diluent, or excipient.

In certain embodiments, other pharmaceutically agent(s) are analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxiolytics, sedatives, hypnotics, antipsychotics, cardiovascular drugs,  
10 corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics, and anti-narcoleptics.

In certain embodiments, the pharmaceutically active agents that can be aceclofenac, acetaminophen, atomoxetine, almotriptan, alprazolam, amantadine, amcinonide, aminocyclopropane, amitriptyline, amlodipine, amoxapine, amphetamine, aripiprazole, aspirin,  
15 atomoxetine, azasetron, azatadine, beclomethasone, benactyzine, benoxaprofen, bermoprofen, betamethasone, bicifadine, bromocriptine, budesonide, buprenorphine, bupropion, buspirone, butorphanol, butriptyline, caffeine, carbamazepine, carbidopa, carisoprodol, celecoxib, chlordiazepoxide, chlorpromazine, choline salicylate, citalopram, clomipramine, clonazepam, clonidine, clonitazene, clorazepate, clotiazepam, cloxazolam, clozapine, codeine, corticosterone,  
20 cortisone, cyclobenzaprine, cyproheptadine, demexiptiline, desipramine, desomorphine, dexamethasone, dexanabinol, dextroamphetamine sulfate, dextromoramide, dextropropoxyphene, dezocine, diazepam, dibenzepin, diclofenac sodium, diflunisal, dihydrocodeine, dihydroergotamine, dihydromorphine, dimetacrine, divalproex, dizatriptan, dolasetron, donepezil, dothiepin, doxepin, duloxetine, ergotamine, escitalopram, estazolam, ethosuximide, etodolac,  
25 femoxetine, fenamates, fenoprofen, fentanyl, fludiazepam, fluoxetine, fluphenazine, flurazepam, flurbiprofen, flutazolam, fluvoxamine, frovatriptan, gabapentin, galantamine, gepirone, granisetron, haloperidol, huperzine A, hydrocodone, hydrocortisone, hydromorphone, hydroxyzine, ibuprofen, imipramine, indiplon, indomethacin, indoprofen, iprindole, ipsapirone, ketanserin, ketoprofen, ketorolac, lesopitron, levodopa, lipase, lofepramine, lorazepam, loxapine,  
30 maprotiline, mazindol, mefenamic acid, melatonin, melitracen, memantine, meperidine, meprobamate, mesalamine, metapramine, metaxalone, methadone, methadone,

methamphetamine, methocarbamol, methyldopa, methylphenidate, methylsalicylate, metoclopramide, mianserin, mifepristone, milnacipran, minaprine, mirtazapine, moclobemide, molindone, morphine, morphine hydrochloride, nabumetone, nadolol, naproxen, naratriptan, nefazodone, neurontin, nomifensine, nortriptyline, olanzapine, olsalazine, ondansetron, 5 opipramol, orphenadrine, oxaflozane, oxaprozin, oxazepam, oxitriptan, oxycodone, oxymorphone, pancrelipase, parecoxib, paroxetine, pemoline, pentazocine, pepsin, perphenazine, phenacetin, phendimetrazine, phenmetrazine, phenylbutazone, phenytoin, phosphatidylserine, pimozide, pirlindole, piroxicam, pizotifen, pizotiline, pramipexole, prednisolone, prednisone, pregabalin, propranolol, propizepine, propoxyphene, protriptyline, quazepam, quinupramine, reboxetine, 10 reserpine, risperidone, ritanserin, rivastigmine, rizatriptan, rofecoxib, ropinirole, rotigotine, salsalate, sertraline, sibutramine, sildenafil, sulfasalazine, sulindac, sumatriptan, tacrine, temazepam, tetrabenazine, thiazides, thioridazine, thiothixene, tiapride, taziprinone, tizanidine, tofenacin, tolmetin, toloxatone, topiramate, tramadol, trazodone, triazolam, trifluoperazine, trimethobenzamide, trimipramine, tropisetron, valdecoxib, valproic acid, venlafaxine, viloxazine, 15 vitamin E, zimeldine, ziprasidone, zolmitriptan, zolpidem, zopiclone, and combinations thereof.

In certain embodiments, this disclosure contemplates kits comprising pharmaceutical compositions comprising an agent, antisense oligonucleotide, or nucleobase polymer an agent, antisense oligonucleotide, or nucleobase polymer as reported herein and optionally another therapeutic agent in same or separate pharmaceutical composition or container. The kits may 20 contain a transfer device such a needle, syringe, cannula, capillary tube, pipette, or pipette tip.

In certain embodiments, an agent, antisense oligonucleotide, or nucleobase polymer as reported herein may be contained in a storage container, dispensing container, sealed, or unsealed, such a vial, bottle, ampule, blister pack, bag (plastic), or box. In certain embodiments, other agents may be contained in a storage container, sealed, or unsealed, such a vial, bottle, ampule, blister 25 pack, or box. In certain embodiments, the kit further comprises written instructions for using an agent, antisense oligonucleotide, or nucleobase polymer as reported herein and optionally other agents for treating and/or preventing a condition in a subject as reported herein.

### **Modulating ELAVL3 expression**

30 Loss of nuclear TDP-43 function leads to misprocessing of RNA targets of TDP-43. In addition to regulating alternative splicing of annotated cassette exons, TDP-43 plays a role in

repressing the aberrant inclusion of non-conserved cryptic (unannotated) exons. The inclusion of these cryptic exons results in novel RNA transcript variants that are either subject to nonsense mediated decay, translated to produce truncated proteins, or translated to (potentially non-functional) protein isoforms. Preventing the inclusion of these cryptic exons can restore the function of these transcripts and resulting proteins. It is contemplated that inclusion of a cryptic exon in the ELAVL3 gene results in neuronal toxicity. Thus, antisense oligonucleotides reported herein may be used to prevent the inclusion of this cryptic exon and restore ELAVL3 expression.

Basescope in situ hybridization was used to confirm the presence of ELAVL3 cryptic exon in the hippocampus of an FTLD-TDP case. The top of Figure 6 shows a schematic overview of the design of antisense oligonucleotides targeting the ELAVL3 cryptic exon. ASOs targeting the exon splicing enhancer (ESE) robustly prevented ELAVL3 cryptic exon inclusion and normalized ELAVL3 expression.

#### **Delivery of ELAVL3 cryptic exon targeting SSOs that reduce cryptic exon inclusion and normalize ELAVL3 expression in iPSNs**

One objective of experiments is to define the efficacy, dose-response curves, and timing of delivery of ELAVL3 cryptic exon targeting SSOs that reduce cryptic exon inclusion and normalize ELAVL3 expression in iPSNs. Splice switching oligonucleotides (SSOs) are short, modified, antisense oligonucleotides that base-pair with cis regulatory sequences of target RNAs through Watson-Crick interactions. Although it is not intended that certain embodiments, of this disclosure be limited by any particular mechanism, it is contemplated that unlike “gapmer” antisense oligonucleotides (ASOs), SSOs do not induce mRNA cleavage but rather modulate splicing by sterically blocking interactions of splicing factors with cis-regulatory sequences of pre-mRNA transcripts. Several cis-regulatory regions are typically present in a pre-mRNA transcript including intronic splicing silencers (ISS), exonic splicing enhancers (ESE), intron splicing enhancers (ISE), and exonic splicing silencers (ESS). Hinderance of appropriate splicing factor interactions with these cis-regulatory sequences can either promote or inhibit splicing of a particular exon.

SSOs have shown significant therapeutic promise to restore aberrant, disease-causing, RNA splicing events and improve clinical outcomes associated with splicing related disorders. For example, spinal muscular atrophy (SMA) is a severe neuromuscular disorder caused by mutations that inhibit proper splicing of exon 7 in the survival of motor neuron 1 (SMN1) gene and result in

a truncated SMN protein that is rapidly degraded. SMN1 is paralogous to the survival of motor neuron 2 (SMN2) gene; both SMN1 and SMN2 encode the same protein, survival motor neuron (SMN). However, SMN2, differs from SMN1 at the RNA level by a single nucleotide change in position 6 of exon 7 that alters the strength of the 3' splice site and results in a rapidly degraded truncated SMN protein. An intronic splicing silencer (ISS) was identified downstream of exon 7 in SMN2. Oligonucleotide mediated blocking of this ISS promoted inclusion of exon 7 in SMN2 and produced full length, functional SMN protein.

Experiments were developed to determine whether the reduction of ELAVL3 due to inclusion of a cryptic exon contributes to the molecular cascades that may underlie neurodegeneration. Contemplated are siRNAs targeting TARDBP to promote ELAVL3 cryptic exon inclusion and reduced total ELAVL3 expression in iPSNs. Cells are treated with SSOs at a concentration to correct aberrant ELAVL3 splicing and normalize ELAVL3 expression. One can assess changes in gene expression, alternative splicing, alternative polyadenylation, and protein abundance between non-targeting control and ELAVL3 cryptic exon targeting SSO conditions. Experiments can be performed to determine whether SSO mediated normalization of ELAVL3 mitigates observed neurotoxicity phenotypes.

**CLAIMS**

1. A nucleobase polymer comprising a sequence capable of binding ELAVL3 cryptic exon pre-mRNA, mRNA, or nascent RNA.
2. The nucleobase polymer of claim 1, comprising or consisting of SEQ ID NO: 1-9 or greater than 5 nucleotide fragments thereof.
3. The nucleobase polymer of claim 1, wherein the nucleobase polymer comprises monomers of 2'-O-methylribose, 2'-O-methoxyethyl ribose, or 2'-fluororibose.
4. The nucleobase polymer of claim 1, wherein the nucleobase polymer comprises monomers of 1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (LNA).
5. The nucleobase polymer of claim 1, wherein the nucleobase polymer comprises monomers of phosphorothioate, methylphosphonate, or phosphorodiamidate.
6. The nucleobase polymer of claim 1, wherein the nucleobase polymer comprises monomers of piperazine phosphorodiamidate, P-(2-(hydroxymethyl)morpholino)-N,N-dimethylphosphoramidate, morpholin-2-ylmethanol, or (2-(hydroxymethyl)morpholino)(piperazin-1-yl)phosphinate.
7. The nucleobase polymer of claim 1, wherein the nucleobase polymer comprises monomers of N-(2-aminoethyl) glycine (peptide nucleic acids).
8. The nucleobase polymer of claim 1, wherein the nucleobase polymer is conjugated to a label, fluorescent dye, or particle.
9. A recombinant vector encoding a nucleic acid of any of claims 1-2.
10. A lipid particle comprising a nucleobase polymer of any of claims 1-9.

11. A pharmaceutical composition comprising a nucleobase polymer of any of claims 1-8 or recombinant vector encoding a nucleobase polymer of any of claims 1-2 and or lipid particle of claim 9 a pharmaceutically acceptable excipient.
12. A method of treating a neurological disease or condition comprising administering an effective amount of a nucleobase polymer of any of claims 1-8 or recombinant vector encoding a nucleobase polymer of any of claims 1-2 or pharmaceutical composition comprising the same to a subject in need thereof.
13. A method of improving memory or preventing memory loss comprising administering an effective amount of a nucleobase polymer of any of claims 1-8, a recombinant vector encoding a nucleobase polymer of any of claims 1-2 or pharmaceutical composition comprising the same to a subject in need thereof.