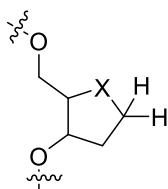


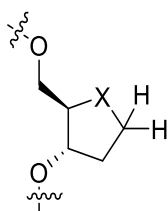
age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

## SUMMARY

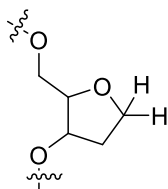
- 5 **[0008a]** In a first aspect of the present disclosure, there is provided an oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, wherein the oligonucleotide is 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 nucleotides in length, wherein at least one nucleoside linkage of the oligonucleotide is a modified linkage, and, wherein two or three nucleotides are
- 10 independently replaced with any one of the following formulae



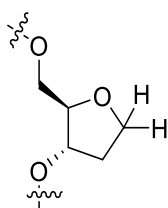
Formula (II), wherein X is selected from -CH<sub>2</sub>- and -O-;



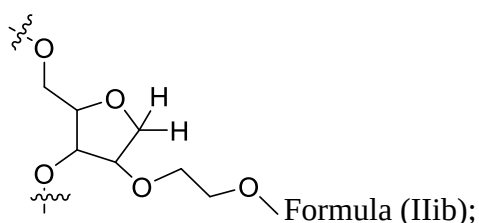
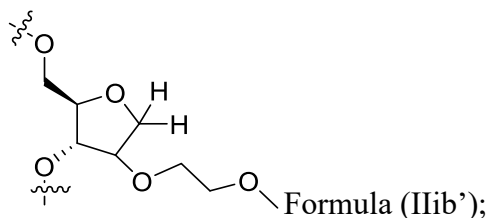
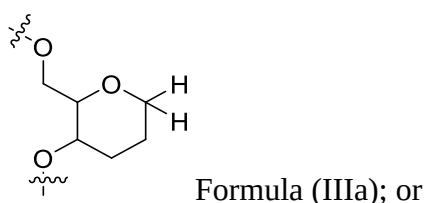
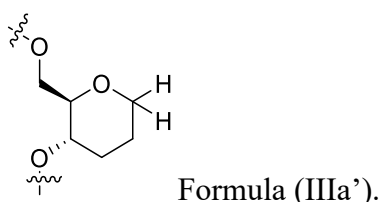
Formula (II'), wherein X is selected from -CH<sub>2</sub>- and -O-;



Formula (Iia);



Formula (Iia');



- 5 **[0008b]** In another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive
- 10 supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries, neuropathies, TDP43 proteinopathies, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-
- 15 dementia complex, multisystem proteinopathy, CTE, or autism.

**[0008c]** In yet another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with

FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries, neuropathies, TDP43 proteinopathies, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, or autism.

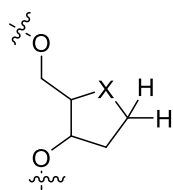
**[0008d]** In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

**[0008e]** In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

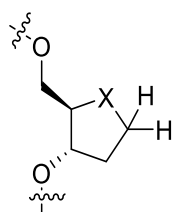
**[0008f]** In yet another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnesic mild cognitive impairment, corticobasal degeneration (CBD), a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucopolysaccharidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, or autism.

**[0008g]** In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnesic mild cognitive impairment, corticobasal degeneration (CBD), a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucopolysaccharidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, or autism.

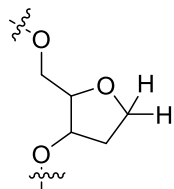
**[0008h]** In another aspect of the present disclosure, there is provided a modified oligonucleotide comprising a sequence that is at least 85% identical to SEQ ID NO: 2812 (GGCAGCTGGAAGAGACATACCCA), wherein the modified oligonucleotide is 23, 24, 25, 26, or 27 nucleotides in length, wherein at least one nucleoside linkage of the oligonucleotide is a modified linkage and wherein two or three nucleotides are independently replaced with a formula which is any one of the following formulas:



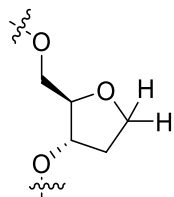
Formula (II), wherein X is selected from -CH<sub>2</sub>- and -O-;



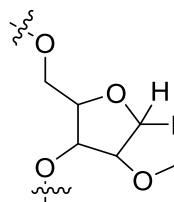
Formula (II'), wherein X is selected from -CH<sub>2</sub>- and -O-;



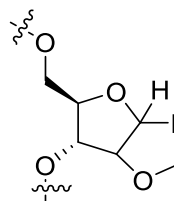
Formula (IIa);



Formula (IIa');

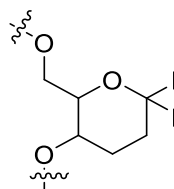


Formula (IIib);

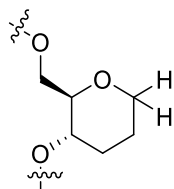


Formula (IIib');

5



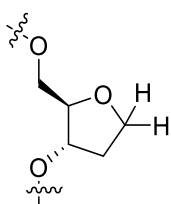
Formula (IIIa); or



Formula (IIIa').

**[0008i]** In yet another aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD, and wherein the medicament is to be administered intrathecally to the subject.

**[0008j]** In a further aspect of the present disclosure, there is provided a modified oligonucleotide comprising a sequence that is at least 90% identical to SEQ ID NO: 2812 (GGCAGCTGGAAGAGACATACCCA), wherein the oligonucleotide is 23 nucleotides in length, wherein the nucleotide at position 8 and the nucleotide at position 16 of SEQ ID NO:

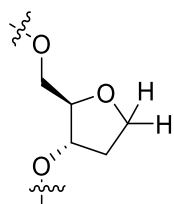


2812 are each replaced with Formula (Iia') and wherein at least one linkage is a modified nucleoside linkage.

**[0008k]** In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the modified oligonucleotide disclosed herein and a pharmaceutically acceptable excipient.

**[0008l]** In yet another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD.

**[0008m]** In a further aspect of the present disclosure, there is provided an oligonucleotide comprising SEQ ID NO: 5254 (GGCAGCTSGAAGAGASATACCCA), wherein S is



Formula (Iia'), each nucleotide comprises a modified sugar moiety which is a 2'-O-(2-methoxyethyl) (2'-MOE), each cytidine is a 5-methylcytosine (5-MeC), each nucleoside linkage is a phosphorothioate linkage, and wherein the oligonucleotide is 23 nucleotides in length.

**[0008n]** In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the oligonucleotide disclosed herein and a pharmaceutically acceptable excipient.

**[0008o]** In yet another aspect of the present disclosure, there is provided a use of a

5 pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS).

**[0008p]** In a further aspect of the present disclosure, there is provided a use of an oligonucleotide disclosed herein in the manufacture of a medicament for treating a neurological disease or a

10 neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD.

**[0008q]** In another aspect of the present disclosure, there is provided an oligonucleotide disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

**[0009]** Described herein are oligonucleotides comprising one or more spacers and comprising a

15 sequence that is at least 85% complementary to an equal length portion of a UNC13A transcript. In one example, the present disclosure provides UNC13A oligonucleotides that target a UNC13A transcript (for example, a mis-spliced UNC13A transcript). In various examples, the oligonucleotides target a transcript for the treatment of neurological diseases, including motor neuron diseases, and/or neuropathies. For example, UNC13A oligonucleotides can be used to

20 treat PD, ALS, FTD, ALS with FTD, and AD.

**[0010]** In one example the present disclosure provides a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one

25 (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage. In various examples, the oligonucleotide comprises a spacer.

**[0011]** In one example the present disclosure provides a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer. In various examples, the oligonucleotide comprises a segment with at most 11 linked nucleosides. In various examples, the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides. In various examples, the oligonucleotide comprises a segment with at most 7 linked nucleosides. In certain examples, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides. In certain examples, every segment of the oligonucleotide comprises at most 7 linked nucleosides.

**[0012]** In various examples, the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or

SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various examples, the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the

5 sequences in Tables 3A, 3B, 4 and 5.. In various examples, the oligonucleotide comprises a sequence that shares 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.. In various examples, the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of  
10 any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

**[0013]** In various examples, the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence  
15 that shares at least 85% identity with an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208. In various examples, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208. In various examples, the oligonucleotide comprises a segment with at  
20 most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208.

**[0014]** In various examples, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various examples, the  
25 oligonucleotide is at least 19 oligonucleotide units in length. In various examples, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

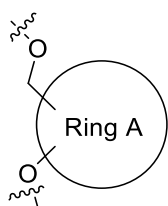
**[0015]** In various examples, the spacer is located between positions 10 and 15 of the oligonucleotide. In various examples, the spacer is located between positions 7 and 11 of the  
30 oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various examples, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various examples, the

spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various examples, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

**[0016]** In various examples, the spacer is located between positions 2 and 5 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides. In various examples, at least two of the three spacers are adjacent to a guanine nucleobase. In various examples, each of the at least two of the three spacers immediately precede a guanine nucleobase.

**[0017]** In various examples, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

**[0018]** In certain examples, each of the first, second or third spacers is independently represented by Formula (X), wherein:

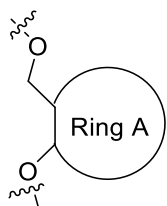


Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  $\text{---}\overset{\text{O}}{\underset{\text{O}}{\text{---}}}\text{---}$  symbol represents the point of connection to an internucleoside linkage.

**[0019]** In various examples, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



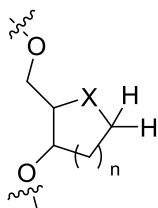
Formula (Xa).

**[0020]** In some examples, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

**[0021]** In further examples, ring A is tetrahydrofuranyl.

**[0022]** In other examples, ring A is tetrahydropyranyl.

**[0023]** In various examples, each of the first, second or third spacers is independently represented by Formula I, wherein:

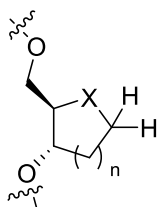


Formula (I)

X is selected from -CH<sub>2</sub>-- and -O-; and

n is 0, 1, 2 or 3.

**[0024]** In various examples, each of the first, second or third spacers is independently represented by Formula I', wherein:

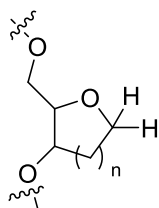


Formula (I')

X is selected from -CH<sub>2</sub>-- and -O-; and

n is 0, 1, 2 or 3.

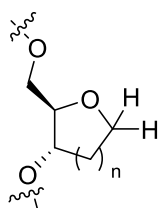
**[0025]** In various examples, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

$n$  is 0, 1, 2 or 3.

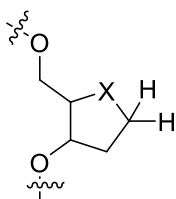
5 **[0026]** In various examples, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

$n$  is 0, 1, 2 or 3.

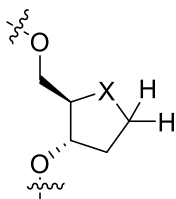
**[0027]** In certain examples, each of the first, second or third spacers is independently  
10 represented by Formula II, wherein:



Formula (II); and

X is selected from -CH<sub>2</sub>- and -O-.

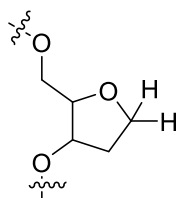
**[0028]** In further examples, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

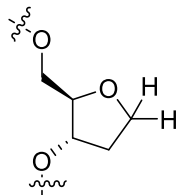
X is selected from -CH<sub>2</sub>- and -O-.

**[0029]** In various examples, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



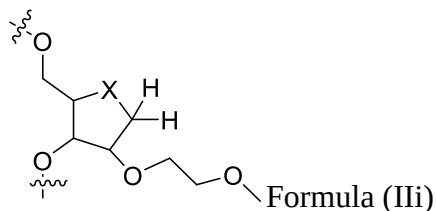
Formula (Iia).

**[0030]** In further examples, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

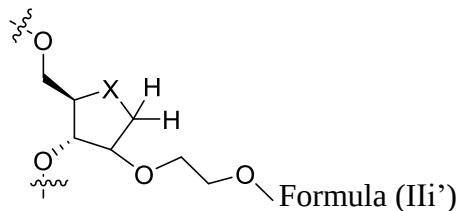
5 **[0031]** In some examples, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH<sub>2</sub>- and -O-.

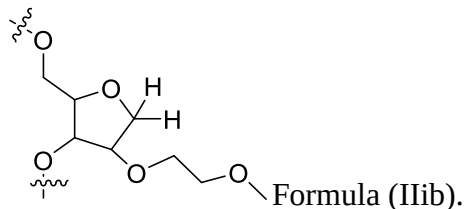
**[0032]** In some examples, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

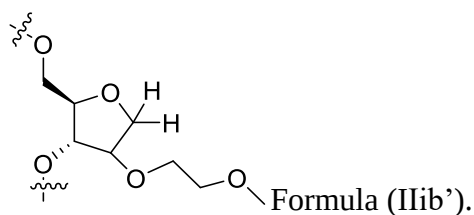
10 X is selected from -CH<sub>2</sub>- and -O-.

**[0033]** In some examples, the spacer is represented by Formula (IIib), wherein:

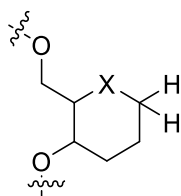


Formula (IIib).

**[0034]** In some examples, the spacer is represented by Formula (IIib'), wherein:



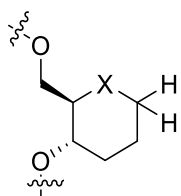
**[0035]** In various examples, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

5 X is selected from -CH<sub>2</sub>- and -O-.

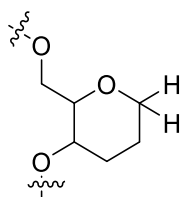
**[0036]** In further examples, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

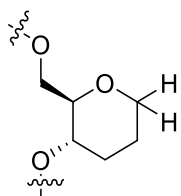
X is selected from -CH<sub>2</sub>- and -O-.

10 **[0037]** In some examples, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

**[0038]** In further examples, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



15 Formula (IIIa').

**[0039]** In various examples, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various examples, the oligonucleotide comprising the spacer has a GC

content of at least 20%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 50%.

**[0040]** In various examples, the oligonucleotide is between 12 and 40 oligonucleotide units in length.

**[0041]** In various examples, at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

**[0042]** In various examples, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various examples, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various examples, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond. In various examples, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

**[0043]** In various examples, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a

phosphodiester bond. In various examples, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds. In various examples, the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds. In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various examples, the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

**[0044]** Additionally disclosed herein is a compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. Additionally disclosed herein is an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various examples, the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various examples, the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or

SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various examples, the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

**[0045]** In various examples, an internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various examples, the modified internucleoside linkage of the

oligonucleotide is a phosphorothioate linkage. In various examples, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various examples, the phosphorothioate linkage is in one of a *Rp* configuration or a *Sp* configuration. In various examples, the oligonucleotide comprises at least one modified sugar moiety. In various examples, the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid (tcDNA) (e.g., tricyclic nucleic acid with ethyl (2'-O-CH<sub>2</sub>-CH<sub>2</sub>-4'C) as the bridge or tricyclic nucleic acid with methyl substituted methyl (2'-O-CH(CH<sub>2</sub>)-4'C) bridge), constrained ethyl 2'-4'-bridged nucleic acid (cEt), S-cEt, tcDNA, hexitol nucleic acids (HNA), tricyclic analog (e.g., tcDNA), and unlocked nucleic acids.

**[0046]** In various examples, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various examples, the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein. In various examples, the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein. In various examples, the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.

In various examples, the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein. In various examples, increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. In various examples, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In various examples, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

**[0047]** Additionally disclosed is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient an oligonucleotide of any of the oligonucleotides disclosed above. In various examples, the neurological disease selected from the group consisting of: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord

injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism. In various examples, the neurological disease is ALS. In various examples, the neurological disease is FTD. In various examples, the neurological disease is ALS with FTD. In various examples, the neurological disease is AD. In various examples, the neurological disease is PD. In various examples, the neuropathy is chemotherapy induced neuropathy.

**[0048]** Additionally disclosed is a method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the motor neuron to an oligonucleotide of any of the oligonucleotides disclosed above. Additionally disclosed is a method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to an oligonucleotide of any of the oligonucleotides disclosed above.

**[0049]** In various examples, the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various examples, the neuropathy is chemotherapy induced neuropathy. In various examples, the exposing is performed *in vivo* or *ex vivo*. In various examples, the exposing comprises administering the oligonucleotide to a patient in need thereof. In various examples, the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. In various examples, the oligonucleotide is administered orally. In various examples, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various examples, the patient is a human.

**[0050]** Additionally disclosed herein is a pharmaceutical composition comprising the oligonucleotide of any one of the oligonucleotides disclosed above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In various examples, the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal,

intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

**[0051]** Additionally disclosed herein is a method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need

5 thereof a therapeutically effective amount of a pharmaceutical composition disclosed above. In various examples, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, 10 progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such 15 a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucopolysaccharidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP- 20 43 With Sclerosis (CARTS), Gaucher's disease, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism. In various examples, the neurological disease is ALS. In various examples, the neurological disease is FTD. In various examples, the neurological disease is ALS with FTD. In various examples, the neuropathy is chemotherapy induced neuropathy. In 25 various examples, the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, intravenously, intramuscularly, transdermally, or intraduodenally. In various examples, wherein the pharmaceutical composition is administered intrathecally, intrathalamically intracerebroventricularly, or intracisternally. In various examples, 30 a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various examples, the patient is human.

**[0052]** Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro- $\beta$ -D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

**[0053]** Additionally disclosed herein is a method for treating ALS in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a

phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

**[0054]** Additionally disclosed herein is a method for treating FTD in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

**[0055]** Additionally disclosed herein is a method for treating ALS with FTD in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

**[0056]** In various examples, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various examples, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various examples, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond. In various

examples, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

**[0057]** In various examples, one or more bases immediately succeeding a spacer in the

oligonucleotide are linked through phosphodiester bonds. In various examples, only the base

5 immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a

phosphodiester bond. In various examples, two bases immediately preceding the spacer in the

oligonucleotide are linked through phosphodiester bonds. In various examples, one or more

bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester

bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide

10 are linked through phosphodiester bonds. In various examples, one base immediately preceding

the spacer and one base immediately succeeding the spacer are linked through phosphodiester

bonds. In various examples, the oligonucleotide includes a second spacer, and wherein one or

more bases immediately preceding the second spacer in the oligonucleotide are linked through

phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer

15 in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base

immediately preceding the second spacer and one base immediately succeeding the second

spacer are linked through phosphodiester bonds. In various examples, the oligonucleotide

comprises a range of bases that are linked through phosphodiester bonds, the range of bases

comprising at least two bases. In various examples, the oligonucleotide comprises a range of

20 bases that are linked through phosphodiester bonds, the range of bases comprising at least five

bases. In various examples, the oligonucleotide comprises two or more spacers, and wherein the

range of bases are positioned between the at least two spacers. In various examples, the

oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

**[0058]** In various examples, at least one (*i.e.*, one or more) internucleoside linkage of the

25 oligonucleotide is a phosphorothioate linkage. In various examples, all internucleoside linkages

of the oligonucleotide are phosphorothioate linkages.

**[0059]** Additionally disclosed herein is an oligonucleotide and a pharmaceutically acceptable

excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an

equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a

30 sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof,

wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of

increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a

functional UNC13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

**[0060]** In various examples, the oligonucleotide comprises one or more chiral centers and/or double bonds. In various examples, the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

**[0061]** Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition disclosed above, in combination with a second therapeutic agent. In various examples, the second therapeutic agent is selected from from Riluzole (Rilutek), PrimeC (combination of celecoxib and ciprofloxacin), Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesterone, KCNQ2/KCNQ3 openers (*e.g.*, retigabine, XEN1101, QRL-101), anticonvulsants and psychostimulant agents, and/or a therapy (*e.g.*, selected from breathing care, physical therapy, occupational therapy, speech therapy, nutritional support), for treating said neurologic disease.

**[0062]** Additionally disclosed herein is a method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition disclosed above, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

**[0063]** In various examples, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various examples, the spacer is located between positions 10 and 15 of the oligonucleotide. In various examples, the spacer is located between positions 7 and 11 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located

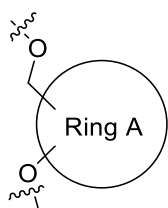
between positions 14 and 22 of the oligonucleotide. In various examples, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various examples, the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various examples, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

**[0064]** In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various examples, the spacer is located between positions 2 and 5 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

**[0065]** In various examples, at least two of the three spacers are adjacent to a guanine nucleobase. In various examples, each of the at least two of the three spacers immediately precede a guanine nucleobase.

**[0066]** In various examples, of the methods described herein, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

**[0067]** In certain examples, each of the first, second or third spacers is independently represented by Formula (X), wherein:



Formula (X)

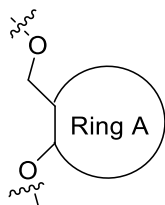
Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2

heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  $\sim$  symbol represents the point of connection to an internucleoside linkage.

**[0068]** In various examples, each of the first, second or third spacers is independently

5 represented by Formula (Xa), wherein:



Formula (Xa).

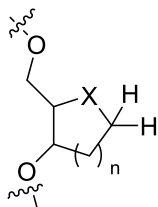
**[0069]** In some examples, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl,

10 tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

**[0070]** In further examples, ring A is tetrahydrofuranyl.

**[0071]** In other examples, ring A is tetrahydropyranyl.

**[0072]** In various examples, each of the first, second or third spacers is independently represented by Formula (I), wherein:

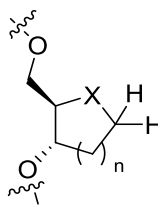


Formula (I)

X is selected from -CH<sub>2</sub>- and -O-; and

n is 0, 1, 2 or 3.

**[0073]** In various examples, the spacer or the second spacer is represented by Formula (I'), wherein:

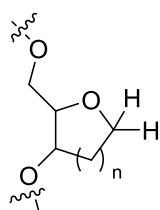


Formula (I')

X is selected from -CH<sub>2</sub>- and -O-; and

n is 0, 1, 2 or 3.

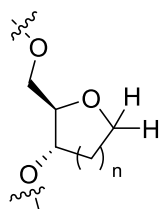
**[0074]** In various examples, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

5 n is 0, 1, 2 or 3.

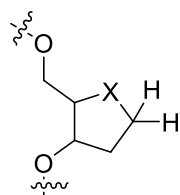
**[0075]** In various examples, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

10 **[0076]** In certain examples, each of the first, second or third spacers is independently represented by Formula II, wherein:

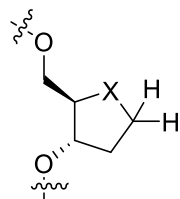


Formula (II); and

X is selected from -CH<sub>2</sub>- and -O-.

**[0077]** In further examples, each of the first, second or third spacers is independently represented by Formula II', wherein:

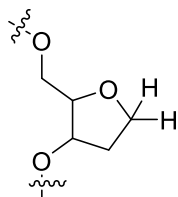
15



Formula (II'); and

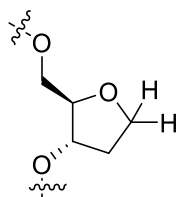
X is selected from -CH<sub>2</sub>- and -O-.

**[0078]** In various examples, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



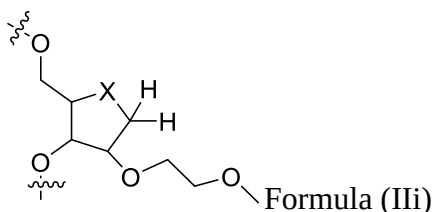
Formula (Iia).

**[0079]** In further examples, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

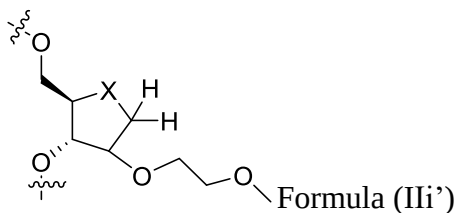
**[0080]** In some examples, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH<sub>2</sub>- and -O-.

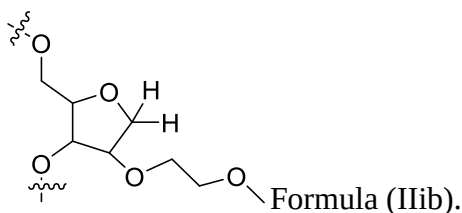
**[0081]** In some examples, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

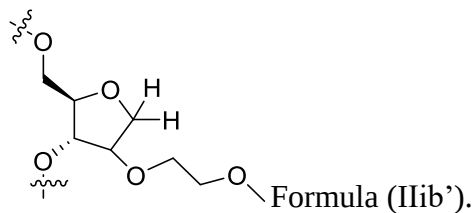
X is selected from -CH<sub>2</sub>- and -O-.

**[0082]** In some examples, the spacer is represented by Formula (IIib), wherein:

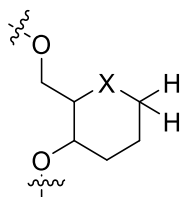


Formula (IIib).

**[0083]** In some examples, the spacer is represented by Formula (Iib'), wherein:



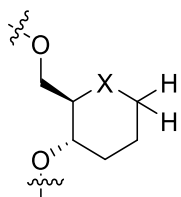
**[0084]** In various examples, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH<sub>2</sub>- and -O-.

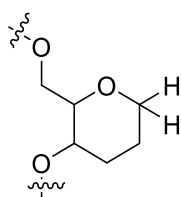
**[0085]** In further examples, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

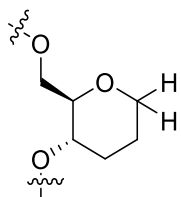
X is selected from -CH<sub>2</sub>- and -O-.

**[0086]** In some examples, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

**[0087]** In further examples, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

**[0088]** In various examples, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 50%.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0089]** Figure 1 shows an example antisense oligonucleotide (AON), a portion of which is complementary to a mRNA transcript or pre-mRNA transcript. Dashed lines indicate positions of the AON which may or may not be occupied by a spacer.

## DETAILED DESCRIPTION

**[0090]** The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here.

These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

**[0091]** Disclosed herein are oligonucleotides capable of targeting a region of a transcript transcribed from a gene. In various embodiments, such oligonucleotides target a UNC13A transcript. Additionally disclosed herein are oligonucleotides, including antisense oligonucleotide sequences, and methods for treating neurological diseases, such as amyotrophic lateral sclerosis and frontotemporal dementia, and/or neuropathies such as chemotherapy induced neuropathy, using same. In various embodiments, the oligonucleotides target a sequence of UNC13A transcripts resulting in the reduction of levels of mis-spliced UNC13A transcripts. Also disclosed are pharmaceutical compositions comprising UNC13A oligonucleotides that target a region of UNC13A transcripts, for treating neurological diseases and/or neuropathies; and manufacture of medicaments containing a disclosed UNC13A oligonucleotide that targets a region of UNC13A transcripts to be used in treating a neurological disease and/or neuropathy.

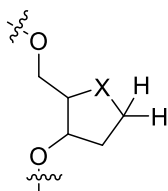
### Definitions

**[0092]** The terms “treat,” “treatment,” “treating,” and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be therapeutic

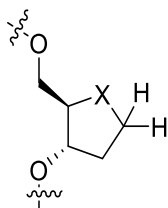
## CLAIMS

### WHAT IS CLAIMED IS:

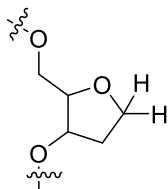
1. An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, wherein the oligonucleotide is 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 nucleotides in length, wherein at least one nucleoside linkage of the oligonucleotide is a modified linkage, and, wherein two or three nucleotides are independently replaced with any one of the following formulae



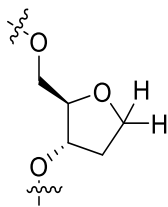
Formula (II), wherein X is selected from -CH<sub>2</sub>- and -O-;



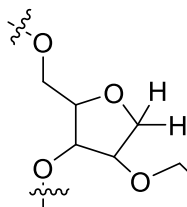
Formula (II'), wherein X is selected from -CH<sub>2</sub>- and -O-;



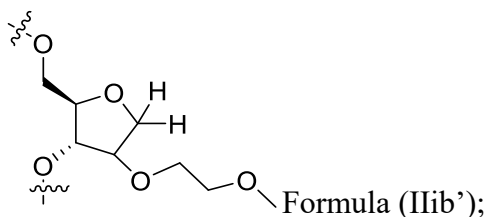
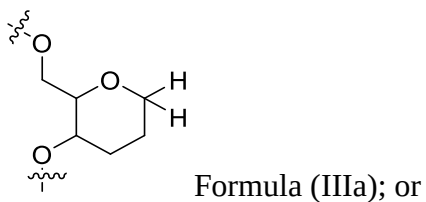
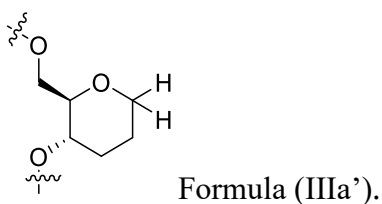
Formula (Iia);



Formula (Iia');

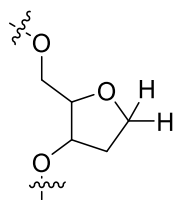


Formula (IIib);



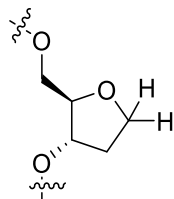
2. The oligonucleotide of claim 1, wherein the oligonucleotide comprises a segment with at most 11, 10, 9, or 8 linked nucleosides.
3. The oligonucleotide of claim 2, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.
4. The oligonucleotide of claim 3, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.
5. The oligonucleotide of claim 1, wherein the oligonucleotide is 23, 24, or 25 nucleotides in length and comprises a sequence that is at least 90% identical to SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573.
6. The oligonucleotide of claim 1, wherein the oligonucleotide is 23, 24, or 25 nucleotides in length and comprises a sequence that is at least 90% identical to SEQ ID NO: 2812, SEQ ID NO: 2801, SEQ ID NO: 5566, or SEQ ID NO: 2834.

7. The oligonucleotide of claim 6, wherein a first nucleotide replaced by a formula is located between positions 10 and 15 of the oligonucleotide.
8. The oligonucleotide of claim 7, wherein the first nucleotide replaced by a formula is located between positions 7 and 11 of the oligonucleotide.
9. The oligonucleotide of claim 8, wherein the oligonucleotide comprises a second nucleotide replaced by a formula, wherein the second nucleotide replaced by a formula is located between positions 14 and 22 of the oligonucleotide.
10. The oligonucleotide of claim 9, wherein the first nucleotide replaced by a formula is located at position 8 of the oligonucleotide, and wherein the second nucleotide replaced by a formula is located at position 16 of the oligonucleotide.
11. The oligonucleotide of claim 9, wherein the oligonucleotide comprises a third nucleotide replaced by a formula, wherein the third nucleotide replaced by a formula is located between positions 21 and 24 of the oligonucleotide.
12. The oligonucleotide of claim 10, wherein the formula is



Formula (Iia).

13. The oligonucleotide of claim 10, wherein the formula is



Formula (Iia').

14. The oligonucleotide of claim 10, wherein the oligonucleotide further comprises a locked nucleic acid (LNA).

15. The oligonucleotide of claim 14, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

16. The oligonucleotide of claim 10, wherein the at least one modified nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

17. The oligonucleotide of claim 16, wherein the at least one modified nucleoside linkage of the oligonucleotide is a phosphorothioate linkage, wherein the phosphorothioate linkage is in one of a *R<sub>p</sub>* configuration or a *S<sub>p</sub>* configuration.

18. The oligonucleotide of claim 10, wherein all nucleoside linkages of the oligonucleotide are modified nucleoside linkages and where all the modified nucleoside linkages are phosphorothioate linkages, wherein the phosphorothioate linkage is in one of a *R<sub>p</sub>* configuration or a *S<sub>p</sub>* configuration.

19. The oligonucleotide of claim 10, wherein the oligonucleotide comprises at least one modified sugar moiety, and wherein the modified sugar moiety is any one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), S-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

20. The oligonucleotide of claim 18, wherein the oligonucleotide comprises at least one modified sugar moiety, and wherein the modified sugar moiety is any one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro

nucleoside, 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), S-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

21. The oligonucleotide of claim 20, wherein the oligonucleotide comprises at least one modified sugar moiety, and wherein the modified sugar moiety is 2'-O-(2-methoxyethyl) (2'-MOE).

22. The oligonucleotide of claim 20, wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, pantothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

23. Use of an oligonucleotide of claim 10 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries, neuropathies, TDP43 proteinopathies, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, or autism.

24. Use of an oligonucleotide of claim 21 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries, neuropathies, TDP43 proteinopathies, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, or autism.

25. The use of claim 24, wherein the oligonucleotide is to be administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly to the subject.
26. A pharmaceutical composition comprising the oligonucleotide of claim 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
27. A pharmaceutical composition comprising the oligonucleotide of claim 21, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
28. Use of a pharmaceutical composition of claim 26 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnesic mild cognitive impairment, corticobasal degeneration (CBD), a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucopolysaccharidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, or autism.
29. Use of a pharmaceutical composition of claim 27 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the neurological disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal

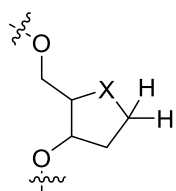
dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnesic mild cognitive impairment, corticobasal degeneration (CBD), a chemotherapy induced neuropathy, Spinocerebellar ataxia (SCA), SCA type 2, Spinal Muscular Atrophy (SMA), Parkinsonism, Niemann-Pick disease type C (NPC), Charcot-Marie-Tooth Disease (CMT), Mucopolysaccharidosis type II (MPSIIA), Mucopolysaccharidosis IV, GM1 gangliosidosis, Sporadic inclusion body myositis (sIBM), Henoch-Schonlein purpura (HSP), Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), Gaucher's disease, facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, or autism.

30. The use of claim 29, wherein the pharmaceutical composition is to be administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly to the subject.

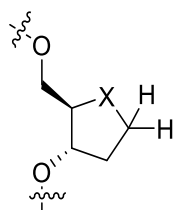
31. The use of claim 28, wherein the medicament is to be administered to the subject, wherein a second therapeutic agent is to be further administered to the subject, and wherein the second therapeutic agent is Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine anxiolytic drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration, BIIB100, levodopa/carbidopa, dopaminergic agents, medroxyprogesterone, KCNQ2/KCNQ3 openers, bioactive scaffolds, anticonvulsants and psychostimulant agents, levodopa and carbidopa (duopa, Rytary, Sinemet, inbrija), istradefylline (Nourianz), safinamide (Xadago), pramipexole (Mirapex), rotigotine (Neupro), ropinirole (Requip), amantadine (Gocovri, Symmetrel, Osmolex), benztropine (Cogentin), trihexyphenidyl (Artane), selegiline (Eldepryl, Zelapar), rasagiline, entacapone

(comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, embryonic dopamine cell implantation, aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralexx), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote), carbamazepine (Tegretol), medroxyprogesterone, Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), zonisamide (zonegran), or a combination thereof.

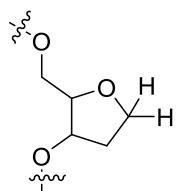
32. A modified oligonucleotide comprising a sequence that is at least 85% identical to SEQ ID NO: 2812 (GGCAGCTGGAAGAGACATACCCA), wherein the modified oligonucleotide is 23, 24, 25, 26, or 27 nucleotides in length, wherein at least one nucleoside linkage of the oligonucleotide is a modified linkage and wherein two or three nucleotides are independently replaced with a formula which is any one of the following formulas:



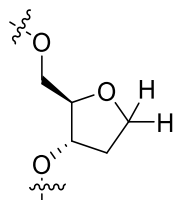
Formula (II), wherein X is selected from  $\text{-CH}_2\text{-}$  and  $\text{-O-}$ ;



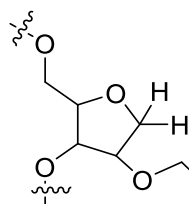
Formula (II'), wherein X is selected from  $\text{-CH}_2\text{-}$  and  $\text{-O-}$ ;



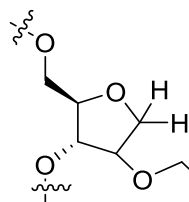
Formula (Iia);



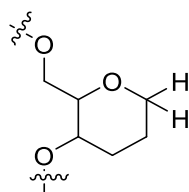
Formula (Iia');



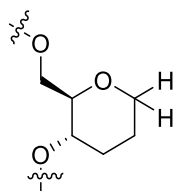
Formula (IIib);



Formula (IIib');



Formula (IIIa); or



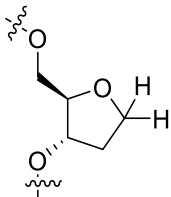
Formula (IIIa').

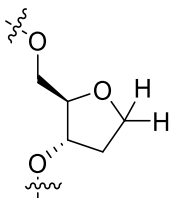
33. The oligonucleotide of claim 32, wherein the oligonucleotide comprises a segment with at most 11, 10, 9, or 8 linked nucleotides.

34. The oligonucleotide of claim 32, wherein the oligonucleotide comprises a segment with at most 7 linked nucleotides.
35. The oligonucleotide of claim 32, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleotides.
36. The oligonucleotide of claim 32, wherein a first nucleotide replaced by a formula is located between positions 10 and 15 of the oligonucleotide.
37. The oligonucleotide of claim 36, wherein the first nucleotide replaced by a formula is located between positions 7 and 11 of the oligonucleotide.
38. The oligonucleotide of claim 37, wherein the oligonucleotide comprises a second nucleotide replaced by a formula, wherein the second nucleotide is located between positions 14 and 22 of the oligonucleotide.
39. The oligonucleotide of claim 38, wherein the first nucleotide is located between positions 7 and 9 of the oligonucleotide, and wherein the second nucleotide is located between positions 15 and 18 of the oligonucleotide.
40. The oligonucleotide of claim 39, wherein the oligonucleotide further comprises a third nucleotide replaced by a formula, wherein the third nucleotide is located between positions 21 and 24 of the oligonucleotide.
41. The oligonucleotide of claim 32, wherein at least one nucleoside linkage is a phosphorothioate linkage and at least one nucleotide comprises a modified sugar moiety, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro- $\beta$ -D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), S-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog.
42. The oligonucleotide of claim 39, wherein the oligonucleotide is 23 nucleotides in length and comprises a sequence that is at least 90% identical to SEQ ID NOs: 2812 (GGCAGCTGGAAGAGACATACCCA).

43. The oligonucleotide of claim 42, wherein the first nucleotide replaced with a formula is located at position 8 of the oligonucleotide, and wherein the second nucleotide replaced with a formula is located at position 16 of the oligonucleotide.

44. The oligonucleotide of claim 43, wherein the first nucleotide at position 8 is replaced

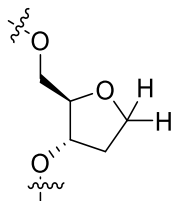
with  Formula (Iia'), and wherein the second nucleotide at position 16 is replaced

with  Formula (Iia').

45. The oligonucleotide of claim 44, wherein at least one nucleoside linkage is a phosphorothioate linkage and at least one nucleotide comprises a modified sugar moiety, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), S-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog.

46. Use of an oligonucleotide of claim 45 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD, and wherein the medicament is to be administered intrathecally to the subject.

47. A modified oligonucleotide comprising a sequence that is at least 90% identical to SEQ ID NO: 2812 (GGCAGCTGGAAGAGACATACCCA), wherein the oligonucleotide is 23 nucleotides in length, wherein the nucleotide at position 8 and the nucleotide at position 16 of



SEQ ID NO: 2812 are each replaced with Formula (Iia') and wherein at least one linkage is a modified nucleoside linkage.

48. The modified oligonucleotide of claim 47, comprising at least one nucleotide which comprises a modified sugar moiety.

49. The modified oligonucleotide of claim 48, wherein each nucleotide comprises a modified sugar moiety which is a 2'-O-(2-methoxyethyl) (2'-MOE).

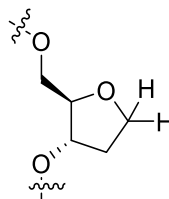
50. The modified oligonucleotide of claim 49, wherein each linkage is a modified nucleoside linkage.

51. The modified oligonucleotide of claim 50, wherein each modified nucleoside linkage is a phosphorohioate linkage.

52. A pharmaceutical composition comprising the modified oligonucleotide of claim 47 and a pharmaceutically acceptable excipient.

53. Use of a pharmaceutical composition of claim 52 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD.

54. An oligonucleotide comprising SEQ ID NO: 5254



(GGCAGCTSGAAGAGASATACCCA), wherein S is Formula (Iia'), each nucleotide comprises a modified sugar moiety which is a 2'-O-(2-methoxyethyl) (2'-MOE), each cytidine is a 5-methylcytosine (5-MeC), each nucleoside linkage is a phosphorohioate linkage, and wherein the oligonucleotide is 23 nucleotides in length.

55. The oligonucleotide of claim 54, consisting of SEQ ID NO: 5254 (GGCAGCTSGAAGAGASATACCCA), wherein S is Formula (Iia'), each nucleotide comprises a modified sugar moiety which is a 2'-O-(2-methoxyethyl) (2'-MOE), each cytidine is a 5-methylcytosine (5-MeC), and each nucleoside linkage is a phosphorothioate linkage.

56. A pharmaceutical composition comprising the oligonucleotide of claim 55 and a pharmaceutically acceptable excipient.

57. Use of a pharmaceutical composition of claim 56 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS).

58. The use of claim 57, wherein the pharmaceutical composition is to be administered intrathecally, intrathalamically, or intracisternally to the subject.

59. The use of claim 58, wherein the medicament is to be administered to the subject, wherein a second therapeutic agent is to be further administered to the subject, and wherein the second therapeutic agent is Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine anxiolytic drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration, BIIB100, levodopa/carbidopa, dopaminergic agents, medroxyprogesterone, KCNQ2/KCNQ3 openers, bioactive scaffolds, anticonvulsants and psychostimulant agents, deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, embryonic dopamine cell implantation, aducanumab (Aduhelm), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Ciprallex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)),

divalproex sodium (Depakote), carbamazepine (Tegretol), medroxyprogesterone, Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), zonisamide (zonegran), or a combination thereof.

60. The oligonucleotide of claim 54, wherein the oligonucleotide further comprises a targeting or a conjugate moiety, wherein the targeting or a conjugate moiety is cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, or an antibody for crossing the blood brain barrier.

61. Use of an oligonucleotide of claim 60 in the manufacture of a medicament for treating a neurological disease or a neuropathy in a subject in need thereof, wherein the disease or the neuropathy is amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or ALS with FTD.

62. An oligonucleotide of any one of claims 10, 21, 45 and 60, or a pharmaceutical composition of any one of claims 26, 27, 52, and 56, for use in therapy.