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(54) **Titre : TRAITEMENT DE MALADIES NEUROLOGIQUES A L'AIDE DE MODULATEURS DE TRANSCRITS DU GENE D'UNC13A**
(54) **Title: TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS**

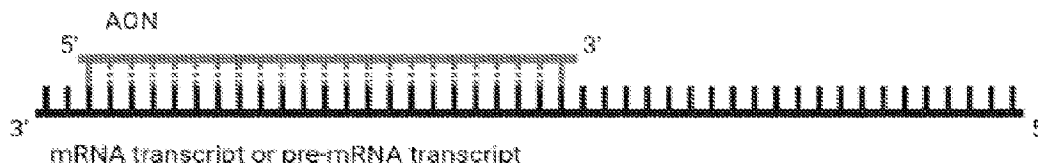


FIGURE 1

(57) **Abrégé/Abstract:**

Disclosed herein are UNC13A oligonucleotides with one or more spacers or without a spacer. In various embodiments, UNC13A oligonucleotides with spacer(s) reduce mis-spliced UNC13A transcripts and increase full length UNC13A transcripts, thereby imparting therapeutic efficacy against neurological diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or Alzheimer's disease (AD).



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Abstract:

Disclosed herein are UNC13A oligonucleotides with one or more spacers or without a spacer. In various embodiments, UNC13A oligonucleotides with spacer(s) reduce mis-spliced UNC13A transcripts and increase full length UNC13A transcripts, thereby imparting therapeutic efficacy against neurological diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or Alzheimer's disease (AD).

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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NOTE POUR LE TOME / VOLUME NOTE:

TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 **[0001]** This application claims the benefit of U.S. Provisional Application No. 63/285,786, filed on December 3, 2021, U.S. Provisional Application No. 63/350,206, filed on June 8, 2022, and U.S. Provisional Application No. 63/398,987, filed on August 18, 2022, each of which is hereby incorporated herein by reference in its entirety for all purposes.

REFERENCE TO A SEQUENCE LISTING XML

10 **[0001.1]** This application contains a sequence listing which has been submitted electronically in XML format. The Sequence Listing XML is incorporated herein by reference. Said XML file is named QRL-014WO_SL.xml and is 64,984,328 KB in size.

FIELD OF THE DISCLOSURE

15 **[0002]** This application relates generally to methods of treating neurological diseases with UNC13A splice-switching antisense oligonucleotides, in particular, UNC13A antisense oligonucleotides with one or more spacers that target an UNC13A transcript.

BACKGROUND

20 **[0003]** Motor neuron diseases are a class of neurological diseases that result in the degeneration and death of motor neurons – those neurons which coordinate voluntary movement of muscles by the brain. Motor neuron diseases may be sporadic or inherited, and may affect upper motor neurons and/or lower motor neurons. Motor neuron diseases include amyotrophic lateral sclerosis, progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, and post-polio syndrome.

25 **[0004]** Amyotrophic lateral sclerosis (ALS) is a group of motor neuron diseases affecting about 15,000 individuals in the United States of America. ALS is characterized by degeneration and death of upper and lower motor neurons, resulting in loss of voluntary muscle control. Motor neuron death is accompanied by muscle fasciculation and atrophy. Early symptoms of ALS include muscle cramps, muscle spasticity, muscle weakness (for example, affecting an arm, a leg, neck, or diaphragm), slurred and nasal speech, and difficulty chewing or swallowing. Loss of
30 strength and control over movements, including those necessary for speech, eating, and

breathing, eventually occur. Disease progression may be accompanied by weight loss, malnourishment, anxiety, depression, increased risk of pneumonia, muscle cramps, neuropathy, and possibly dementia. Most individuals diagnosed with ALS die of respiratory failure within five years of the first appearance of symptoms. Currently, there is no effective treatment for ALS.

[0005] ALS occurs in individuals of all ages, but is most common in individuals between 55 to 75 years of age, with a slightly higher incidence in males. ALS can be characterized as sporadic or familial. Sporadic ALS appears to occur at random and accounts for more than 90% of all incidences of ALS. Familial ALS accounts for 5-10% of all incidences of ALS.

[0006] FTD refers to a spectrum of progressive neurodegenerative diseases caused by loss of neurons in frontal and temporal lobes of the brain. FTD is the third most common form of dementia (following Alzheimer's disease and dementia with Lewy bodies), and the second most common form of dementia in individuals below 65 years of age. FTD is estimated to affect 50,000 to 60,000 individuals in the United States of America. FTD is characterized by changes in behavior and personality, and language dysfunction. Forms of FTD include behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA). ALS with FTD is characterized by symptoms associated with FTD, along with symptoms of ALS such as muscle weakness, atrophy, fasciculation, spasticity, speech impairment (dysarthria), and inability to swallow (dysphagia). Individuals usually succumb to FTD within 5 to 10 years, while ALS with FTD often results in death within 2 to 3 years of the first disease symptoms appearing.

[0007] Like ALS, there is no known cure for FTD, or ALS with FTD, nor a therapeutic known to prevent or retard either disease's progression.

[0008] Thus, there is a pressing need to identify compounds and/or compositions capable of preventing, ameliorating, and treating neurological diseases such as: 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.

SUMMARY

[0009] Described herein are oligonucleotides comprising one or more spacers and comprising a sequence that is at least 85% complementary to an equal length portion of a UNC13A transcript. In one aspect, the present disclosure provides UNC13A oligonucleotides that target a UNC13A transcript (for example, a mis-spliced UNC13A transcript). In various embodiments, 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 treat PD, ALS, FTD, ALS with FTD, and AD.

[0010] In one aspect 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. In various embodiments, the oligonucleotide comprises a spacer.

[0011] In one aspect 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 embodiments, the oligonucleotide comprises a segment with at most 11 linked nucleosides. In various embodiments, the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides. In various embodiments, the oligonucleotide comprises a segment with at most 7 linked nucleosides. In certain embodiments, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides. In certain embodiments, every segment of the oligonucleotide comprises at most 7 linked nucleosides.

[0012] In various embodiments, 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 embodiments, 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 sequences in Tables 3A, 3B, 4 and 5.. In various embodiments, 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 embodiments, the oligonucleotide comprises a sequence that shares 100% 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.

[0013] In various embodiments, the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 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 embodiments, 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 embodiments, 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 90% identity with an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208.

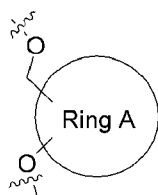
[0014] In various embodiments, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length. In various embodiments,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

[0015] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

[0016] In various embodiments, the spacer is located between positions 2 and 5 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various embodiments, 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 embodiments, at least two of the three spacers are adjacent to a guanine nucleobase. In various embodiments, each of the at least two of the three spacers immediately precede a guanine nucleobase.

[0017] In various embodiments, 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 embodiments, each of the first, second or third spacers is independently represented by Formula (X), wherein:

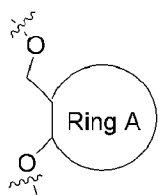


Formula (X)

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  symbol represents the point of connection to an internucleoside linkage.

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



Formula (Xa).

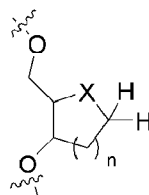
[0020] In some embodiments, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl;

or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidiny, piperidiny, piperaziny, morpholinyl and azepanyl.

[0021] In further embodiments, ring A is tetrahydrofuranyl.

[0022] In other embodiments, ring A is tetrahydropyranyl.

- 5 **[0023]** In various embodiments, each of the first, second or third spacers is independently represented by Formula I, wherein:

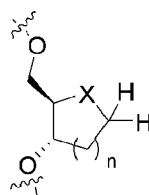


Formula (I)

X is selected from -CH₂-- and -O-; and

n is 0, 1, 2 or 3.

- 10 **[0024]** In various embodiments, each of the first, second or third spacers is independently represented by Formula I', wherein:

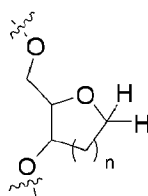


Formula (I')

X is selected from -CH₂-- and -O-; and

n is 0, 1, 2 or 3.

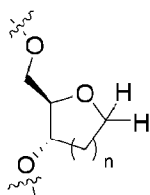
- 15 **[0025]** In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

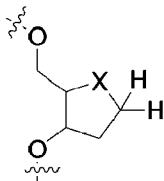
- [0026]** In various embodiments, each of the first, second or third spacers is independently
20 represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

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

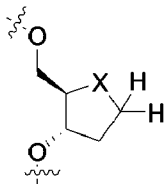


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Formula (II); and

X is selected from -CH₂- and -O-.

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

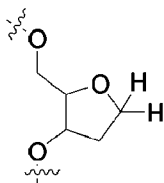


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Formula (II'); and

X is selected from -CH₂- and -O-.

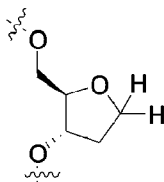
[0029] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



Formula (Iia).

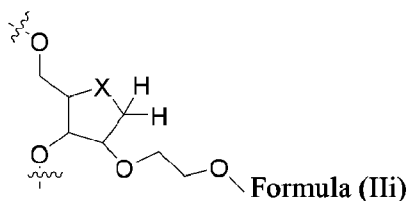
[0030] In further embodiments, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:

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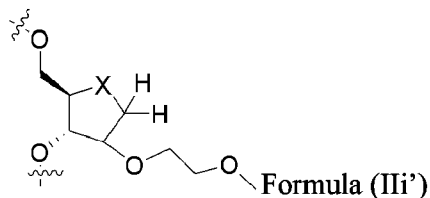
Formula (Iia').

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



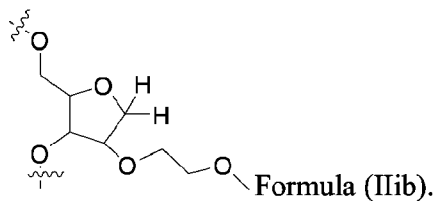
X is selected from -CH₂- and -O-.

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

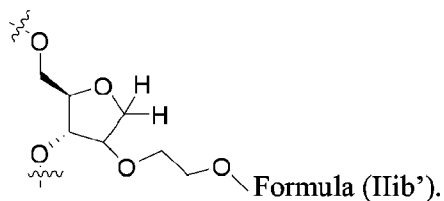


5 X is selected from -CH₂-and -O.

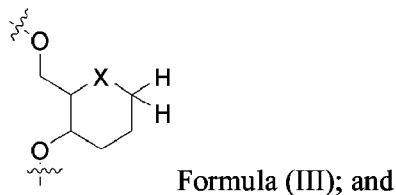
[0033] In some embodiments, the spacer is represented by Formula (IIib), wherein:



[0034] In some embodiments, the spacer is represented by Formula (Iiib'), wherein:

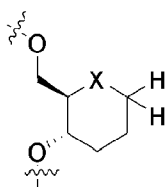


10 **[0035]** In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:



X is selected from -CH₂- and -O-.

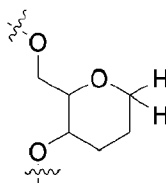
[0036] In further embodiments, each of the first, second or third spacers is independently
15 represented by Formula III', wherein:



Formula (III'); and

X is selected from -CH₂- and -O-.

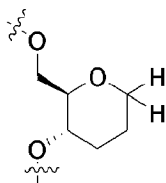
[0037] In some embodiments, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



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Formula (IIIa).

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



Formula (IIIa').

[0039] In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various embodiments, the oligonucleotide comprising the spacer has a GC content of at least 50%.

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

[0041] In various embodiments, 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

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linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

5 [0042] In various embodiments, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various embodiments, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various
10 embodiments, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond. In various
15 embodiments, 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 embodiments, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a
20 phosphodiester bond. In various embodiments, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, 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 embodiments, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked
25 through phosphodiester bonds. In various embodiments, 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 embodiments, one base immediately preceding the second
30 spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various embodiments,

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

[0045] In various embodiments, an internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various embodiments, the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various embodiments, the phosphorothioate linkage is in one of a *Rp* configuration or a *Sp* configuration. In various embodiments, the oligonucleotide comprises at least one modified sugar moiety. In various embodiments, 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- β -D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid (tcDNA) (e.g., tricyclic nucleic acid with ethyl (2'-O-CH₂-CH₂-4'C) as the bridge or tricyclic nucleic acid with methyl substituted methyl (2'-O-CH(CH₂)-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 embodiments, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein. In various

embodiments, the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein. In various embodiments, increase of the full length
5 UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. In various embodiments, 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 embodiments, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

10 **[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 embodiments, 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
15 (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
20 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 embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various
25 embodiments, the neurological disease is AD. In various embodiments, the neurological disease is PD. In various embodiments, 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,
30 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 embodiments, the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various embodiments, the neuropathy is

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

10 **[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 embodiments, 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 thereof a therapeutically effective amount of a pharmaceutical composition disclosed above. In various embodiments, 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, 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) and/or neuropathies such as 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, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease,

and synaptic diseases like autism. In various embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various embodiments, the neuropathy is chemotherapy induced neuropathy. In various embodiments, the pharmaceutical composition is administered

5 topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, intravenously, intramuscularly, transdermally, or intraduodenally. In various embodiments, wherein the pharmaceutical composition is administered intrathecally, intrathalamically

intracerebroventricularly, or intracisternally. In various embodiments, a therapeutically effective

10 amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various embodiments, 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

15 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

20 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

25 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'-

30 O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-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- β -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- β -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- β -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 embodiments, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various embodiments, only one

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

[0057] In various embodiments, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various embodiments, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various embodiments, two bases immediately preceding the spacer in
15 the oligonucleotide are linked through phosphodiester bonds. In various embodiments, 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 embodiments, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked
20 through phosphodiester bonds. In various embodiments, 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 embodiments, one base immediately preceding the second
25 spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various embodiments, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various embodiments,
30 the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers. In various embodiments, the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

[0058] In various embodiments, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, 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 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 embodiments, the oligonucleotide comprises one or more chiral centers and/or double bonds. In various embodiments, 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 embodiments, the second therapeutic agent is selected 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.

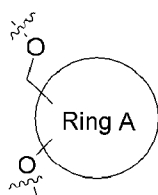
5 [0063] In various embodiments, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various embodiments, the spacer and the
10 second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, 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 embodiments, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the
15 oligonucleotide.

[0064] In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various embodiments, the spacer is located between positions 2 and 5 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer
20 is located between positions 8 and 12 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various embodiments, 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
25 nucleosides.

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

30 [0066] In various embodiments, 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, aminated or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

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

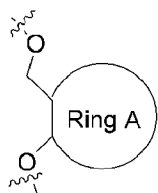


Formula (X)

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  symbol represents the point of connection to an internucleoside linkage.

[0068] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



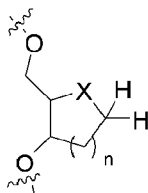
Formula (Xa).

[0069] In some embodiments, 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, pyrrolidiny, piperidiny, piperaziny, morpholiny and azepany.

[0070] In further embodiments, ring A is tetrahydrofuranyl.

[0071] In other embodiments, ring A is tetrahydropyranyl.

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

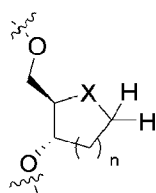


Formula (I)

X is selected from -CH₂- and -O-; and

n is 0, 1, 2 or 3.

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

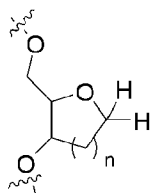


Formula (I')

X is selected from -CH₂- and -O-; and

n is 0, 1, 2 or 3.

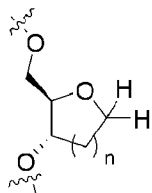
[0074] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

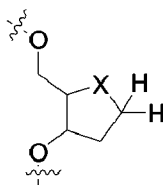
[0075] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

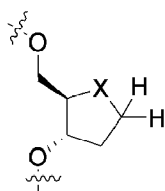
[0076] In certain embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH₂- and -O-.

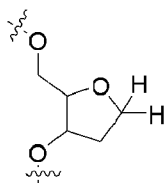
[0077] In further embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

X is selected from -CH₂- and -O-.

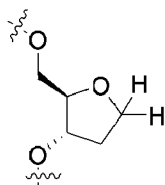
[0078] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



5

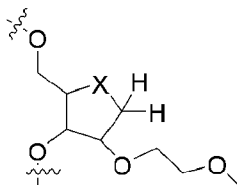
Formula (Iia).

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



Formula (Iia').

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

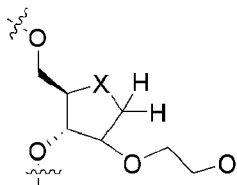


10

Formula (IIi)

X is selected from -CH₂- and -O-.

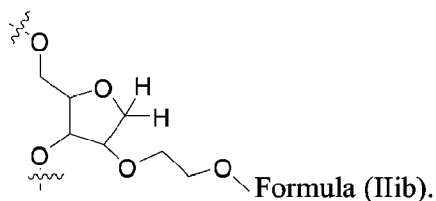
[0081] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



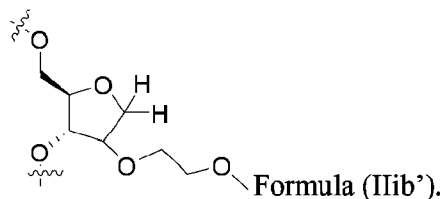
Formula (IIi')

X is selected from -CH₂- and -O-.

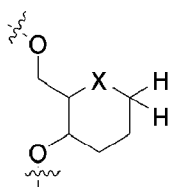
15 **[0082]** In some embodiments, the spacer is represented by Formula (IIib), wherein:



[0083] In some embodiments, the spacer is represented by Formula (Iiib'), wherein:



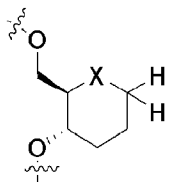
[0084] In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH₂- and -O-.

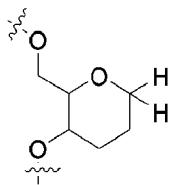
[0085] In further embodiments, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

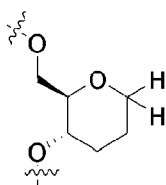
X is selected from -CH₂- and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

5 **[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 in terms of partially or completely curing a disease and/or adverse effect attributed to the disease. The term “treatment” as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) inhibiting the disease, *i.e.*, preventing the disease from increasing in severity or scope; (b) relieving the disease, *i.e.*, causing partial or complete amelioration of the disease; or (c) preventing relapse of the disease, *i.e.*, preventing the disease from returning to an active state following previous successful treatment of symptoms of the disease or treatment of the disease.

15 **[0093]** “Preventing” includes delaying the onset of clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition developing in a subject that may be afflicted with or predisposed to the state, disorder, disease, or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder, disease, or condition. “Preventing” includes prophylactically treating a state, disorder, disease, or condition in or developing in a subject, including prophylactically treating clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition in or developing in a subject.

20 **[0094]** The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein interchangeably refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

25 **[0095]** The term “pharmaceutical composition” as used herein refers to a composition comprising at least one biologically active compound, for example, a UNC13A antisense oligonucleotide (AON), as disclosed herein formulated together with one or more pharmaceutically acceptable excipients.

30 **[0096]** “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or non-human primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals such as an

animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, non-human primates, and the like). In some embodiments, the mammal treated in the methods of the invention is desirably a mammal in whom modulation of UNC13A expression and/or activity is desired.

[0097] As used herein, “UNC13A” (also known as Unc-13 Homolog A, Munc13-1, KIAA1032, unc-13 homolog A (*C. elegans*), or Protein Unc-13 Homolog A) refers to the gene or gene products (*e.g.*, protein or mRNA transcript (including pre-mRNA) encoded by the gene) identified by Entrez Gene ID No. 23025 and allelic variants thereof, as well as orthologs found in non-human species (*e.g.*, non-human primates or mice).

[0098] The term “UNC13A transcript” refers to a UNC13A transcript which can be a UNC13A pre-mRNA sequence or a UNC13A mature RNA sequence. UNC13A transcript sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[0099] The term “UNC13A oligonucleotide,” “UNC13A antisense oligonucleotide,” or “UNC13A AON” refers to an oligonucleotide that is capable of increasing, restoring, or stabilizing full-length UNC13A activity *e.g.*, full length UNC13A expression, for example, full length UNC13A mRNA and/or full length UNC13A protein expression. Generally, a UNC13A oligonucleotide reduces the level of mis-spliced UNC13A transcripts by targeting a UNC13A transcript (*e.g.*, UNC13A pre-mRNA or mis-spliced UNC13A with a target sequence). In various embodiments, a UNC13A oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208. UNC13A target sequences are shown to contain thymine (T), but one of skill in the art will appreciate that thymine (T) can generally be replaced with uracil (U) in RNA sequences.

[00100] In various embodiments, UNC13A oligonucleotides are characterized by having one or more spacers, where each spacer divides up the UNC13A oligonucleotide into segments of linked nucleosides. In various embodiments, UNC13A oligonucleotides have two spacers. In one embodiment, UNC13A oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, UNC13A oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, UNC13A oligonucleotides have one segment with at most 7 linked nucleosides. For example, a UNC13A oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides,

followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various embodiments, UNC13A oligonucleotides have three spacers that divide the UNC13A oligonucleotide into four segments. In various embodiments, each of the four segments of the

5 UNC13A oligonucleotide have at most 7 linked nucleosides.

[00101] As used herein, the term “UNC13A oligonucleotide” encompasses a “UNC13A parent oligonucleotide,” a “UNC13A oligonucleotide with one or more spacers” (e.g., UNC13A oligonucleotide with two spacers or a UNC13A oligonucleotide with three spacers), a “UNC13A oligonucleotide variant with one or more spacers.” Examples of UNC13A oligonucleotides

10 include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NO: 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.

[00102] The term “UNC13A parent oligonucleotide” refers to an oligonucleotide that targets a UNC13A transcript and is capable of increasing, restoring, or stabilizing full-length UNC13A

15 activity e.g., full length UNC13A expression, for example, full length UNC13A mRNA and/or full length UNC13A protein expression. UNC13A parent oligonucleotides do not include a spacer. Examples of UNC13A parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NO: 1-1264. As described hereafter, UNC13A oligonucleotide with spacers and UNC13A oligonucleotide variants are described in relation to a corresponding

20 UNC13A parent oligonucleotide.

[00103] The term “UNC13A oligonucleotide variant” refers to a UNC13A oligonucleotide that represents a modified version of a corresponding UNC13A parent oligonucleotide. For example, a UNC13A oligonucleotide variant represents a shortened version of a UNC13A parent oligonucleotide. In various embodiments, a UNC13A oligonucleotide variant is any one of a

25 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of UNC13A oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NO: 2529-3792. In various embodiments, UNC13A oligonucleotide variants comprise one or more spacers. Such UNC13A oligonucleotide variants comprise a sequence of any one of SEQ ID NO: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID

30 NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

[00104] The term “oligonucleotide with one or more spacers” or “oligonucleotide comprising a spacer” refers to an oligonucleotide with at least one spacer. An oligonucleotide with one or more spacers can, in various embodiments, include one spacer, two spacers, three spacers, four spacer, five spacers, six spacers, seven spacers, eight spacers, nine spacers, or ten spacers. In

various embodiments, an oligonucleotide comprising one or more spacers includes at least one segment with at most 7 linked nucleosides. For example, as described in a 5' to 3' direction, an oligonucleotide comprising a spacer can include a segment with 7 linked nucleosides, followed by a spacer, a second segment with 9 linked nucleosides, followed by a second spacer, and a third segment with 7 linked nucleosides. Here, the first segment of 7 linked nucleosides and the third segment of 7 linked nucleosides each represents segments with at most 7 linked nucleosides. As another example, an oligonucleotide comprising a spacer can include a segment with 10 linked nucleosides, followed by a spacer, a second segment with 10 linked nucleosides, followed by a second spacer, and a third segment with 3 linked nucleosides. Here, the third segment of 3 linked nucleosides represents the segment with at most 7 linked nucleosides. In various embodiments, an oligonucleotide with one or more spacers includes multiple segments with at most 7 linked nucleosides. In various embodiments, every segment of an oligonucleotide with one or more spacers has at most 7 linked nucleosides. For example, the oligonucleotide may be a 23mer and include two spacers that divide the 23mer into three separate segments of 7 linked nucleosides each. Therefore, each segment of the oligonucleotide has at most 7 linked nucleosides.

[00105] Generally, UNC13A oligonucleotides comprising one or more spacers are described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A oligonucleotide variant. Example UNC13A oligonucleotides comprising one or more spacers include any of 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.

[00106] In various embodiments, one or more spacers may be located at one or more positions of an oligonucleotide. A spacer may be located between a first position and a second position of the oligonucleotide. As used herein, a spacer located between a first position and second position encompasses the spacer being located at the first position, located at the second position, or located at any position of the oligonucleotide sandwiched by the first position and the second position.

[00107] In the present specification, the term “therapeutically effective amount” means the amount of an oligonucleotide that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor, or other clinician. In one embodiment, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a transcript comprising a sequence at least 90% identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, or a contiguous 15 to 50 nucleobase portion of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208. The oligonucleotide is administered in therapeutically effective amounts to treat and/or prevent a disease, condition,

disorder, or state, for example, a neurological disease and/or a neuropathy. Alternatively, a therapeutically effective amount of an oligonucleotide is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with reduced UNC13A activity in the motor neurons.

[00108] The phrase “a UNC13A oligonucleotide that targets a UNC13A transcript” refers to a UNC13A oligonucleotide that binds to a UNC13A transcript

[00109] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in a UNC13A oligonucleotide used in the present compositions.

A UNC13A oligonucleotide included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A UNC13A oligonucleotide included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, and lithium salts.

Pharmaceutically acceptable salts of the disclosure include, for example, pharmaceutically acceptable salts of UNC13A oligonucleotides that include a sequence of any 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.

[00110] A UNC13A oligonucleotide of the disclosure may contain one or more chiral centers, groups, linkages, and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term “stereoisomers” when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols “R” or “S” (or “R*p*” or “S*p*”) depending on the configuration of substituents around the stereogenic atom, for example, a stereogenic carbon, phosphorous, or sulfur atom. In some

embodiments, one or more linkages of the compound may have a *Rp* or *Sp* configuration (*e.g.*, one or more phosphorothioate linkages have either a *Rp* or *Sp* configuration). The configuration of each phosphorothioate linkage may be independent of another phosphorothioate linkage (*e.g.*, one phosphorothioate linkage has a *Rp* configuration and a second phosphorothioate linkage has a *Sp* configuration). In various embodiments, the UNC13A oligonucleotide can have a mixed configuration of phosphorothioate linkages. For example, the UNC13A oligonucleotide may have five phosphorothioate linkages in a *Rp* configuration, followed by fifteen phosphorothioate linkages in a *Sp* configuration, followed by five phosphorothioate linkages in a *Rp* configuration. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated “(±)” in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00111] Individual stereoisomers of a UNC13A oligonucleotide of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase super critical fluid chromatography, chiral-phase simulated moving bed chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[00112] The UNC13A oligonucleotide disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

[00113] The disclosure also embraces fluorescently labeled compounds of the invention. The disclosure also embraces isotopically labeled compounds of the invention (*i.e.*, isotopically labeled UNC13A oligonucleotide) which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the

atomic mass or mass number abundantly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{33}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

- 5 [00114] Certain isotopically labeled disclosed compounds (*e.g.*, those labeled with ^3H , ^{14}C , or ^{35}S) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H), carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

10 [00115] As used herein, “2’-O-(2-methoxyethyl)” (also 2’-MOE and 2’-O(CH₂)₂OCH₃ and MOE) refers to an O-methoxyethyl modification of the 2’ position of a furanose ring. A 2’-O-(2-methoxyethyl) is used interchangeably as “2’-O-methoxyethyl” in the present disclosure. A sugar moiety in a nucleoside modified with 2’-MOE is a modified sugar.

- 15 [00116] As used herein, “2’-MOE nucleoside” (also 2’-O-(2-methoxyethyl) nucleoside) means a nucleoside comprising a 2’-MOE modified sugar moiety.

[00117] As used herein, “2’-substituted nucleoside” means a nucleoside comprising a substituent at the 2’-position of the furanose ring other than H or OH. In certain embodiments, 2’ substituted nucleosides include nucleosides with bicyclic sugar modifications.

- 20 [00118] As used herein, “5-methyl cytosine” (5-MeC) means a cytosine modified with a methyl group attached to the 5 position. A 5-methyl cytosine (5-MeC) is a modified nucleobase.

[00119] As used herein, “bicyclic sugar” means a furanose ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

- 25 [00120] As used herein, “bicyclic nucleoside” (also BNA) means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4’-carbon and the 2’-carbon of the sugar ring.

[00121] As used herein, “cap structure” or “terminal cap moiety” means chemical modifications, which have been incorporated at either terminus of an antisense compound.

- 30 [00122] As used herein, “cEt” or “constrained ethyl” means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4’-carbon and the 2’-carbon, wherein the bridge has the formula: 4’-CH(CH₃)—O-2’.

[00123] As used herein, “constrained ethyl nucleoside” (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4’-CH(CH₃)—O-2’ bridge. In some

embodiments, cEt can be modified. In some embodiments, the cEt can be *S*-cEt (in an *S*-constrained ethyl 2'-4'-bridged nucleic acid). In some other embodiments, the cEt can be *R*-cEt.

[00124] As used herein, "internucleoside linkage" refers to the covalent linkage between adjacent nucleosides in an oligonucleotide. In some embodiments, as used herein, "non-natural linkage"

5 refers to a "modified internucleoside linkage."

[00125] As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence. As an example to the contrary, two nucleosides separated by a

10 spacer are not contiguous.

[00126] As used herein, "locked nucleic acid" or "LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to (A) α -L-Methyleneoxy (4'-CH₂—O-2') LNA, (B) β -D-Methyleneoxy (4'-CH₂—O-2') LNA, (C) Ethyleneoxy (4'-(CH₂)₂—O-2') LNA, (D) Aminooxy (4'-CH₂—O—N(R)-2') LNA and (E) Oxyamino (4'-CH₂—N(R)—O-2') LNA; wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00127] As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —[C(R₁)(R₂)]_n—, —C(R₁)=C(R₂)—, —C(R₁)=N—, —C(=NR₁)—, —C(=O)—, —C(=S)—, —O—, —Si(R₁)₂—, —S(=O)_x— and —N(R₁)—; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R₁ and R₂ is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical, substituted C₅-C₇ alicyclic radical, halogen, OJ₁, NJ₁J₂, SJ₁, N₃, COOJ₁, acyl (C(=O)—H), substituted acyl, CN, sulfonyl (S(=O)₂-J₁), or sulfoxyl (S(=O)-J₁); and each J₁ and J₂ is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ aminoalkyl or a protecting group.

[00128] Examples of 4'-2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: —[C(R₁)(R₂)]_n—, —[C(R₁)(R₂)]_n—O—, —C(R₁R₂)—

$N(R_1)-O-$ or $-C(R_1R_2)-O-N(R_1)-$. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2', 4'-(CH₂)₂-O-2', 4'-CH₂-O-N(R₁)-2' and 4'-CH₂-N(R₁)-O-2' bridges, wherein each R₁ and R₂ is, independently, H, a protecting group or C₁-C₁₂ alkyl.

5 [00129] Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a bridge to form the bicyclic sugar moiety. The bridge can be a methylene ($-CH_2-$) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH₂-O-2') LNA is used. Furthermore, in the case of the bicyclic
10 sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH₂CH₂-O-2') LNA is used.

[00130] As used herein, a "spacer" refers to a nucleoside-replacement group (*e.g.*, a non-nucleoside group that replaces a nucleoside present in a UNC13A parent oligonucleotide). The spacer is characterized by the lack of a nucleotide base and by the replacement of the nucleoside
15 sugar moiety with a non-sugar substitute. The non-sugar substitute group of a spacer lacks an aldehyde, ketone, acetal, ketal, hemiacetal or hemiketal group. The non-sugar substitute group of a spacer is thus capable of connecting to the 3' and 5' positions of the nucleosides adjacent to the spacer through an internucleoside linker as described herein, but not capable of forming a covalent bond with a nucleotide base (*i.e.*, not capable of linking a nucleobase to another group,
20 such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide). Generally, a UNC13A oligonucleotide with a spacer is described in relation to a UNC13A parent oligonucleotide, wherein the spacer replaces a nucleoside of the UNC13A parent oligonucleotide. In all embodiments of the present disclosure, a spacer cannot hybridize to a nucleoside comprising a nucleobase at the corresponding position of a UNC13A transcript, within the
25 numerical order of the length of the AON oligonucleotide (*i.e.*, if the spacer is positioned after nucleoside 4 of an AON (*i.e.*, at position 5 from the 5'-end), the spacer is not complementary to the nucleoside (A, C, G, or U) at the same corresponding position of the target UNC13A transcript)).

[00131] As used herein, "mismatch" or a "non-complementary group" refers to the case when a
30 group (*e.g.*, nucleobase) of a first nucleic acid is not capable of pairing with the corresponding group (*e.g.*, nucleobase) of a second or target nucleic acid.

[00132] As used herein, "modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside linkage (*e.g.*, a phosphodiester internucleoside bond).

- 5 **[00133]** As used herein, “modified nucleobase” means any nucleobase other than adenine, cytosine, guanine, thymine, or uracil. Examples of a modified nucleobase include 5-methyl cytosine, pseudouridine, or 5-methoxyuridine. An “unmodified nucleobase” means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).
- [00134]** As used herein, a “modified nucleoside” means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. Modified nucleosides include abasic nucleosides, which lack a nucleobase. However, modified nucleosides do not include
10 spacers or other groups that are incapable of linking a nucleobase.
- [00135]** As used herein, “linked nucleosides” are nucleosides that are connected in a contiguous sequence (*i.e.*, no additional nucleosides are presented between those that are linked). In various embodiments, an oligonucleotide may have different segments of linked nucleosides connected through a spacer. Here, the spacer (*i.e.*, nucleoside replacement) is not considered a nucleoside
15 and therefore, divides up the oligonucleotide into two segments of linked nucleosides. The oligonucleotide may have a first segment of Y linked nucleosides (*e.g.*, Y nucleosides that are connected in a contiguous sequence), followed by a spacer, and then a second segment of Z linked nucleosides. Here, the Y and Z linked nucleosides is described in either the 5’ to 3’ direction or the 3’ to 5’ direction. In various embodiments, the first segment consists of 7 or
20 fewer linked nucleosides (*e.g.*, Y = 7 or fewer) whereas the second segment comprises 8 or more linked nucleosides (*e.g.*, Z = 8 or more).
- [00136]** As used herein, “modified oligonucleotide” means an oligonucleotide comprising at least one (*i.e.*, one or more) modified internucleoside linkage, modified sugar, and/or modified nucleobase.
- 25 **[00137]** As used herein, “modified sugar” or “modified sugar moiety” means a modified furanosyl sugar moiety or a modified sugar moiety having other than a furanosyl moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide.
- [00138]** As used herein, “monomer” means a single unit of an oligomer. Monomers include, but
30 are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.
- [00139]** As used herein, “motif” means the pattern of unmodified and modified nucleosides in an antisense compound.
- [00140]** As used herein, “natural sugar moiety” means a sugar moiety found in DNA (2’-H) or RNA (2’-OH).

[00141] As used herein, “naturally occurring internucleoside linkage” means a 3’ to 5’ phosphodiester linkage.

[00142] As used herein, “non-complementary nucleobases” refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

5 **[00143]** As used herein, “nucleic acid” refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, double-stranded nucleic acids, non-coding RNA, small interfering ribonucleic acids (siRNA), short-hairpin RNA (shRNA), and microRNAs (miRNA).

[00144] As used herein, “nucleobase” means a heterocyclic moiety capable of base pairing with a
10 base of another nucleic acid.

[00145] As used herein, “nucleobase complementarity” refers to a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase refers to a nucleobase of an antisense compound that is
15 capable of base pairing with a corresponding nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair.

20 **[00146]** As used herein, “nucleobase sequence” means the order of nucleobases independent of any sugar, linkage, and/or nucleobase modification.

[00147] As used herein, “nucleoside” refers to a nucleobase linked to a sugar. The term “nucleoside” also includes a “modified nucleoside” which has independently, a modified sugar moiety and/or modified nucleobase.

25 **[00148]** As used herein, “nucleoside mimetic” includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo, or tricyclo sugar mimetics, *e.g.*, non-furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside
30 and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by a phosphorodiamidate or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate

wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system.

“Mimetic” refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

5 [00149] As used herein, “nucleotide” means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

[00150] As used herein, “oligomeric compound” or “oligomer” means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

10 [00151] As used herein, “oligonucleotide” means a polymer of one or more segments of linked nucleosides each of which can be modified or unmodified, independent one from another.

[00152] As used herein, “hotspot region” is a range of nucleobases on a target nucleic acid amenable to oligomeric compound-mediated modulation of the splicing of the target nucleic acid.

[00153] As used herein, “hybridization” means the pairing or annealing of complementary
15 oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding between complementary nucleobases.

[00154] As used herein, “increasing the amount of activity” refers to more transcriptional expression, more accurate splicing resulting in full length mature mRNA and/or protein
20 expression, and/or more activity relative to the transcriptional expression or activity in an untreated or control sample.

Antisense Therapeutics

[00155] Antisense therapeutics are a class of nucleic acid-based compounds that can be used to modulate a transcript, such as mRNA. In various embodiments, antisense therapeutics comprise
25 one or more spacers and can be used to modulate a transcript that is transcribed from a gene, such as a UNC13A pre-mRNA.

[00156] Antisense therapeutics may be single- or double-stranded deoxyribonucleic acid (DNA)-based, ribonucleic acid (RNA)-based, or DNA/RNA chemical analogue compounds. In general, antisense therapeutics are designed to include a sequence that is complementary or nearly
30 complementary to an mRNA or pre-mRNA sequence transcribed from a given gene in order to promote binding between the antisense therapeutic and the pre-mRNA or mRNA. In certain embodiments, antisense therapeutics act by binding to an mRNA or pre-mRNA, thereby inhibiting protein translation, altering pre-mRNA splicing into mature mRNA (*e.g.*, by preventing appropriate proteins such as splicing activator proteins from binding), and/or causing

destruction of mRNA. In certain embodiments, the antisense therapeutic sequence is complementary to a portion of a targeted gene's or mRNA's sense sequence. In certain embodiments, antisense therapeutics described herein are oligonucleotide-based compounds that include an oligonucleotide sequence complementary to a pre-mRNA sense, or a portion thereof, and one or more spacers. In certain embodiments, antisense therapeutics described herein can also be nucleotide chemical analog-based compounds.

[00157] In certain embodiments, an oligonucleotide, such as disclosed herein, may be an oligonucleotide sequence of 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length, or 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 oligonucleotide units in length. As used herein, an "oligonucleotide unit" refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide.

[00158] In particular embodiments, the oligonucleotides are 25 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides are 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, or at least 27 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 26 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 27 oligonucleotide units in length.

[00159] In certain embodiments, AONs may include chemically modified nucleosides (for example, 2'-O-methylated nucleosides or 2'-O-(2-methoxyethyl) nucleosides) as well as modified internucleoside linkages (for example, phosphorothioate linkages). In certain embodiments, AONs described herein include oligonucleotide sequences that are complementary

to RNA sequences, such as UNC13A mRNA sequences. In certain embodiments, AONs described herein can include chemically modified nucleosides and modified internucleoside linkages (for example, phosphorothioate linkages). In particular embodiments, AONs described herein include one or more spacers.

5 [00160] In various embodiments, the oligonucleotides comprise one or more spacers. In particular embodiments, the oligonucleotides comprise one spacer. In various embodiments, the oligonucleotides comprise two spacers. For example, the oligonucleotide includes 23 oligonucleotide units with 21 nucleobases and two nucleoside replacement groups (e.g., two spacers). Further embodiments of oligonucleotides with one spacer and oligonucleotides with
10 two spacers are described herein. In various embodiments, the oligonucleotides comprise three spacers.

[00161] In some embodiments, an antisense oligonucleotide can be, but is not limited to, inhibitors of a gene transcript (for example, shRNAs, siRNAs, PNAs, LNAs, 2'-O-methyl (2'OMe) antisense oligonucleotide (AON), 2'-O-(2-methoxyethyl) (MOE) AON, or morpholino
15 oligomers (e.g., phosphorodiamidate morpholino (PMO))), or compositions that include such compounds. In some embodiments an oligonucleotide is an antisense oligonucleotide (AON) comprising 2'OMe (e.g., a AON comprising one or more 2'OMe modified sugar), MOE (e.g., a AON comprising one or more MOE modified sugar), peptide nucleic acids (e.g., a AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl
20 methylene linkage as repeating units in place of a sugar-phosphate backbone), locked nucleic acids (e.g., a AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (e.g., a AON comprising one or more cET sugar), constrained methoxyethyl (cMOE) (e.g., a AON comprising one or more cMOE sugar), morpholino oligomer (e.g., a AON comprising a backbone comprising one or more PMO),
25 deoxy-2'-fluoro nucleoside (e.g., a AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tricyclo-DNAs (tcDNA) (e.g., a AON comprising one or more tcDNA modified sugar), 2'-O,4'-C-Ethylene-bridged nucleic acid (ENA) (e.g., a AON comprising one or more ENA modified sugar), or hexitol nucleic acids (HNA) (e.g., a AON comprising one or more HNA modified sugar). In some embodiments, a AON comprises one or more internucleoside
30 linkage independently selected from a phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage,

phosphoramidate linkage, a phosphoramidothioate linkage, thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

5 **[00162]** Peptide nucleic acids (PNAs) are short, artificially synthesized polymers with a structure that mimics DNA or RNA. PNAs include a backbone composed of repeating N-(2-aminoethyl)-glycine units linked by peptide bonds. In certain embodiments, PNAs described herein can be used as antisense therapeutics that bind to RNA sequences with high specificity and increase, restore, and/or stabilize levels (*e.g.*, full length UNC13A mRNA or protein levels) and/or activity
10 (*e.g.*, biological activity, for example, UNC13A activity).

[00163] Locked nucleic acids (LNAs) are oligonucleotide sequences that include one or more modified RNA nucleotides in which the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon. LNAs are believed to have higher T_m's than analogous oligonucleotide sequences. In certain embodiments, LNAs described herein can be used as
15 antisense therapeutics that bind to RNA sequences with high specificity. For example, LNAs can bind to UNC13A pre-mRNA and prevent mis-splicing of UNC13A pre-mRNA, and increase, restore, and/or stabilize UNC13A levels (*e.g.*, UNC13A mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, UNC13A activity).

[00164] Morpholino oligomers are oligonucleotide compounds that include DNA bases attached
20 to a backbone of methylenemorpholine rings linked through phosphorodiamidate groups. In certain embodiments, morpholino oligomers of the present invention can be designed to bind to specific pre-mRNA sequence of interest. For example, morpholino oligomers bind to UNC13A pre-mRNA thereby preventing mis-splicing of the pre-mRNA, and increase, restore, and/or stabilize UNC13A levels (*e.g.*, UNC13A mRNA or protein levels) and/or activity (*e.g.*,
25 biological activity, for example, UNC13A activity). In certain embodiments, UNC13A morpholino oligomers described herein can be used as antisense therapeutics that bind to UNC13A pre-mRNA sequences with high specificity and prevent mis-splicing of UNC13A pre-mRNA, and increase, restore, and/or stabilize UNC13A levels (*e.g.*, UNC13A mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, UNC13A activity). In certain
30 embodiments, UNC13A morpholino oligomers described herein can also be used to bind UNC13A pre-mRNA sequences, altering UNC13A pre-mRNA splicing and UNC13A gene expression, and increase, restore, and/or stabilize UNC13A levels (*e.g.*, UNC13A mRNA or protein levels) and/or activity (*e.g.*, biological activity, for example, UNC13A activity).

UNC13A Oligonucleotides Complementary to UNC13A Transcript

[00165] In some embodiments, a UNC13A AON includes a sequence that is at least % complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208). In some embodiments, a UNC13A AON includes a sequence that is between 90-95% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208). In particular embodiments, a UNC13A AON includes a sequence that is at least 85% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208). In particular embodiments, a UNC13A AON includes a sequence that is between 84% to 88% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208). In particular embodiments, a UNC13A AON includes a sequence that is between 89% to 92% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a mis-spliced UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065). In particular embodiments, a UNC13A AON includes a sequence that is between 94% to 96% complementary to a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to a region of a UNC13A transcript (*e.g.*, SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208).

[00166] In various embodiments, a UNC13A AON 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 embodiments, a UNC13A AON 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 sequences in Tables 3A, 3B, 4 and 5.

[00167] In some embodiments, the UNC13A AON comprises a spacer and has a segment having at most 7 linked nucleosides. In some embodiments, the UNC13A AON comprises a spacer and has a segment having at most 6, 5, 4, 3, or 2 linked nucleosides.

[00168] UNC13A AON binding specificity can be assessed via measurement of parameters such as dissociation constant, melting temperature, or other criteria such as changes in protein or RNA expression levels or other assays that measure UNC13A activity or expression.

[00169] In some embodiments, a UNC13A AON can include a non-duplexed oligonucleotide. In

5 some embodiments, a UNC13A AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a UNC13A pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

10 **[00170]** In some embodiments, a UNC13A AON can target UNC13A pre-mRNAs produced from UNC13A genes of one or more species. For example, a UNC13A AON can target a UNC13A pre-mRNA of a mammalian UNC13A gene, for example, a human (*i.e.*, *Homo sapiens*) UNC13A gene. In particular embodiments, the UNC13A AON targets a human UNC13A pre-mRNA. In some embodiments, the UNC13A AON includes a nucleobase sequence that is
15 complementary to a nucleobase sequence of a UNC13A gene or a UNC13A pre-mRNA or a portion thereof.

[00171] UNC13A AONs described herein include antisense oligonucleotides comprising the oligonucleotide sequences listed in Table 1 below:

Table 1. Example UNC13A AON Sequences.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
1	GGAGGGGCGGAGCAATGACCCTCAC	1265	GTGAGGGTCATTGCTCGGCCCCCTCC
2	GGGAGGGGCGGAGCAATGACCCTCA	1266	TGAGGGTCATTGCTCGGCCCCCTCCC
3	TGGGAGGGGCGGAGCAATGACCCTC	1267	GAGGGTCATTGCTCGGCCCCCTCCCA
4	ATGGGAGGGGCGGAGCAATGACCCT	1268	AGGGTCATTGCTCGGCCCCCTCCCAT
5	CATGGGAGGGGCGGAGCAATGACCC	1269	GGGTCATTGCTCGGCCCCCTCCCATG
6	GCATGGGAGGGGCGGAGCAATGACC	1270	GGTCATTGCTCGGCCCCCTCCCATGC
7	GGCATGGGAGGGGCGGAGCAATGAC	1271	GTCATTGCTCGGCCCCCTCCCATGCC
8	TGGCATGGGAGGGGCGGAGCAATGA	1272	TCATTGCTCGGCCCCCTCCCATGCCA
9	GTGGCATGGGAGGGGCGGAGCAATG	1273	CATTGCTCGGCCCCCTCCCATGCCAC
10	AGTGGCATGGGAGGGGCGGAGCAAT	1274	ATTGCTCGGCCCCCTCCCATGCCACT
11	AAGTGGCATGGGAGGGGCGGAGCAA	1275	TTGCTCGGCCCCCTCCCATGCCACTT
12	GAAGTGGCATGGGAGGGGCGGAGCA	1276	TGCTCGGCCCCCTCCCATGCCACTTC
13	GGAAGTGGCATGGGAGGGGCGGAGC	1277	GCTCGGCCCCCTCCCATGCCACTTCC
14	TGGAAGTGGCATGGGAGGGGCGGAG	1278	CTCGGCCCCCTCCCATGCCACTTCCA
15	GTGGAAGTGGCATGGGAGGGGCGGA	1279	TCGGCCCCCTCCCATGCCACTTCCAC
16	AGTGAAGTGGCATGGGAGGGGCGCG	1280	CGGCCCCCTCCCATGCCACTTCCACT

17	GAGTGGAAGTGGCATGGGAGGGGCC	1281	GGCCCCCTCCCATGCCACTTCCACTC
18	TGAGTGGAAGTGGCATGGGAGGGGC	1282	GCCCCCTCCCATGCCACTTCCACTCA
19	GTGAGTGGAAGTGGCATGGGAGGGG	1283	CCCCTCCCATGCCACTTCCACTCAC
20	GGTGAGTGGAAGTGGCATGGGAGGG	1284	CCCTCCCATGCCACTTCCACTCACC
21	TGGTGAGTGGAAGTGGCATGGGAGG	1285	CCTCCCATGCCACTTCCACTCACCA
22	ATGGTGAGTGGAAGTGGCATGGGAG	1286	CTCCCATGCCACTTCCACTCACCAT
23	AATGGTGAGTGGAAGTGGCATGGGA	1287	TCCCATGCCACTTCCACTCACCATT
24	GAATGGTGAGTGGAAGTGGCATGGG	1288	CCCATGCCACTTCCACTCACCATT
25	GGAATGGTGAGTGGAAGTGGCATGG	1289	CCATGCCACTTCCACTCACCATTCC
26	AGGAATGGTGAGTGGAAGTGGCATG	1290	CATGCCACTTCCACTCACCATTCCCT
27	CAGGAATGGTGAGTGGAAGTGGCAT	1291	ATGCCACTTCCACTCACCATTCCCTG
28	GCAGGAATGGTGAGTGGAAGTGGCA	1292	TGCCACTTCCACTCACCATTCCCTGC
29	GGCAGGAATGGTGAGTGGAAGTGGC	1293	GCCACTTCCACTCACCATTCCCTGCC
30	AGGCAGGAATGGTGAGTGGAAGTGG	1294	CCACTTCCACTCACCATTCCCTGCCT
31	CAGGCAGGAATGGTGAGTGGAAGTG	1295	CACTTCCACTCACCATTCCCTGCCTG
32	GCAGGCAGGAATGGTGAGTGGAAGT	1296	ACTTCCACTCACCATTCCCTGCCTGC
33	GGCAGGCAGGAATGGTGAGTGGAAG	1297	CTTCCACTCACCATTCCCTGCCTGCC
34	GGGCAGGCAGGAATGGTGAGTGGA	1298	TTCCACTCACCATTCCCTGCCTGCCC
35	TGGGCAGGCAGGAATGGTGAGTGGA	1299	TCCACTCACCATTCCCTGCCTGCCCA
36	CTGGGCAGGCAGGAATGGTGAGTGG	1300	CCACTCACCATTCCCTGCCTGCCCAG
37	GCTGGGCAGGCAGGAATGGTGAGTG	1301	CACTCACCATTCCCTGCCTGCCCAGC
38	AGCTGGGCAGGCAGGAATGGTGAGT	1302	ACTCACCATTCCCTGCCTGCCCAGCT
39	GAGCTGGGCAGGCAGGAATGGTGAG	1303	CTCACCATTCCCTGCCTGCCCAGCTC
40	AGAGCTGGGCAGGCAGGAATGGTGA	1304	TCACCATTCCCTGCCTGCCCAGCTCT
41	AAGAGCTGGGCAGGCAGGAATGGTG	1305	CACCATTCCCTGCCTGCCCAGCTCTT
42	GAAGAGCTGGGCAGGCAGGAATGGT	1306	ACCATTCCCTGCCTGCCCAGCTCTTC
43	GGAAGAGCTGGGCAGGCAGGAATGG	1307	CCATTCCCTGCCTGCCCAGCTCTTCC
44	AGGAAGAGCTGGGCAGGCAGGAATG	1308	CATTCCCTGCCTGCCCAGCTCTTCCT
45	GAGGAAGAGCTGGGCAGGCAGGAAT	1309	ATTCCTGCCTGCCCAGCTCTTCCTC
46	AGAGGAAGAGCTGGGCAGGCAGGAA	1310	TTCCTGCCTGCCCAGCTCTTCCTCT
47	AAGAGGAAGAGCTGGGCAGGCAGGA	1311	TCCTGCCTGCCCAGCTCTTCCTCTT
48	AAAGAGGAAGAGCTGGGCAGGCAGG	1312	CCTGCCTGCCCAGCTCTTCCTCTTT
49	GAAAGAGGAAGAGCTGGGCAGGCAG	1313	CTGCCTGCCCAGCTCTTCCTCTTTC
50	AGAAAGAGGAAGAGCTGGGCAGGCA	1314	TGCCTGCCCAGCTCTTCCTCTTTCT
51	CAGAAAGAGGAAGAGCTGGGCAGGC	1315	GCCTGCCCAGCTCTTCCTCTTTCTG
52	CCAGAAAGAGGAAGAGCTGGGCAGG	1316	CCTGCCCAGCTCTTCCTCTTTCTGG
53	GCCAGAAAGAGGAAGAGCTGGGCAG	1317	CTGCCCAGCTCTTCCTCTTTCTGGC
54	GGCCAGAAAGAGGAAGAGCTGGGCA	1318	TGCCCAGCTCTTCCTCTTTCTGGCC
55	TGGCCAGAAAGAGGAAGAGCTGGGC	1319	GCCCAGCTCTTCCTCTTTCTGGCCA
56	GTGGCCAGAAAGAGGAAGAGCTGGG	1320	CCCAGCTCTTCCTCTTTCTGGCCAC
57	TGTGGCCAGAAAGAGGAAGAGCTGG	1321	CCAGCTCTTCCTCTTTCTGGCCACA
58	GTGTGGCCAGAAAGAGGAAGAGCTG	1322	CAGCTCTTCCTCTTTCTGGCCACAC
59	GGTGTGGCCAGAAAGAGGAAGAGCT	1323	AGCTCTTCCTCTTTCTGGCCACACC

60	TGGTGTGGCCAGAAAGAGGAAGAGC	1324	GCTCTTCCTCTTTCTGGCCACACCA
61	ATGGTGTGGCCAGAAAGAGGAAGAG	1325	CTCTTCCTCTTTCTGGCCACACCAT
62	GATGGTGTGGCCAGAAAGAGGAAGA	1326	TCTTCCTCTTTCTGGCCACACCATC
63	GGATGGTGTGGCCAGAAAGAGGAAG	1327	CTTCCTCTTTCTGGCCACACCATCC
64	TGGATGGTGTGGCCAGAAAGAGGAA	1328	TTCTCTTTCTGGCCACACCATCCA
65	GTGGATGGTGTGGCCAGAAAGAGGA	1329	TCCTCTTTCTGGCCACACCATCCAC
66	TGTGGATGGTGTGGCCAGAAAGAGG	1330	CCTCTTTCTGGCCACACCATCCACA
67	GTGTGGATGGTGTGGCCAGAAAGAG	1331	CTCTTTCTGGCCACACCATCCACAC
68	AGTGTGGATGGTGTGGCCAGAAAGA	1332	TCTTTCTGGCCACACCATCCACACT
69	GAGTGTGGATGGTGTGGCCAGAAAG	1333	CTTTCTGGCCACACCATCCACACTC
70	AGAGTGTGGATGGTGTGGCCAGAAA	1334	TTTCTGGCCACACCATCCACACTCT
71	GAGAGTGTGGATGGTGTGGCCAGAA	1335	TTCTGGCCACACCATCCACACTCTC
72	GGAGAGTGTGGATGGTGTGGCCAGA	1336	TCTGGCCACACCATCCACACTCTCC
73	AGGAGAGTGTGGATGGTGTGGCCAG	1337	CTGGCCACACCATCCACACTCTCCT
74	CAGGAGAGTGTGGATGGTGTGGCCA	1338	TGGCCACACCATCCACACTCTCCTG
75	CCAGGAGAGTGTGGATGGTGTGGCC	1339	GGCCACACCATCCACACTCTCCTGG
76	GCCAGGAGAGTGTGGATGGTGTGGC	1340	GCCACACCATCCACACTCTCCTGGC
77	GGCCAGGAGAGTGTGGATGGTGTGG	1341	CCACACCATCCACACTCTCCTGGCC
78	GGGCCAGGAGAGTGTGGATGGTGTG	1342	CACACCATCCACACTCTCCTGGCCC
79	AGGGCCAGGAGAGTGTGGATGGTGT	1343	ACACCATCCACACTCTCCTGGCCCT
80	GAGGGCCAGGAGAGTGTGGATGGTG	1344	CACCATCCACACTCTCCTGGCCCTC
81	AGAGGGCCAGGAGAGTGTGGATGGT	1345	ACCATCCACACTCTCCTGGCCCTCT
82	CAGAGGGCCAGGAGAGTGTGGATGG	1346	CCATCCACACTCTCCTGGCCCTCTG
83	TCAGAGGGCCAGGAGAGTGTGGATG	1347	CATCCACACTCTCCTGGCCCTCTGA
84	CTCAGAGGGCCAGGAGAGTGTGGAT	1348	ATCCACACTCTCCTGGCCCTCTGAG
85	TCTCAGAGGGCCAGGAGAGTGTGGA	1349	TCCACACTCTCCTGGCCCTCTGAGA
86	GTCTCAGAGGGCCAGGAGAGTGTGG	1350	CCACACTCTCCTGGCCCTCTGAGAC
87	AGTCTCAGAGGGCCAGGAGAGTGTG	1351	CACACTCTCCTGGCCCTCTGAGACT
88	CAGTCTCAGAGGGCCAGGAGAGTGT	1352	ACACTCTCCTGGCCCTCTGAGACTG
89	GCAGTCTCAGAGGGCCAGGAGAGTG	1353	CACTCTCCTGGCCCTCTGAGACTGC
90	GGCAGTCTCAGAGGGCCAGGAGAGT	1354	ACTCTCCTGGCCCTCTGAGACTGCC
91	GGGCAGTCTCAGAGGGCCAGGAGAG	1355	CTCTCCTGGCCCTCTGAGACTGCCC
92	CGGGCAGTCTCAGAGGGCCAGGAGA	1356	TCTCCTGGCCCTCTGAGACTGCCCCG
93	GCGGGCAGTCTCAGAGGGCCAGGAG	1357	CTCCTGGCCCTCTGAGACTGCCCCG
94	GGCGGGCAGTCTCAGAGGGCCAGGA	1358	TCCTGGCCCTCTGAGACTGCCCCGCC
95	TGGCGGGCAGTCTCAGAGGGCCAGG	1359	CCTGGCCCTCTGAGACTGCCCCGCCA
96	ATGGCGGGCAGTCTCAGAGGGCCAG	1360	CTGGCCCTCTGAGACTGCCCCGCCAT
97	CATGGCGGGCAGTCTCAGAGGGCCA	1361	TGGCCCTCTGAGACTGCCCCGCCATG
98	GCATGGCGGGCAGTCTCAGAGGGCC	1362	GGCCCTCTGAGACTGCCCCGCCATGC
99	GGCATGGCGGGCAGTCTCAGAGGGC	1363	GCCCTCTGAGACTGCCCCGCCATGCC
100	TGGCATGGCGGGCAGTCTCAGAGGG	1364	CCCTCTGAGACTGCCCCGCCATGCCA
101	ATGGCATGGCGGGCAGTCTCAGAGG	1365	CCTCTGAGACTGCCCCGCCATGCCAT
102	AATGGCATGGCGGGCAGTCTCAGAG	1366	CTCTGAGACTGCCCCGCCATGCCATT

103	GAATGGCATGGCGGGCAGTCTCAGA	1367	TCTGAGACTGCCCCGCCATGCCATTCC
104	GGAATGGCATGGCGGGCAGTCTCAG	1368	CTGAGACTGCCCCGCCATGCCATTCC
105	GGGAATGGCATGGCGGGCAGTCTCA	1369	TGAGACTGCCCCGCCATGCCATTCCC
106	AGGGAATGGCATGGCGGGCAGTCTC	1370	GAGACTGCCCCGCCATGCCATTCCCT
107	AAGGGAATGGCATGGCGGGCAGTCT	1371	AGACTGCCCCGCCATGCCATTCCCTT
108	AAAGGGAATGGCATGGCGGGCAGTC	1372	GACTGCCCCGCCATGCCATTCCCTTT
109	TAAAGGGAATGGCATGGCGGGCAGT	1373	ACTGCCCCGCCATGCCATTCCCTTTA
110	GTAAAGGGAATGGCATGGCGGGCAG	1374	CTGCCCCGCCATGCCATTCCCTTTAC
111	GGTAAAGGGAATGGCATGGCGGGCA	1375	TGCCCCGCCATGCCATTCCCTTTACC
112	AGGTAAAGGGAATGGCATGGCGGGC	1376	GCCCCGCCATGCCATTCCCTTTACCT
113	CAGGTAAAGGGAATGGCATGGCGGG	1377	CCCGGCCATGCCATTCCCTTTACCTG
114	CCAGGTAAAGGGAATGGCATGGCGG	1378	CCGCCATGCCATTCCCTTTACCTGG
115	TCCAGGTAAAGGGAATGGCATGGCG	1379	CGCCATGCCATTCCCTTTACCTGGA
116	TTCCAGGTAAAGGGAATGGCATGGC	1380	GCCATGCCATTCCCTTTACCTGGAA
117	TTTCCAGGTAAAGGGAATGGCATGG	1381	CCATGCCATTCCCTTTACCTGGAAA
118	TTTTCCAGGTAAAGGGAATGGCATG	1382	CATGCCATTCCCTTTACCTGGAAAA
119	GTTTTCCAGGTAAAGGGAATGGCAT	1383	ATGCCATTCCCTTTACCTGGAAAAC
120	AGTTTTCCAGGTAAAGGGAATGGCA	1384	TGCCATTCCCTTTACCTGGAAAAC
121	GAGTTTTCCAGGTAAAGGGAATGGC	1385	GCCATTCCCTTTACCTGGAAAAC
122	GGAGTTTTCCAGGTAAAGGGAATGG	1386	CCATTCCCTTTACCTGGAAAAC
123	AGGAGTTTTCCAGGTAAAGGGAATG	1387	CATTCCCTTTACCTGGAAAAC
124	GAGGAGTTTTCCAGGTAAAGGGAAT	1388	ATTCCCTTTACCTGGAAAAC
125	GGAGGAGTTTTCCAGGTAAAGGGAA	1389	TTCCCTTTACCTGGAAAAC
126	GGGAGGAGTTTTCCAGGTAAAGGGA	1390	TCCCTTTACCTGGAAAAC
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128	TAGGGAGGAGTTTTCCAGGTAAAGG	1392	CCTTTACCTGGAAAAC
129	ATAGGGAGGAGTTTTCCAGGTAAAG	1393	CTTTACCTGGAAAAC
130	GATAGGGAGGAGTTTTCCAGGTAAA	1394	TTTACCTGGAAAAC
131	GGATAGGGAGGAGTTTTCCAGGTAA	1395	TTACCTGGAAAAC
132	TGGATAGGGAGGAGTTTTCCAGGTAA	1396	TACCTGGAAAAC
133	ATGGATAGGGAGGAGTTTTCCAGGT	1397	ACCTGGAAAAC
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135	TGATGGATAGGGAGGAGTTTTCCAG	1399	CTGGAAAAC
136	TTGATGGATAGGGAGGAGTTTTCCA	1400	TGGAAAAC
137	TTTGATGGATAGGGAGGAGTTTTCC	1401	GGAAAAC
138	CTTTGATGGATAGGGAGGAGTTTTC	1402	GAAAAC
139	ACTTTGATGGATAGGGAGGAGTTTT	1403	AAAAC
140	GACTTTGATGGATAGGGAGGAGTTT	1404	AAAC
141	GGACTTTGATGGATAGGGAGGAGTT	1405	AACT
142	TGGACTTTGATGGATAGGGAGGAGT	1406	ACT
143	CTGGACTTTGATGGATAGGGAGGAG	1407	CTC
144	TCTGGACTTTGATGGATAGGGAGGA	1408	TCCT
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147	GAATCTGGACTTTGATGGATAGGGA	1411	TCCCTATCCATCAAAGTCCAGATTC
148	TGAATCTGGACTTTGATGGATAGGG	1412	CCCTATCCATCAAAGTCCAGATTCA
149	CTGAATCTGGACTTTGATGGATAGG	1413	CCTATCCATCAAAGTCCAGATTCAG
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152	ACCCTGAATCTGGACTTTGATGGAT	1416	ATCCATCAAAGTCCAGATTCAGGGT
153	GACCCTGAATCTGGACTTTGATGGGA	1417	TCCATCAAAGTCCAGATTCAGGGTC
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156	GGTGACCCTGAATCTGGACTTTGAT	1420	ATCAAAGTCCAGATTCAGGGTCACC
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158	GAGGTGACCCTGAATCTGGACTTTG	1422	CAAAGTCCAGATTCAGGGTCACCTC
159	GGAGGTGACCCTGAATCTGGACTTT	1423	AAAGTCCAGATTCAGGGTCACCTCC
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161	GAGGAGGTGACCCTGAATCTGGACT	1425	AGTCCAGATTCAGGGTCACCTCCTC
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163	CAGAGGAGGTGACCCTGAATCTGGA	1427	TCCAGATTCAGGGTCACCTCCTCTG
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165	CCCAGAGGAGGTGACCCTGAATCTG	1429	CAGATTCAGGGTCACCTCCTCTGGG
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167	TTCCCAGAGGAGGTGACCCTGAATC	1431	GATTCAGGGTCACCTCCTCTGGGAA
168	CTTCCCAGAGGAGGTGACCCTGAAT	1432	ATTTCAGGGTCACCTCCTCTGGGAAG
169	GCTTCCCAGAGGAGGTGACCCTGAA	1433	TTCAGGGTCACCTCCTCTGGGAAGC
170	GGCTTCCCAGAGGAGGTGACCCTGA	1434	TCAGGGTCACCTCCTCTGGGAAGCC
171	GGGCTTCCCAGAGGAGGTGACCCTG	1435	CAGGGTCACCTCCTCTGGGAAGCCC
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173	GTGGGCTTCCCAGAGGAGGTGACCC	1437	GGGTCACCTCCTCTGGGAAGCCCAC
174	GGTGGGCTTCCCAGAGGAGGTGACC	1438	GGTCACCTCCTCTGGGAAGCCCACC
175	AGGTGGGCTTCCCAGAGGAGGTGAC	1439	GTCACCTCCTCTGGGAAGCCCACCT
176	AAGGTGGGCTTCCCAGAGGAGGTGA	1440	TCACCTCCTCTGGGAAGCCCACCTT
177	CAAGGTGGGCTTCCCAGAGGAGGTG	1441	CACCTCCTCTGGGAAGCCCACCTTG
178	CCAAGGTGGGCTTCCCAGAGGAGGT	1442	ACCTCCTCTGGGAAGCCCACCTTGG
179	GCCAAGGTGGGCTTCCCAGAGGAGG	1443	CCTCCTCTGGGAAGCCCACCTTGGC
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186	CCTGGAGGCCAAGGTGGGCTTCCCA	1450	TGGGAAGCCCACCTTGGCCTCCAGG
187	ACCTGGAGGCCAAGGTGGGCTTCCC	1451	GGAAGCCCACCTTGGCCTCCAGGT
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189	CAACCTGGAGGCCAAGGTGGGCTTC	1453	GAAGCCCACCTTGGCCTCCAGGTTG
190	TCAACCTGGAGGCCAAGGTGGGCTT	1454	AAGCCCACCTTGGCCTCCAGGTTGA
191	GTCAACCTGGAGGCCAAGGTGGGCT	1455	AGCCCACCTTGGCCTCCAGGTTGAC
192	AGTCAACCTGGAGGCCAAGGTGGGC	1456	GCCCACCTTGGCCTCCAGGTTGACT
193	GAGTCAACCTGGAGGCCAAGGTGGG	1457	CCCACCTTGGCCTCCAGGTTGACTC
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196	TGAGAGTCAACCTGGAGGCCAAGGT	1460	ACCTTGGCCTCCAGGTTGACTCTCA
197	GTGAGAGTCAACCTGGAGGCCAAGG	1461	CCTTGGCCTCCAGGTTGACTCTCAC
198	AGTGAGAGTCAACCTGGAGGCCAAG	1462	CTTGGCCTCCAGGTTGACTCTCACT
199	TAGTGAGAGTCAACCTGGAGGCCAA	1463	TTGGCCTCCAGGTTGACTCTCACTA
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201	AGTAGTGAGAGTCAACCTGGAGGCC	1465	GGCCTCCAGGTTGACTCTCACTACT
202	GAGTAGTGAGAGTCAACCTGGAGGC	1466	GCCTCCAGGTTGACTCTCACTACTC
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213	AACCTGATGATGAGTAGTGAGAGTC	1477	GACTCTCACTACTCATCATCAGGTT
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229	CTGGAATAGAAGGAAGAACCTGATG	1493	CATCAGGTTCTTCCTTCTATTCCAG
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232	GGGCTGGAATAGAAGGAAGAACCTG	1496	CAGGTTCTTCCTTCTATTCCAGCCC
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367	CATCTGTTCAATCATTCAATTCATT	1631	GAATGAATGAATGATTGAACAGATG
368	TCATCTGTTCAATCATTCAATTCATT	1632	AATGAATGAATGATTGAACAGATGA
369	TTCATCTGTTCAATCATTCAATTCAT	1633	ATGAATGAATGATTGAACAGATGAA
370	ATTCATCTGTTCAATCATTCAATTC	1634	TGAATGAATGATTGAACAGATGAAT
371	CATTCATCTGTTCAATCATTCAATTC	1635	GAATGAATGATTGAACAGATGAATG
372	TCATTCATCTGTTCAATCATTCAATTC	1636	AATGAATGATTGAACAGATGAATGA
373	CTCATTCATCTGTTCAATCATTCAAT	1637	ATGAATGATTGAACAGATGAATGAG
374	ACTCATTCATCTGTTCAATCATTCA	1638	TGAATGATTGAACAGATGAATGAGT
375	CATCATTCATCTGTTCAATCATTCA	1639	GAATGATTGAACAGATGAATGAGTG
376	TCACTCATTCATCTGTTCAATCATT	1640	AATGATTGAACAGATGAATGAGTGA
377	ATCACTCATTCATCTGTTCAATCAT	1641	ATGATTGAACAGATGAATGAGTGAT
378	CATCACTCATTCATCTGTTCAATCA	1642	TGATTGAACAGATGAATGAGTGATG
379	TCATCACTCATTCATCTGTTCAATC	1643	GATTGAACAGATGAATGAGTGATGA
380	CTCATCACTCATTCATCTGTTCAAT	1644	ATTGAACAGATGAATGAGTGATGAG
381	ACTCATCACTCATTCATCTGTTCAA	1645	TTGAACAGATGAATGAGTGATGAGT
382	TACTCATCACTCATTCATCTGTTCA	1646	TGAACAGATGAATGAGTGATGAGTA
383	CTACTCATCACTCATTCATCTGTTT	1647	GAACAGATGAATGAGTGATGAGTAG
384	TCTACTCATCACTCATTCATCTGTT	1648	AACAGATGAATGAGTGATGAGTAGA
385	ATCTACTCATCACTCATTCATCTGT	1649	ACAGATGAATGAGTGATGAGTAGAT
386	TATCTACTCATCACTCATTCATCTG	1650	CAGATGAATGAGTGATGAGTAGATA
387	TTATCTACTCATCACTCATTCATCT	1651	AGATGAATGAGTGATGAGTAGATAA
388	TTTATCTACTCATCACTCATTCATC	1652	GATGAATGAGTGATGAGTAGATAAAA
389	TTTTATCTACTCATCACTCATTCAT	1653	ATGAATGAGTGATGAGTAGATAAAAA
390	CTTTTATCTACTCATCACTCATTC	1654	TGAATGAGTGATGAGTAGATAAAAAG
391	CCTTTTATCTACTCATCACTCATTC	1655	GAATGAGTGATGAGTAGATAAAAAGG
392	TCCTTTTATCTACTCATCACTCATTC	1656	AATGAGTGATGAGTAGATAAAAAGGA
393	ATCCTTTTATCTACTCATCACTCAT	1657	ATGAGTGATGAGTAGATAAAAAGGAT
394	CATCCTTTTATCTACTCATCACTCA	1658	TGAGTGATGAGTAGATAAAAAGGATG
395	CCATCCTTTTATCTACTCATCACTC	1659	GAGTGATGAGTAGATAAAAAGGATGG
396	TCCATCCTTTTATCTACTCATCACT	1660	AGTGATGAGTAGATAAAAAGGATGGA
397	ATCCATCCTTTTATCTACTCATCAC	1661	GTGATGAGTAGATAAAAAGGATGGAT
398	CATCCATCCTTTTATCTACTCATCA	1662	TGATGAGTAGATAAAAAGGATGGATG
399	CCATCCATCCTTTTATCTACTCATC	1663	GATGAGTAGATAAAAAGGATGGATGG
400	TCCATCCATCCTTTTATCTACTCAT	1664	ATGAGTAGATAAAAAGGATGGATGGA
401	CTCCATCCATCCTTTTATCTACTCA	1665	TGAGTAGATAAAAAGGATGGATGGAG
402	TCTCCATCCATCCTTTTATCTACTC	1666	GAGTAGATAAAAAGGATGGATGGAGA
403	CTCTCCATCCATCCTTTTATCTACT	1667	AGTAGATAAAAAGGATGGATGGAGAG

404	TCTCTCCATCCATCCTTTTATCTAC	1668	GTAGATAAAAGGATGGATGGAGAGA
405	ATCTCTCCATCCATCCTTTTATCTA	1669	TAGATAAAAGGATGGATGGAGAGAT
406	CATCTCTCCATCCATCCTTTTATCT	1670	AGATAAAAGGATGGATGGAGAGATG
407	CCATCTCTCCATCCATCCTTTTATC	1671	GATAAAAGGATGGATGGAGAGATGG
408	CCCATCTCTCCATCCATCCTTTTAT	1672	ATAAAAGGATGGATGGAGAGATGGG
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411	TCACCCATCTCTCCATCCATCCTTT	1675	AAAGGATGGATGGAGAGATGGGTGA
412	CTCACCCATCTCTCCATCCATCCTT	1676	AAGGATGGATGGAGAGATGGGTGAG
413	ACTCACCCATCTCTCCATCCATCCT	1677	AGGATGGATGGAGAGATGGGTGAGT
414	TACTCACCCATCTCTCCATCCATCC	1678	GGATGGATGGAGAGATGGGTGAGTA
415	GTACTCACCCATCTCTCCATCCATC	1679	GATGGATGGAGAGATGGGTGAGTAC
416	TGTACTCACCCATCTCTCCATCCAT	1680	ATGGATGGAGAGATGGGTGAGTACA
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418	CATGTACTCACCCATCTCTCCATCC	1682	GGATGGAGAGATGGGTGAGTACATG
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421	ATCCATGTACTCACCCATCTCTCCA	1685	TGGAGAGATGGGTGAGTACATGGAT
422	CATCCATGTACTCACCCATCTCTCC	1686	GGAGAGATGGGTGAGTACATGGATG
423	CCATCCATGTACTCACCCATCTCTC	1687	GAGAGATGGGTGAGTACATGGATGG
424	TCCATCCATGTACTCACCCATCTCT	1688	AGAGATGGGTGAGTACATGGATGGA
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432	TCCATCTATCCATCCATGTACTCAC	1696	GTGAGTACATGGATGGATAGATGGA
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438	AACTCATCCATCTATCCATCCATGT	1702	ACATGGATGGATAGATGGATGAGTT
439	CAACTCATCCATCTATCCATCCATG	1703	CATGGATGGATAGATGGATGAGTTG
440	CCAACATCCATCTATCCATCCAT	1704	ATGGATGGATAGATGGATGAGTTGG
441	ACCAACTCATCCATCTATCCATCCA	1705	TGGATGGATAGATGGATGAGTTGGT
442	CACCAACTCATCCATCTATCCATCC	1706	GGATGGATAGATGGATGAGTTGGTG
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444	CCCACCAACTCATCCATCTATCCAT	1708	ATGGATAGATGGATGAGTTGGTGGG
445	ACCCACCAACTCATCCATCTATCCA	1709	TGGATAGATGGATGAGTTGGTGGGT
446	TACCCACCAACTCATCCATCTATCC	1710	GGATAGATGGATGAGTTGGTGGGTA

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450	AATCTACCCACCAACTCATCCATCT	1714	AGATGGATGAGTTGGTGGGTAGATT
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452	CGAATCTACCCACCAACTCATCCAT	1716	ATGGATGAGTTGGTGGGTAGATTTCG
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455	CCACGAATCTACCCACCAACTCATC	1719	GATGAGTTGGTGGGTAGATTTCGTGG
456	GCCACGAATCTACCCACCAACTCAT	1720	ATGAGTTGGTGGGTAGATTTCGTGGC
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626	ATCATCTATCCAGCAATCTATCTAT	1890	ATAGATAGATTGCTGGATAGATGAT
627	AATCATCTATCCAGCAATCTATCTA	1891	TAGATAGATTGCTGGATAGATGATT
628	CAATCATCTATCCAGCAATCTATCT	1892	AGATAGATTGCTGGATAGATGATTG
629	TCAATCATCTATCCAGCAATCTATC	1893	GATAGATTGCTGGATAGATGATTGA
630	GTCAATCATCTATCCAGCAATCTAT	1894	ATAGATTGCTGGATAGATGATTGAC
631	AGTCAATCATCTATCCAGCAATCTA	1895	TAGATTGCTGGATAGATGATTGACT
632	CAGTCAATCATCTATCCAGCAATCT	1896	AGATTGCTGGATAGATGATTGACTG
633	CCAGTCAATCATCTATCCAGCAATC	1897	GATTGCTGGATAGATGATTGACTGG
634	CCCAGTCAATCATCTATCCAGCAAT	1898	ATTGCTGGATAGATGATTGACTGGG
635	ACCCAGTCAATCATCTATCCAGCAA	1899	TTGCTGGATAGATGATTGACTGGGT
636	CACCCAGTCAATCATCTATCCAGCA	1900	TGCTGGATAGATGATTGACTGGGTG
637	CCACCCAGTCAATCATCTATCCAGC	1901	GCTGGATAGATGATTGACTGGGTGG
638	TCCACCCAGTCAATCATCTATCCAG	1902	CTGGATAGATGATTGACTGGGTGGA
639	ATCCACCCAGTCAATCATCTATCCA	1903	TGGATAGATGATTGACTGGGTGGAT
640	TATCCACCCAGTCAATCATCTATCC	1904	GGATAGATGATTGACTGGGTGGATA
641	CTATCCACCCAGTCAATCATCTATC	1905	GATAGATGATTGACTGGGTGGATAG
642	TCTATCCACCCAGTCAATCATCTAT	1906	ATAGATGATTGACTGGGTGGATAGA
643	ATCTATCCACCCAGTCAATCATCTA	1907	TAGATGATTGACTGGGTGGATAGAT
644	CATCTATCCACCCAGTCAATCATCT	1908	AGATGATTGACTGGGTGGATAGATG
645	TCATCTATCCACCCAGTCAATCATC	1909	GATGATTGACTGGGTGGATAGATGA
646	TTCATCTATCCACCCAGTCAATCAT	1910	ATGATTGACTGGGTGGATAGATGAA
647	TTTCATCTATCCACCCAGTCAATCA	1911	TGATTGACTGGGTGGATAGATGAAA
648	ATTTTCATCTATCCACCCAGTCAATC	1912	GATTGACTGGGTGGATAGATGAAAT
649	CATTTTCATCTATCCACCCAGTCAAT	1913	ATTGACTGGGTGGATAGATGAAATG
650	ACATTTTCATCTATCCACCCAGTCAA	1914	TTGACTGGGTGGATAGATGAAATGT
651	AACATTTTCATCTATCCACCCAGTCA	1915	TGACTGGGTGGATAGATGAAATGTT
652	CAACATTTTCATCTATCCACCCAGTC	1916	GACTGGGTGGATAGATGAAATGTTG
653	CCAACATTTTCATCTATCCACCCAGT	1917	ACTGGGTGGATAGATGAAATGTTGG
654	TCCAACATTTTCATCTATCCACCCAG	1918	CTGGGTGGATAGATGAAATGTTGGA
655	ATCCAACATTTTCATCTATCCACCCA	1919	TGGGTGGATAGATGAAATGTTGGAT
656	CATCCAACATTTTCATCTATCCACCC	1920	GGGTGGATAGATGAAATGTTGGATG
657	TCATCCAACATTTTCATCTATCCACC	1921	GGTGGATAGATGAAATGTTGGATGA
658	CTCATCCAACATTTTCATCTATCCAC	1922	GTGGATAGATGAAATGTTGGATGAG
659	GCTCATCCAACATTTTCATCTATCCA	1923	TGGATAGATGAAATGTTGGATGAGC
660	TGCTCATCCAACATTTTCATCTATCC	1924	GGATAGATGAAATGTTGGATGAGCA
661	CTGCTCATCCAACATTTTCATCTATC	1925	GATAGATGAAATGTTGGATGAGCAG

662	TCTGCTCATCCAACATTTTCATCTAT	1926	ATAGATGAAATGTTGGATGAGCAGA
663	ATCTGCTCATCCAACATTTTCATCTA	1927	TAGATGAAATGTTGGATGAGCAGAT
664	AATCTGCTCATCCAACATTTTCATCT	1928	AGATGAAATGTTGGATGAGCAGATT
665	TAATCTGCTCATCCAACATTTTCATC	1929	GATGAAATGTTGGATGAGCAGATTA
666	TTAATCTGCTCATCCAACATTTTCAT	1930	ATGAAATGTTGGATGAGCAGATTAA
667	CTTAATCTGCTCATCCAACATTTTCA	1931	TGAAATGTTGGATGAGCAGATTAAAG
668	ACTTAATCTGCTCATCCAACATTTTC	1932	GAAATGTTGGATGAGCAGATTAAAGT
669	AACTTAATCTGCTCATCCAACATTTT	1933	AAATGTTGGATGAGCAGATTAAAGTT
670	CAACTTAATCTGCTCATCCAACATT	1934	AATGTTGGATGAGCAGATTAAAGTTG
671	ACAACCTTAATCTGCTCATCCAACAT	1935	ATGTTGGATGAGCAGATTAAAGTTGT
672	TACAACCTTAATCTGCTCATCCAACA	1936	TGTTGGATGAGCAGATTAAAGTTGTA
673	ATACAACCTTAATCTGCTCATCCAAC	1937	GTTGGATGAGCAGATTAAAGTTGTAT
674	AATACAACCTTAATCTGCTCATCCAA	1938	TTGGATGAGCAGATTAAAGTTGTATT
675	CAATACAACCTTAATCTGCTCATCCA	1939	TGGATGAGCAGATTAAAGTTGTATTG
676	CCAATACAACCTTAATCTGCTCATCC	1940	GGATGAGCAGATTAAAGTTGTATTGG
677	TCCAATACAACCTTAATCTGCTCATC	1941	GATGAGCAGATTAAAGTTGTATTGGA
678	ATCCAATACAACCTTAATCTGCTCAT	1942	ATGAGCAGATTAAAGTTGTATTGGAT
679	CATCCAATACAACCTTAATCTGCTCA	1943	TGAGCAGATTAAAGTTGTATTGGATG
680	CCATCCAATACAACCTTAATCTGCTC	1944	GAGCAGATTAAAGTTGTATTGGATGG
681	CCCATCCAATACAACCTTAATCTGCT	1945	AGCAGATTAAAGTTGTATTGGATGGG
682	TCCCATCCAATACAACCTTAATCTGC	1946	GCAGATTAAAGTTGTATTGGATGGGA
683	ATCCCATCCAATACAACCTTAATCTG	1947	CAGATTAAAGTTGTATTGGATGGGAT
684	CATCCCATCCAATACAACCTTAATCT	1948	AGATTAAAGTTGTATTGGATGGGATG
685	CCATCCCATCCAATACAACCTTAATC	1949	GATTAAAGTTGTATTGGATGGGATGG
686	TCCATCCCATCCAATACAACCTTAAT	1950	ATTAAGTTGTATTGGATGGGATGGA
687	ATCCATCCCATCCAATACAACCTTAA	1951	TTAAGTTGTATTGGATGGGATGGAT
688	CATCCATCCCATCCAATACAACCTTA	1952	TAAGTTGTATTGGATGGGATGGATG
689	CCATCCATCCCATCCAATACAACCTT	1953	AAGTTGTATTGGATGGGATGGATGG
690	TCCATCCATCCCATCCAATACAACCT	1954	AGTTGTATTGGATGGGATGGATGGA
691	TTCCATCCATCCCATCCAATACAAC	1955	GTTGTATTGGATGGGATGGATGGAA
692	CTTCCATCCATCCCATCCAATACAA	1956	TTGTATTGGATGGGATGGATGGAAG
693	ACTTCCATCCATCCCATCCAATACA	1957	TGTATTGGATGGGATGGATGGAAGT
694	CACTTCCATCCATCCCATCCAATAC	1958	GTATTGGATGGGATGGATGGAAGTG
695	ACACTTCCATCCATCCCATCCAATA	1959	TATTGGATGGGATGGATGGAAGTGT
696	CACACTTCCATCCATCCCATCCAAT	1960	ATTGGATGGGATGGATGGAAGTGTG
697	CCACACTTCCATCCATCCCATCCAA	1961	TTGGATGGGATGGATGGAAGTGTGG
698	ACCACACTTCCATCCATCCCATCCA	1962	TGGATGGGATGGATGGAAGTGTGGT
699	AACCACACTTCCATCCATCCCATCC	1963	GGATGGGATGGATGGAAGTGTGGTT
700	CAACCACACTTCCATCCATCCCATC	1964	GATGGGATGGATGGAAGTGTGGTTG
701	TCAACCACACTTCCATCCATCCCAT	1965	ATGGGATGGATGGAAGTGTGGTTGA
702	CTCAACCACACTTCCATCCATCCCA	1966	TGGGATGGATGGAAGTGTGGTTGAG
703	ACTCAACCACACTTCCATCCATCCC	1967	GGGATGGATGGAAGTGTGGTTGAGT
704	AACTCAACCACACTTCCATCCATCC	1968	GGATGGATGGAAGTGTGGTTGAGTT

705	TAACTCAACCACACTTCCATCCATC	1969	GATGGATGGAAGTGTGGTTGAGTTA
706	ATAACTCAACCACACTTCCATCCAT	1970	ATGGATGGAAGTGTGGTTGAGTTAT
707	AATAACTCAACCACACTTCCATCCA	1971	TGGATGGAAGTGTGGTTGAGTTATT
708	TAATAACTCAACCACACTTCCATCC	1972	GGATGGAAGTGTGGTTGAGTTATTA
709	CTAATAACTCAACCACACTTCCATC	1973	GATGGAAGTGTGGTTGAGTTATTAG
710	TCTAATAACTCAACCACACTTCCAT	1974	ATGGAAGTGTGGTTGAGTTATTAGA
711	TTCTAATAACTCAACCACACTTCCA	1975	TGGAAGTGTGGTTGAGTTATTAGAA
712	CTTCTAATAACTCAACCACACTTCC	1976	GGAAGTGTGGTTGAGTTATTAGAAG
713	CCTTCTAATAACTCAACCACACTTC	1977	GAAGTGTGGTTGAGTTATTAGAAGG
714	TCCTTCTAATAACTCAACCACACTT	1978	AAGTGTGGTTGAGTTATTAGAAGGA
715	TTCTTCTAATAACTCAACCACACT	1979	AGTGTGGTTGAGTTATTAGAAGGAA
716	CTTCTTCTAATAACTCAACCACAC	1980	GTGTGGTTGAGTTATTAGAAGGAAG
717	TCTTCTTCTAATAACTCAACCACA	1981	TGTGGTTGAGTTATTAGAAGGAAGA
718	ATCTTCTTCTAATAACTCAACCAC	1982	GTGGTTGAGTTATTAGAAGGAAGAT
719	AATCTTCTTCTAATAACTCAACCA	1983	TGGTTGAGTTATTAGAAGGAAGATT
720	CAATCTTCTTCTAATAACTCAACC	1984	GGTTGAGTTATTAGAAGGAAGATTG
721	TCAATCTTCTTCTAATAACTCAAC	1985	GTTGAGTTATTAGAAGGAAGATTGA
722	CTCAATCTTCTTCTAATAACTCAA	1986	TTGAGTTATTAGAAGGAAGATTGAG
723	ACTCAATCTTCTTCTAATAACTCA	1987	TGAGTTATTAGAAGGAAGATTGAGT
724	TACTCAATCTTCTTCTAATAACTC	1988	GAGTTATTAGAAGGAAGATTGAGTA
725	CTACTCAATCTTCTTCTAATAACT	1989	AGTTATTAGAAGGAAGATTGAGTAG
726	TCTACTCAATCTTCTTCTAATAAC	1990	GTTATTAGAAGGAAGATTGAGTAGA
727	ATCTACTCAATCTTCTTCTAATAA	1991	TTATTAGAAGGAAGATTGAGTAGAT
728	TATCTACTCAATCTTCTTCTAATA	1992	TATTAGAAGGAAGATTGAGTAGATA
729	CTATCTACTCAATCTTCTTCTAAT	1993	ATTAGAAGGAAGATTGAGTAGATAG
730	CCTATCTACTCAATCTTCTTCTAA	1994	TTAGAAGGAAGATTGAGTAGATAGG
731	ACCTATCTACTCAATCTTCTTCTA	1995	TAGAAGGAAGATTGAGTAGATAGGT
732	CACCTATCTACTCAATCTTCTTCT	1996	AGAAGGAAGATTGAGTAGATAGGTG
733	TCACCTATCTACTCAATCTTCTTCT	1997	GAAGGAAGATTGAGTAGATAGGTGA
734	TTACCTATCTACTCAATCTTCTTCT	1998	AAGGAAGATTGAGTAGATAGGTGAA
735	ATTCACCTATCTACTCAATCTTCTT	1999	AGGAAGATTGAGTAGATAGGTGAAT
736	AATTCACCTATCTACTCAATCTTCT	2000	GGAAGATTGAGTAGATAGGTGAATT
737	AAATTCACCTATCTACTCAATCTTCT	2001	GAAGATTGAGTAGATAGGTGAATTT
738	CAAATTCACCTATCTACTCAATCTT	2002	AAGATTGAGTAGATAGGTGAATTTG
739	ACAAATTCACCTATCTACTCAATCT	2003	AGATTGAGTAGATAGGTGAATTTGT
740	AACAAATTCACCTATCTACTCAATC	2004	GATTGAGTAGATAGGTGAATTTGTT
741	CAACAAATTCACCTATCTACTCAAT	2005	ATTGAGTAGATAGGTGAATTTGTTG
742	TCAACAAATTCACCTATCTACTCAA	2006	TTGAGTAGATAGGTGAATTTGTTGA
743	ATCAACAAATTCACCTATCTACTCA	2007	TGAGTAGATAGGTGAATTTGTTGAT
744	TATCAACAAATTCACCTATCTACTC	2008	GAGTAGATAGGTGAATTTGTTGATA
745	CTATCAACAAATTCACCTATCTACT	2009	AGTAGATAGGTGAATTTGTTGATAG
746	ACTATCAACAAATTCACCTATCTAC	2010	GTAGATAGGTGAATTTGTTGATAGT
747	GACTATCAACAAATTCACCTATCTA	2011	TAGATAGGTGAATTTGTTGATAGTC

748	TGACTATCAACAAATTCACCTATCT	2012	AGATAGGTGAATTTGTTGATAGTCA
749	CTGACTATCAACAAATTCACCTATC	2013	GATAGGTGAATTTGTTGATAGTCAG
750	TCTGACTATCAACAAATTCACCTAT	2014	ATAGGTGAATTTGTTGATAGTCAGA
751	ATCTGACTATCAACAAATTCACCTA	2015	TAGGTGAATTTGTTGATAGTCAGAT
752	CATCTGACTATCAACAAATTCACCT	2016	AGGTGAATTTGTTGATAGTCAGATG
753	CCATCTGACTATCAACAAATTCACC	2017	GGTGAATTTGTTGATAGTCAGATGG
754	CCCATCTGACTATCAACAAATTCAC	2018	GTGAATTTGTTGATAGTCAGATGGG
755	ACCCATCTGACTATCAACAAATTC	2019	TGAATTTGTTGATAGTCAGATGGGT
756	TACCCATCTGACTATCAACAAATTC	2020	GAATTTGTTGATAGTCAGATGGGTA
757	CTACCCATCTGACTATCAACAAAT	2021	AATTTGTTGATAGTCAGATGGGTAG
758	TCTACCCATCTGACTATCAACAAAT	2022	ATTTGTTGATAGTCAGATGGGTAGA
759	ATCTACCCATCTGACTATCAACAAA	2023	TTTGTTGATAGTCAGATGGGTAGAT
760	TATCTACCCATCTGACTATCAACAA	2024	TTGTTGATAGTCAGATGGGTAGATA
761	CTATCTACCCATCTGACTATCAACA	2025	TGTTGATAGTCAGATGGGTAGATAG
762	CCTATCTACCCATCTGACTATCAAC	2026	GTTGATAGTCAGATGGGTAGATAGG
763	ACCTATCTACCCATCTGACTATCAA	2027	TTGATAGTCAGATGGGTAGATAGGT
764	TACCTATCTACCCATCTGACTATCA	2028	TGATAGTCAGATGGGTAGATAGGTA
765	CTACCTATCTACCCATCTGACTATC	2029	GATAGTCAGATGGGTAGATAGGTAG
766	TCTACCTATCTACCCATCTGACTAT	2030	ATAGTCAGATGGGTAGATAGGTAGA
767	ATCTACCTATCTACCCATCTGACTA	2031	TAGTCAGATGGGTAGATAGGTAGAT
768	CATCTACCTATCTACCCATCTGACT	2032	AGTCAGATGGGTAGATAGGTAGATG
769	CCATCTACCTATCTACCCATCTGAC	2033	GTCAGATGGGTAGATAGGTAGATGG
770	TCCATCTACCTATCTACCCATCTGA	2034	TCAGATGGGTAGATAGGTAGATGGA
771	ATCCATCTACCTATCTACCCATCTG	2035	CAGATGGGTAGATAGGTAGATGGAT
772	CATCCATCTACCTATCTACCCATCT	2036	AGATGGGTAGATAGGTAGATGGATG
773	CCATCCATCTACCTATCTACCCATC	2037	GATGGGTAGATAGGTAGATGGATGG
774	TCCATCCATCTACCTATCTACCCAT	2038	ATGGGTAGATAGGTAGATGGATGGA
775	ATCCATCCATCTACCTATCTACCCA	2039	TGGGTAGATAGGTAGATGGATGGAT
776	CATCCATCCATCTACCTATCTACCC	2040	GGGTAGATAGGTAGATGGATGGATG
777	CCATCCATCCATCTACCTATCTACC	2041	GGTAGATAGGTAGATGGATGGATGG
778	TCCATCCATCCATCTACCTATCTAC	2042	GTAGATAGGTAGATGGATGGATGGA
779	ATCCATCCATCCATCTACCTATCTA	2043	TAGATAGGTAGATGGATGGATGGAT
780	CATCCATCCATCCATCTACCTATCT	2044	AGATAGGTAGATGGATGGATGGATG
781	CCATCCATCCATCCATCTACCTATC	2045	GATAGGTAGATGGATGGATGGATGG
782	TCCATCCATCCATCCATCTACCTAT	2046	ATAGGTAGATGGATGGATGGATGGA
783	ATCCATCCATCCATCCATCTACCTA	2047	TAGGTAGATGGATGGATGGATGGAT
784	CATCCATCCATCCATCCATCTACCT	2048	AGGTAGATGGATGGATGGATGGATG
785	CCATCCATCCATCCATCCATCTACC	2049	GGTAGATGGATGGATGGATGGATGG
786	TCCATCCATCCATCCATCCATCTAC	2050	GTAGATGGATGGATGGATGGATGGA
787	ATCCATCCATCCATCCATCCATCTA	2051	TAGATGGATGGATGGATGGATGGAT
788	CATCCATCCATCCATCCATCCATCT	2052	AGATGGATGGATGGATGGATGGATG
789	ACATCCATCCATCCATCCATCCATC	2053	GATGGATGGATGGATGGATGGATGT
790	TACATCCATCCATCCATCCATCCAT	2054	ATGGATGGATGGATGGATGGATGTA

791	ATACATCCATCCATCCATCCATCCA	2055	TGGATGGATGGATGGATGGATGTAT
792	TATACATCCATCCATCCATCCATCC	2056	GGATGGATGGATGGATGGATGTATA
793	CTATACATCCATCCATCCATCCATC	2057	GATGGATGGATGGATGGATGTATAG
794	CCTATACATCCATCCATCCATCCAT	2058	ATGGATGGATGGATGGATGTATAGG
795	GCCTATACATCCATCCATCCATCCA	2059	TGGATGGATGGATGGATGTATAGGC
796	TGCCTATACATCCATCCATCCATCC	2060	GGATGGATGGATGGATGTATAGGCA
797	CTGCCTATACATCCATCCATCCATC	2061	GATGGATGGATGGATGTATAGGCAG
798	TCTGCCTATACATCCATCCATCCAT	2062	ATGGATGGATGGATGTATAGGCAGA
799	ATCTGCCTATACATCCATCCATCCA	2063	TGGATGGATGGATGTATAGGCAGAT
800	CATCTGCCTATACATCCATCCATCC	2064	GGATGGATGGATGTATAGGCAGATG
801	CCATCTGCCTATACATCCATCCATC	2065	GATGGATGGATGTATAGGCAGATGG
802	TCCATCTGCCTATACATCCATCCAT	2066	ATGGATGGATGTATAGGCAGATGGA
803	GTCCATCTGCCTATACATCCATCCA	2067	TGGATGGATGTATAGGCAGATGGAC
804	TGTCCATCTGCCTATACATCCATCC	2068	GGATGGATGTATAGGCAGATGGACA
805	TTGTCCATCTGCCTATACATCCATC	2069	GATGGATGTATAGGCAGATGGACAA
806	TTTGTCCATCTGCCTATACATCCAT	2070	ATGGATGTATAGGCAGATGGACAAA
807	ATTTGTCCATCTGCCTATACATCCA	2071	TGGATGTATAGGCAGATGGACAAAT
808	CATTTGTCCATCTGCCTATACATCC	2072	GGATGTATAGGCAGATGGACAAATG
809	CCATTTGTCCATCTGCCTATACATC	2073	GATGTATAGGCAGATGGACAAATGG
810	TCCATTTGTCCATCTGCCTATACAT	2074	ATGTATAGGCAGATGGACAAATGGA
811	ATCCATTTGTCCATCTGCCTATACA	2075	TGTATAGGCAGATGGACAAATGGAT
812	CATCCATTTGTCCATCTGCCTATAC	2076	GTATAGGCAGATGGACAAATGGATG
813	TCATCCATTTGTCCATCTGCCTATA	2077	TATAGGCAGATGGACAAATGGATGA
814	TTCATCCATTTGTCCATCTGCCTAT	2078	ATAGGCAGATGGACAAATGGATGAA
815	ATTCATCCATTTGTCCATCTGCCTA	2079	TAGGCAGATGGACAAATGGATGAAT
816	CATTCATCCATTTGTCCATCTGCCT	2080	AGGCAGATGGACAAATGGATGAATG
817	CCATTCATCCATTTGTCCATCTGCC	2081	GGCAGATGGACAAATGGATGAATGG
818	CCCATTCATCCATTTGTCCATCTGC	2082	GCAGATGGACAAATGGATGAATGGG
819	ACCCATTCATCCATTTGTCCATCTG	2083	CAGATGGACAAATGGATGAATGGGT
820	CACCCATTCATCCATTTGTCCATCT	2084	AGATGGACAAATGGATGAATGGGTG
821	CCACCCATTCATCCATTTGTCCATC	2085	GATGGACAAATGGATGAATGGGTGG
822	CCCACCCATTCATCCATTTGTCCAT	2086	ATGGACAAATGGATGAATGGGTGGG
823	ACCCACCCATTCATCCATTTGTCCA	2087	TGGACAAATGGATGAATGGGTGGGT
824	CACCCACCCATTCATCCATTTGTCC	2088	GGACAAATGGATGAATGGGTGGGTG
825	CCACCCACCCATTCATCCATTTGTC	2089	GACAAATGGATGAATGGGTGGGTGG
826	TCCACCCACCCATTCATCCATTTGT	2090	ACAAATGGATGAATGGGTGGGTGGA
827	ATCCACCCACCCATTCATCCATTTG	2091	CAAATGGATGAATGGGTGGGTGGAT
828	CATCCACCCACCCATTCATCCATTT	2092	AAATGGATGAATGGGTGGGTGGATG
829	TCATCCACCCACCCATTCATCCATT	2093	AATGGATGAATGGGTGGGTGGATGA
830	TTCATCCACCCACCCATTCATCCAT	2094	ATGGATGAATGGGTGGGTGGATGAA
831	ATTCATCCACCCACCCATTCATCCA	2095	TGGATGAATGGGTGGGTGGATGAAT
832	CATTCATCCACCCACCCATTCATCC	2096	GGATGAATGGGTGGGTGGATGAATG
833	CCATTCATCCACCCACCCATTCATC	2097	GATGAATGGGTGGGTGGATGAATGG

834	TCCATTTCATCCACCCACCCATTCAT	2098	ATGAATGGGTGGGTGGATGAATGGA
835	TTCCATTTCATCCACCCACCCATTCA	2099	TGAATGGGTGGGTGGATGAATGGAA
836	CTTCCATTTCATCCACCCACCCATTC	2100	GAATGGGTGGGTGGATGAATGGAAG
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838	TCCTTCCATTTCATCCACCCACCCAT	2102	ATGGGTGGGTGGATGAATGGAAGGA
839	ATCCTTCCATTTCATCCACCCACCCA	2103	TGGGTGGGTGGATGAATGGAAGGAT
840	CATCCTTCCATTTCATCCACCCACCC	2104	GGGTGGGTGGATGAATGGAAGGATG
841	ACATCCTTCCATTTCATCCACCCACC	2105	GGTGGGTGGATGAATGGAAGGATGT
842	CACATCCTTCCATTTCATCCACCCAC	2106	GTGGGTGGATGAATGGAAGGATGTG
843	ACACATCCTTCCATTTCATCCACCCA	2107	TGGGTGGATGAATGGAAGGATGTGT
844	CACACATCCTTCCATTTCATCCACCC	2108	GGGTGGATGAATGGAAGGATGTGTG
845	CCACACATCCTTCCATTTCATCCACC	2109	GGTGGATGAATGGAAGGATGTGTGG
846	ACCACACATCCTTCCATTTCATCCAC	2110	GTGGATGAATGGAAGGATGTGTGGT
847	AACCACACATCCTTCCATTTCATCCA	2111	TGGATGAATGGAAGGATGTGTGGTT
848	CAACCACACATCCTTCCATTTCATCC	2112	GGATGAATGGAAGGATGTGTGGTTG
849	TCAACCACACATCCTTCCATTTCATC	2113	GATGAATGGAAGGATGTGTGGTTGA
850	TTCAACCACACATCCTTCCATTTCAT	2114	ATGAATGGAAGGATGTGTGGTTGAA
851	GTTCAACCACACATCCTTCCATTTC	2115	TGAATGGAAGGATGTGTGGTTGAAC
852	AGTTCAACCACACATCCTTCCATTTC	2116	GAATGGAAGGATGTGTGGTTGAACT
853	TAGTTCAACCACACATCCTTCCATT	2117	AATGGAAGGATGTGTGGTTGAACTA
854	ATAGTTCAACCACACATCCTTCCAT	2118	ATGGAAGGATGTGTGGTTGAACTAT
855	AATAGTTCAACCACACATCCTTCCA	2119	TGGAAGGATGTGTGGTTGAACTATT
856	CAATAGTTCAACCACACATCCTTCC	2120	GGAAGGATGTGTGGTTGAACTATTG
857	GCAATAGTTCAACCACACATCCTTC	2121	GAAGGATGTGTGGTTGAACTATTGC
858	TGCAATAGTTCAACCACACATCCTT	2122	AAGGATGTGTGGTTGAACTATTGCA
859	TTGCAATAGTTCAACCACACATCCT	2123	AGGATGTGTGGTTGAACTATTGCAA
860	CTTGCAATAGTTCAACCACACATCC	2124	GGATGTGTGGTTGAACTATTGCAAG
861	ACTTGCAATAGTTCAACCACACATC	2125	GATGTGTGGTTGAACTATTGCAAGT
862	TACTTGCAATAGTTCAACCACACAT	2126	ATGTGTGGTTGAACTATTGCAAGTA
863	ATACTTGCAATAGTTCAACCACACA	2127	TGTGTGGTTGAACTATTGCAAGTAT
864	AATACTTGCAATAGTTCAACCACAC	2128	GTGTGGTTGAACTATTGCAAGTATT
865	CAATACTTGCAATAGTTCAACCACA	2129	TGTGGTTGAACTATTGCAAGTATTG
866	TCAATACTTGCAATAGTTCAACCAC	2130	GTGGTTGAACTATTGCAAGTATTGA
867	ATCAATACTTGCAATAGTTCAACCA	2131	TGGTTGAACTATTGCAAGTATTGAT
868	TATCAATACTTGCAATAGTTCAACC	2132	GGTTGAACTATTGCAAGTATTGATA
869	TTATCAATACTTGCAATAGTTCAAC	2133	GTTGAACTATTGCAAGTATTGATAA
870	ATTATCAATACTTGCAATAGTTCAA	2134	TTGAACTATTGCAAGTATTGATAAT
871	AATTATCAATACTTGCAATAGTTCA	2135	TGAACTATTGCAAGTATTGATAATT
872	CAATTATCAATACTTGCAATAGTTC	2136	GAACTATTGCAAGTATTGATAATTG
873	CCAATTATCAATACTTGCAATAGTT	2137	AACTATTGCAAGTATTGATAATTGG
874	CCCAATTATCAATACTTGCAATAGT	2138	ACTATTGCAAGTATTGATAATTGGG
875	ACCCAATTATCAATACTTGCAATAG	2139	CTATTGCAAGTATTGATAATTGGGT
876	AACCCAATTATCAATACTTGCAATA	2140	TATTGCAAGTATTGATAATTGGGTT

877	GAACCCAATTATCAATACTTGCAAT	2141	ATTGCAAGTATTGATAATTGGGTTTC
878	TGAACCCAATTATCAATACTTGCAA	2142	TTGCAAGTATTGATAATTGGGTTTCA
879	ATGAACCCAATTATCAATACTTGCA	2143	TGCAAGTATTGATAATTGGGTTTCAT
880	TATGAACCCAATTATCAATACTTGC	2144	GCAAGTATTGATAATTGGGTTTCATA
881	TTATGAACCCAATTATCAATACTTG	2145	CAAGTATTGATAATTGGGTTTCATAA
882	ATTATGAACCCAATTATCAATACTT	2146	AAGTATTGATAATTGGGTTTCATAAT
883	AATTATGAACCCAATTATCAATACT	2147	AGTATTGATAATTGGGTTTCATAATT
884	AAATTATGAACCCAATTATCAATAC	2148	GTATTGATAATTGGGTTTCATAATTT
885	GAAATTATGAACCCAATTATCAATA	2149	TATTGATAATTGGGTTTCATAATTTCT
886	AGAAATTATGAACCCAATTATCAAT	2150	ATTGATAATTGGGTTTCATAATTTCT
887	CAGAAATTATGAACCCAATTATCAA	2151	TTGATAATTGGGTTTCATAATTTCTG
888	TCAGAAATTATGAACCCAATTATCA	2152	TGATAATTGGGTTTCATAATTTCTGA
889	TTCAGAAATTATGAACCCAATTATC	2153	GATAATTGGGTTTCATAATTTCTGAA
890	ATTCAGAAATTATGAACCCAATTAT	2154	ATAATTGGGTTTCATAATTTCTGAAT
891	TATTCAGAAATTATGAACCCAATTA	2155	TAATTGGGTTTCATAATTTCTGAATA
892	ATATTCAGAAATTATGAACCCAATT	2156	AATTGGGTTTCATAATTTCTGAATAT
893	AATATTCAGAAATTATGAACCCAAT	2157	ATTGGGTTTCATAATTTCTGAATATT
894	AAATATTCAGAAATTATGAACCCAA	2158	TTGGGTTTCATAATTTCTGAATATTT
895	TAAATATTCAGAAATTATGAACCCA	2159	TGGGTTTCATAATTTCTGAATATTTA
896	CTAAATATTCAGAAATTATGAACCC	2160	GGGTTTCATAATTTCTGAATATTTAG
897	TCTAAATATTCAGAAATTATGAACC	2161	GGTTCATAATTTCTGAATATTTAGA
898	ATCTAAATATTCAGAAATTATGAAC	2162	GTTTCATAATTTCTGAATATTTAGAT
899	CATCTAAATATTCAGAAATTATGAA	2163	TTCATAATTTCTGAATATTTAGATG
900	CCATCTAAATATTCAGAAATTATGA	2164	TCATAATTTCTGAATATTTAGATGG
901	TCCATCTAAATATTCAGAAATTATG	2165	CATAATTTCTGAATATTTAGATGGA
902	ATCCATCTAAATATTCAGAAATTAT	2166	ATAATTTCTGAATATTTAGATGGAT
903	CATCCATCTAAATATTCAGAAATTA	2167	TAATTTCTGAATATTTAGATGGATG
904	CCATCCATCTAAATATTCAGAAATT	2168	AATTTCTGAATATTTAGATGGATGG
905	ACCATCCATCTAAATATTCAGAAAT	2169	ATTTCTGAATATTTAGATGGATGGT
906	AACCATCCATCTAAATATTCAGAAA	2170	TTTCTGAATATTTAGATGGATGGTT
907	CAACCATCCATCTAAATATTCAGAA	2171	TTCTGAATATTTAGATGGATGGTTG
908	ACAACCATCCATCTAAATATTCAGA	2172	TCTGAATATTTAGATGGATGGTTGT
909	CACAACCATCCATCTAAATATTCAG	2173	CTGAATATTTAGATGGATGGTTGTG
910	TCACAACCATCCATCTAAATATTCA	2174	TGAATATTTAGATGGATGGTTGTGA
911	CTCACAACCATCCATCTAAATATTC	2175	GAATATTTAGATGGATGGTTGTGAG
912	ACTCACAACCATCCATCTAAATATT	2176	AATATTTAGATGGATGGTTGTGAGT
913	CACTCACAACCATCCATCTAAATAT	2177	ATATTTAGATGGATGGTTGTGAGTG
914	CCACTCACAACCATCCATCTAAATA	2178	TATTTAGATGGATGGTTGTGAGTGG
915	GCCACTCACAACCATCCATCTAAAT	2179	ATTTAGATGGATGGTTGTGAGTGGC
916	AGCCACTCACAACCATCCATCTAAA	2180	TTTAGATGGATGGTTGTGAGTGGCT
917	CAGCCACTCACAACCATCCATCTAA	2181	TTAGATGGATGGTTGTGAGTGGCTG
918	CCAGCCACTCACAACCATCCATCTA	2182	TAGATGGATGGTTGTGAGTGGCTGG
919	ACCAGCCACTCACAACCATCCATCT	2183	AGATGGATGGTTGTGAGTGGCTGGT

920	CACCAGCCACTCACAACCATCCATC	2184	GATGGATGGTTGTGAGTGGCTGGTG
921	CCACCAGCCACTCACAACCATCCAT	2185	ATGGATGGTTGTGAGTGGCTGGTGG
922	TCCACCAGCCACTCACAACCATCCA	2186	TGGATGGTTGTGAGTGGCTGGTGGA
923	GTCCACCAGCCACTCACAACCATCC	2187	GGATGGTTGTGAGTGGCTGGTGGAC
924	TGTCCACCAGCCACTCACAACCATC	2188	GATGGTTGTGAGTGGCTGGTGGACA
925	CTGTCCACCAGCCACTCACAACCAT	2189	ATGGTTGTGAGTGGCTGGTGGACAG
926	TCTGTCCACCAGCCACTCACAACCA	2190	TGGTTGTGAGTGGCTGGTGGACAGA
927	GTCTGTCCACCAGCCACTCACAACC	2191	GGTTGTGAGTGGCTGGTGGACAGAC
928	CGTCTGTCCACCAGCCACTCACAAC	2192	GTTGTGAGTGGCTGGTGGACAGACG
929	TCGTCTGTCCACCAGCCACTCACA	2193	TTGTGAGTGGCTGGTGGACAGACGA
930	TTCGTCTGTCCACCAGCCACTCACA	2194	TGTGAGTGGCTGGTGGACAGACGAA
931	TTTCGTCTGTCCACCAGCCACTCAC	2195	GTGAGTGGCTGGTGGACAGACGAAA
932	TTTTCGTCTGTCCACCAGCCACTCA	2196	TGAGTGGCTGGTGGACAGACGAAAA
933	TTTTTCGTCTGTCCACCAGCCACTC	2197	GAGTGGCTGGTGGACAGACGAAAAA
934	ATTTTTTCGTCTGTCCACCAGCCACT	2198	AGTGGCTGGTGGACAGACGAAAAAAT
935	CATTTTTTCGTCTGTCCACCAGCCAC	2199	GTGGCTGGTGGACAGACGAAAAAATG
936	CCATTTTTTCGTCTGTCCACCAGCCA	2200	TGGCTGGTGGACAGACGAAAAAATGG
937	TCCATTTTTTCGTCTGTCCACCAGCC	2201	GGCTGGTGGACAGACGAAAAAATGGA
938	ATCCATTTTTTCGTCTGTCCACCAGC	2202	GCTGGTGGACAGACGAAAAAATGGAT
939	CATCCATTTTTTCGTCTGTCCACCAG	2203	CTGGTGGACAGACGAAAAAATGGATG
940	CCATCCATTTTTTCGTCTGTCCACCA	2204	TGGTGGACAGACGAAAAAATGGATGG
941	ACCATCCATTTTTTCGTCTGTCCACC	2205	GGTGGACAGACGAAAAAATGGATGGT
942	AACCATCCATTTTTTCGTCTGTCCAC	2206	GTGGACAGACGAAAAAATGGATGGTT
943	CAACCATCCATTTTTTCGTCTGTCCA	2207	TGGACAGACGAAAAAATGGATGGTTG
944	CCAACCATCCATTTTTTCGTCTGTCC	2208	GGACAGACGAAAAAATGGATGGTTGG
945	TCCAACCATCCATTTTTTCGTCTGTCT	2209	GACAGACGAAAAAATGGATGGTTGGA
946	ATCCAACCATCCATTTTTTCGTCTGT	2210	ACAGACGAAAAAATGGATGGTTGGAT
947	TATCCAACCATCCATTTTTTCGTCTG	2211	CAGACGAAAAAATGGATGGTTGGATA
948	TTATCCAACCATCCATTTTTTCGTCT	2212	AGACGAAAAAATGGATGGTTGGATAA
949	TTTATCCAACCATCCATTTTTTCGTCT	2213	GACGAAAAAATGGATGGTTGGATAAA
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952	CAATTTATCCAACCATCCATTTTTTC	2216	GAAAAAATGGATGGTTGGATAAATTG
953	TCAATTTATCCAACCATCCATTTTTT	2217	AAAAAATGGATGGTTGGATAAATTGA
954	ATCAATTTATCCAACCATCCATTTTT	2218	AAAATGGATGGTTGGATAAATTGAT
955	CATCAATTTATCCAACCATCCATTTT	2219	AAATGGATGGTTGGATAAATTGATG
956	CCATCAATTTATCCAACCATCCATT	2220	AATGGATGGTTGGATAAATTGATGG
957	CCCATCAATTTATCCAACCATCCAT	2221	ATGGATGGTTGGATAAATTGATGGG
958	ACCCATCAATTTATCCAACCATCCA	2222	TGGATGGTTGGATAAATTGATGGGT
959	CACCCATCAATTTATCCAACCATCC	2223	GGATGGTTGGATAAATTGATGGGTG
960	CCACCCATCAATTTATCCAACCATC	2224	GATGGTTGGATAAATTGATGGGTGG
961	TCCACCCATCAATTTATCCAACCAT	2225	ATGGTTGGATAAATTGATGGGTGGA
962	ATCCACCCATCAATTTATCCAACCA	2226	TGGTTGGATAAATTGATGGGTGGAT

963	CATCCACCCATCAATTTATCCAACC	2227	GGTTGGATAAAATTGATGGGTGGATG
964	CCATCCACCCATCAATTTATCCAAC	2228	GTTGGATAAAATTGATGGGTGGATGG
965	TCCATCCACCCATCAATTTATCCAA	2229	TTGGATAAAATTGATGGGTGGATGGA
966	ATCCATCCACCCATCAATTTATCCA	2230	TGGATAAAATTGATGGGTGGATGGAT
967	CATCCATCCACCCATCAATTTATCC	2231	GGATAAAATTGATGGGTGGATGGATG
968	CCATCCATCCACCCATCAATTTATC	2232	GATAAAATTGATGGGTGGATGGATGG
969	ACCATCCATCCACCCATCAATTTAT	2233	ATAAAATTGATGGGTGGATGGATGGT
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971	CAACCATCCATCCACCCATCAATTT	2235	AAATTGATGGGTGGATGGATGGTTG
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973	ACCAACCATCCATCCACCCATCAAT	2237	ATTGATGGGTGGATGGATGGTTGGT
974	AACCAACCATCCATCCACCCATCAA	2238	TTGATGGGTGGATGGATGGTTGGTT
975	CAACCAACCATCCATCCACCCATCA	2239	TGATGGGTGGATGGATGGTTGGTTG
976	ACAACCAACCATCCATCCACCCATC	2240	GATGGGTGGATGGATGGTTGGTTGT
977	TACAACCAACCATCCATCCACCCAT	2241	ATGGGTGGATGGATGGTTGGTTGTA
978	ATACAACCAACCATCCATCCACCCA	2242	TGGGTGGATGGATGGTTGGTTGTAT
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980	TCATACAACCAACCATCCATCCACC	2244	GGTGGATGGATGGTTGGTTGTATGA
981	TTCATACAACCAACCATCCATCCAC	2245	GTGGATGGATGGTTGGTTGTATGAA
982	TTTCATACAACCAACCATCCATCCA	2246	TGGATGGATGGTTGGTTGTATGAAA
983	CTTTCATACAACCAACCATCCATCC	2247	GGATGGATGGTTGGTTGTATGAAAG
984	TCTTTCATACAACCAACCATCCATC	2248	GATGGATGGTTGGTTGTATGAAAGA
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986	ATTCTTTCATACAACCAACCATCCA	2250	TGGATGGTTGGTTGTATGAAAGAAT
987	CATTCTTTCATACAACCAACCATCC	2251	GGATGGTTGGTTGTATGAAAGAATG
988	TCATTCTTTCATACAACCAACCATC	2252	GATGGTTGGTTGTATGAAAGAATGA
989	TTCATTCTTTCATACAACCAACCAT	2253	ATGGTTGGTTGTATGAAAGAATGAA
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991	CATTCAATTCTTTCATACAACCAACC	2255	GGTTGGTTGTATGAAAGAATGAATG
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999	TACCCAATCATTCAATTCTTTCATAC	2263	GTATGAAAGAATGAATGATTGGGTA
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1001	CCTACCCAATCATTCAATTCTTTCAT	2265	ATGAAAGAATGAATGATTGGGTAGG
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1003	CACCTACCCAATCATTCAATTCTTTC	2267	GAAAGAATGAATGATTGGGTAGGTG
1004	CCACCTACCCAATCATTCAATTCTTT	2268	AAAGAATGAATGATTGGGTAGGTGG
1005	TCCACCTACCCAATCATTCAATTCTT	2269	AAGAATGAATGATTGGGTAGGTGGA

1006	ATCCACCTACCCAATCATTCAATTCT	2270	AGAATGAATGATTGGGTAGGTGGAT
1007	AATCCACCTACCCAATCATTCAATC	2271	GAATGAATGATTGGGTAGGTGGATT
1008	TAATCCACCTACCCAATCATTCAAT	2272	AATGAATGATTGGGTAGGTGGATTA
1009	TTAATCCACCTACCCAATCATTCAAT	2273	ATGAATGATTGGGTAGGTGGATTAA
1010	CTTAATCCACCTACCCAATCATTCA	2274	TGAATGATTGGGTAGGTGGATTAAAG
1011	ACTTAATCCACCTACCCAATCATTCT	2275	GAATGATTGGGTAGGTGGATTAAAGT
1012	AACTTAATCCACCTACCCAATCATT	2276	AATGATTGGGTAGGTGGATTAAAGTT
1013	CAACTTAATCCACCTACCCAATCAT	2277	ATGATTGGGTAGGTGGATTAAAGTTG
1014	GCAACTTAATCCACCTACCCAATCA	2278	TGATTGGGTAGGTGGATTAAAGTTGC
1015	CGCAACTTAATCCACCTACCCAATC	2279	GATTGGGTAGGTGGATTAAAGTTGCG
1016	CCGCAACTTAATCCACCTACCCAAT	2280	ATTGGGTAGGTGGATTAAAGTTGCGG
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1019	GATCCGCAACTTAATCCACCTACCC	2283	GGGTAGGTGGATTAAAGTTGCGGATC
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1022	ATTGATCCGCAACTTAATCCACCTA	2286	TAGGTGGATTAAAGTTGCGGATCAAT
1023	CATTGATCCGCAACTTAATCCACCT	2287	AGGTGGATTAAAGTTGCGGATCAATG
1024	ACATTGATCCGCAACTTAATCCACC	2288	GGTGGATTAAAGTTGCGGATCAATGT
1025	TACATTGATCCGCAACTTAATCCAC	2289	GTGGATTAAAGTTGCGGATCAATGTA
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1128	CACACACCCACCCATCTAACTACCC	2392	GGGTAGTTAGATGGGTGGGTGTGTG
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1130	TCCACACACCCACCCATCTAACTAC	2394	GTAGTTAGATGGGTGGGTGTGTGGA
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1132	CATCCACACACCCACCCATCTAACT	2396	AGTTAGATGGGTGGGTGTGTGGATG
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1135	ATCCATCCACACACCCACCCATCTA	2399	TAGATGGGTGGGTGTGTGGATGGAT
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1144	TACTCTTTTATCCATCCACACACCC	2408	GGGTGTGTGGATGGATAAAAAGAGTA
1145	CTACTCTTTTATCCATCCACACACC	2409	GGTGTGTGGATGGATAAAAAGAGTAG
1146	TCTACTCTTTTATCCATCCACACAC	2410	GTGTGTGGATGGATAAAAAGAGTAGA
1147	ATCTACTCTTTTATCCATCCACACA	2411	TGTGTGGATGGATAAAAAGAGTAGAT
1148	CATCTACTCTTTTATCCATCCACAC	2412	GTGTGGATGGATAAAAAGAGTAGATG
1149	TCATCTACTCTTTTATCCATCCACA	2413	TGTGGATGGATAAAAAGAGTAGATGA
1150	TTCATCTACTCTTTTATCCATCCAC	2414	GTGGATGGATAAAAAGAGTAGATGAA
1151	ATTCATCTACTCTTTTATCCATCCA	2415	TGGATGGATAAAAAGAGTAGATGAAT
1152	CATTCATCTACTCTTTTATCCATCC	2416	GGATGGATAAAAAGAGTAGATGAATG
1153	TCATTCATCTACTCTTTTATCCATC	2417	GATGGATAAAAAGAGTAGATGAATGA
1154	TTCATTCATCTACTCTTTTATCCAT	2418	ATGGATAAAAAGAGTAGATGAATGAA
1155	ATTCATTCATCTACTCTTTTATCCA	2419	TGGATAAAAAGAGTAGATGAATGAAT
1156	AATTCATTCATCTACTCTTTTATCC	2420	GGATAAAAAGAGTAGATGAATGAATT
1157	TAATTCATTCATCTACTCTTTTATC	2421	GATAAAAAGAGTAGATGAATGAATTA
1158	TTAATTCATTCATCTACTCTTTTAT	2422	ATAAAAAGAGTAGATGAATGAATTAA
1159	ATTAATTCATTCATCTACTCTTTTA	2423	TAAAAGAGTAGATGAATGAATTAAT
1160	CATTAATTCATTCATCTACTCTTTT	2424	AAAAGAGTAGATGAATGAATTAATG
1161	TCATTAATTCATTCATCTACTCTTT	2425	AAAGAGTAGATGAATGAATTAATGA
1162	TTCATTAATTCATTCATCTACTCTT	2426	AAGAGTAGATGAATGAATTAATGAA
1163	ATTCATTAATTCATTCATCTACTCT	2427	AGAGTAGATGAATGAATTAATGAAT
1164	TATTCATTAATTCATTCATCTACTC	2428	GAGTAGATGAATGAATTAATGAATA
1165	TTATTCATTAATTCATTCATCTACT	2429	AGTAGATGAATGAATTAATGAATAA
1166	TTTATTCATTAATTCATTCATCTAC	2430	GTAGATGAATGAATTAATGAATAAA
1167	GTTTATTCATTAATTCATTCATCTA	2431	TAGATGAATGAATTAATGAATAAAC
1168	TGTTTATTCATTAATTCATTCATCT	2432	AGATGAATGAATTAATGAATAAACA
1169	CTGTTTATTCATTAATTCATTCATC	2433	GATGAATGAATTAATGAATAAACAG
1170	CCTGTTTATTCATTAATTCATTCAT	2434	ATGAATGAATTAATGAATAAACAGG
1171	GCCTGTTTATTCATTAATTCATTCA	2435	TGAATGAATTAATGAATAAACAGGC
1172	TGCCTGTTTATTCATTAATTCATT	2436	GAATGAATTAATGAATAAACAGGCA
1173	CTGCCTGTTTATTCATTAATTCATT	2437	AATGAATTAATGAATAAACAGGCAG
1174	TCTGCCTGTTTATTCATTAATTCAT	2438	ATGAATTAATGAATAAACAGGCAGA
1175	ATCTGCCTGTTTATTCATTAATTC	2439	TGAATTAATGAATAAACAGGCAGAT
1176	CATCTGCCTGTTTATTCATTAATTC	2440	GAATTAATGAATAAACAGGCAGATG
1177	CCATCTGCCTGTTTATTCATTAATT	2441	AATTAATGAATAAACAGGCAGATGG

1178	TCCATCTGCCTGTTTATTCATTAAT	2442	ATTAATGAATAAACAGGCAGATGGA
1179	ATCCATCTGCCTGTTTATTCATTAA	2443	TTAATGAATAAACAGGCAGATGGAT
1180	CATCCATCTGCCTGTTTATTCATTA	2444	TAATGAATAAACAGGCAGATGGATG
1181	TCATCCATCTGCCTGTTTATTCATT	2445	AATGAATAAACAGGCAGATGGATGA
1182	ATCATCCATCTGCCTGTTTATTCAT	2446	ATGAATAAACAGGCAGATGGATGAT
1183	CATCATCCATCTGCCTGTTTATTCAT	2447	TGAATAAACAGGCAGATGGATGATG
1184	ACATCATCCATCTGCCTGTTTATTC	2448	GAATAAACAGGCAGATGGATGATGT
1185	TACATCATCCATCTGCCTGTTTATT	2449	AATAAACAGGCAGATGGATGATGTA
1186	TTACATCATCCATCTGCCTGTTTAT	2450	ATAAACAGGCAGATGGATGATGTAA
1187	CTTACATCATCCATCTGCCTGTTTA	2451	TAAACAGGCAGATGGATGATGTAAG
1188	GCTTACATCATCCATCTGCCTGTTT	2452	AAACAGGCAGATGGATGATGTAAGC
1189	AGCTTACATCATCCATCTGCCTGTT	2453	AACAGGCAGATGGATGATGTAAGCT
1190	CAGCTTACATCATCCATCTGCCTGT	2454	ACAGGCAGATGGATGATGTAAGCTG
1191	GCAGCTTACATCATCCATCTGCCTG	2455	CAGGCAGATGGATGATGTAAGCTGC
1192	GGCAGCTTACATCATCCATCTGCCT	2456	AGGCAGATGGATGATGTAAGCTGCC
1193	GGGCAGCTTACATCATCCATCTGCC	2457	GGCAGATGGATGATGTAAGCTGCCC
1194	GGGGCAGCTTACATCATCCATCTGC	2458	GCAGATGGATGATGTAAGCTGCCCC
1195	TGGGGCAGCTTACATCATCCATCTG	2459	CAGATGGATGATGTAAGCTGCCCCA
1196	CTGGGGCAGCTTACATCATCCATCT	2460	AGATGGATGATGTAAGCTGCCCCAG
1197	TCTGGGGCAGCTTACATCATCCATC	2461	GATGGATGATGTAAGCTGCCCCAGA
1198	GTCTGGGGCAGCTTACATCATCCAT	2462	ATGGATGATGTAAGCTGCCCCAGAC
1199	GGTCTGGGGCAGCTTACATCATCCA	2463	TGGATGATGTAAGCTGCCCCAGACC
1200	GGGTCTGGGGCAGCTTACATCATCC	2464	GGATGATGTAAGCTGCCCCAGACCC
1201	AGGGTCTGGGGCAGCTTACATCATC	2465	GATGATGTAAGCTGCCCCAGACCCT
1202	CAGGGTCTGGGGCAGCTTACATCAT	2466	ATGATGTAAGCTGCCCCAGACCCTG
1203	CCAGGGTCTGGGGCAGCTTACATCA	2467	TGATGTAAGCTGCCCCAGACCCTGG
1204	CCCAGGGTCTGGGGCAGCTTACATC	2468	GATGTAAGCTGCCCCAGACCCTGGG
1205	TCCCAGGGTCTGGGGCAGCTTACAT	2469	ATGTAAGCTGCCCCAGACCCTGGGA
1206	GTCCCAGGGTCTGGGGCAGCTTACA	2470	TGTAAGCTGCCCCAGACCCTGGGAC
1207	GGTCCCAGGGTCTGGGGCAGCTTAC	2471	GTAAGCTGCCCCAGACCCTGGGACC
1208	AGGTCCCAGGGTCTGGGGCAGCTTA	2472	TAAGCTGCCCCAGACCCTGGGACCT
1209	GAGGTCCCAGGGTCTGGGGCAGCTT	2473	AAGCTGCCCCAGACCCTGGGACCTC
1210	AGAGGTCCCAGGGTCTGGGGCAGCT	2474	AGCTGCCCCAGACCCTGGGACCTCT
1211	CAGAGGTCCCAGGGTCTGGGGCAGC	2475	GCTGCCCCAGACCCTGGGACCTCTG
1212	TCAGAGGTCCCAGGGTCTGGGGCAG	2476	CTGCCCCAGACCCTGGGACCTCTGA
1213	GTCAGAGGTCCCAGGGTCTGGGGCA	2477	TGCCCCAGACCCTGGGACCTCTGAC
1214	GGTCAGAGGTCCCAGGGTCTGGGGC	2478	GCCCCAGACCCTGGGACCTCTGACC
1215	GGGTCAGAGGTCCCAGGGTCTGGGG	2479	CCCCAGACCCTGGGACCTCTGACCC
1216	GGGGTCAGAGGTCCCAGGGTCTGGG	2480	CCCAGACCCTGGGACCTCTGACCCC
1217	GGGGGTCAGAGGTCCCAGGGTCTGG	2481	CCAGACCCTGGGACCTCTGACCCCC
1218	CGGGGGTCAGAGGTCCCAGGGTCTG	2482	CAGACCCTGGGACCTCTGACCCCCG
1219	CCGGGGGTCAGAGGTCCCAGGGTCT	2483	AGACCCTGGGACCTCTGACCCCCGG
1220	GCCGGGGGTCAGAGGTCCCAGGGTC	2484	GACCCTGGGACCTCTGACCCCCGGC

1221	CGCCGGGGGTCAGAGGTCCCAGGGT	2485	ACCCTGGGACCTCTGACCCCCGGCG
1222	TCGCCGGGGGTCAGAGGTCCCAGGG	2486	CCCTGGGACCTCTGACCCCCGGCGA
1223	GTCGCCGGGGGTCAGAGGTCCCAGG	2487	CCTGGGACCTCTGACCCCCGGCGAC
1224	GGTCGCCGGGGGTCAGAGGTCCCAG	2488	CTGGGACCTCTGACCCCCGGCGACC
1225	GGGTGCCGGGGGTCAGAGGTCCCA	2489	TGGGACCTCTGACCCCCGGCGACCC
1226	GGGGTCGCCGGGGGTCAGAGGTCCC	2490	GGGACCTCTGACCCCCGGCGACCCC
1227	AGGGGTCGCCGGGGGTCAGAGGTCC	2491	GGACCTCTGACCCCCGGCGACCCCT
1228	AAGGGGTCGCCGGGGGTCAGAGGTC	2492	GACCTCTGACCCCCGGCGACCCCTT
1229	CAAGGGGTCGCCGGGGGTCAGAGGT	2493	ACCTCTGACCCCCGGCGACCCCTTG
1230	GCAAGGGGTCGCCGGGGGTCAGAGG	2494	CCTCTGACCCCCGGCGACCCCTTGC
1231	TGCAAGGGGTCGCCGGGGGTCAGAG	2495	CTCTGACCCCCGGCGACCCCTTGCA
1232	GTGCAAGGGGTCGCCGGGGGTCAGA	2496	TCTGACCCCCGGCGACCCCTTGAC
1233	AGTGCAAGGGGTCGCCGGGGGTCAG	2497	CTGACCCCCGGCGACCCCTTGCACT
1234	GAGTGCAAGGGGTCGCCGGGGGTCA	2498	TGACCCCCGGCGACCCCTTGCACTC
1235	AGAGTGCAAGGGGTCGCCGGGGGTC	2499	GACCCCCGGCGACCCCTTGCACTCT
1236	GAGAGTGCAAGGGGTCGCCGGGGGT	2500	ACCCCCGGCGACCCCTTGCACTCTC
1237	GGAGAGTGCAAGGGGTCGCCGGGGG	2501	CCCCGGCGACCCCTTGCACTCTCC
1238	TGGAGAGTGCAAGGGGTCGCCGGGG	2502	CCCCGGCGACCCCTTGCACTCTCCA
1239	ATGGAGAGTGCAAGGGGTCGCCGGG	2503	CCCGGCGACCCCTTGCACTCTCCAT
1240	CATGGAGAGTGCAAGGGGTCGCCGG	2504	CCGGCGACCCCTTGCACTCTCCATG
1241	TCATGGAGAGTGCAAGGGGTCGCCG	2505	CGGCGACCCCTTGCACTCTCCATGA
1242	GTCATGGAGAGTGCAAGGGGTCGCC	2506	GGCGACCCCTTGCACTCTCCATGAC
1243	TGTCATGGAGAGTGCAAGGGGTCGC	2507	GCGACCCCTTGCACTCTCCATGACA
1244	GTGTCATGGAGAGTGCAAGGGGTCG	2508	CGACCCCTTGCACTCTCCATGACAC
1245	AGTGTCATGGAGAGTGCAAGGGGTC	2509	GACCCCTTGCACTCTCCATGACACT
1246	AAGTGTCATGGAGAGTGCAAGGGGT	2510	ACCCCTTGCACTCTCCATGACACTT
1247	AAAGTGTCATGGAGAGTGCAAGGGG	2511	CCCCTTGCACTCTCCATGACACTTT
1248	GAAAGTGTCATGGAGAGTGCAAGGG	2512	CCCTTGCACTCTCCATGACACTTTC
1249	AGAAAGTGTCATGGAGAGTGCAAGG	2513	CCTTGCACTCTCCATGACACTTTCT
1250	GAGAAAGTGTCATGGAGAGTGCAAG	2514	CTTGCACTCTCCATGACACTTTCTC
1251	AGAGAAAGTGTCATGGAGAGTGCAA	2515	TTGCACTCTCCATGACACTTTCTCT
1252	GAGAGAAAGTGTCATGGAGAGTGCA	2516	TGCACTCTCCATGACACTTTCTCTC
1253	GGAGAGAAAGTGTCATGGAGAGTGC	2517	GCACTCTCCATGACACTTTCTCTCC
1254	GGGAGAGAAAGTGTCATGGAGAGTG	2518	CACTCTCCATGACACTTTCTCTCCC
1255	TGGGAGAGAAAGTGTCATGGAGAGT	2519	ACTCTCCATGACACTTTCTCTCCCA
1256	ATGGGAGAGAAAGTGTCATGGAGAG	2520	CTCTCCATGACACTTTCTCTCCCAT
1257	CATGGGAGAGAAAGTGTCATGGAGA	2521	TCTCCATGACACTTTCTCTCCCATG
1258	CCATGGGAGAGAAAGTGTCATGGAG	2522	CTCCATGACACTTTCTCTCCCATGG
1259	ACCATGGGAGAGAAAGTGTCATGGA	2523	TCCATGACACTTTCTCTCCCATGGT
1260	CACCATGGGAGAGAAAGTGTCATGG	2524	CCATGACACTTTCTCTCCCATGGTG
1261	CCACCATGGGAGAGAAAGTGTCATG	2525	CATGACACTTTCTCTCCCATGGTGG
1262	GCCACCATGGGAGAGAAAGTGTCAT	2526	ATGACACTTTCTCTCCCATGGTGCC
1263	TGCCACCATGGGAGAGAAAGTGTC	2527	TGACACTTTCTCTCCCATGGTGCCA

1264	CTGCCACCATGGGAGAGAAAGTGTC	2528	GACACTTTCTCTCCCATGGTGGCAG
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* At least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide sequence is independently selected from 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.

UNC13A Transcript

[00172] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 5057.

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15  GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCGGCGTGAGCCAAGCGGGGCTGCAGCC
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20  GCCCAGCTGGGAGCAGGATTTTCATGTTTCGAGATTAACCGTCTGGATTGTTGGGACTGACGGTGGAGGTGTGG
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25  TCCAAGATGAGCAAGACAAGCCTCTGCCTGTCCCCAGCAACCAGTGCTGCAACTGGAATTATTTGGCTG
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 30 TCCAGTCCAGCTGATGCCATGGGACTGGGGGTTTCTGTCTCAGCTCTGTTTCTCCAGACTGGGGTCT
 GAGGACTCTCAGGACCCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGCTTACGCC
 TAGTGGAATTATGTATTGGGGCAGGGTCAGTGTGAGAATACACATCCGCATGCATGTCTGTCCATGTCTG
 TCCGTACCAACCTTCCCCCTCCACACGGACCTGGGCACATAGGAGGTGTCTGAGCCTGACACATGGGACA
 GAGAGTGGACATGGCTGAGACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCTGAAAGCCTTTTGA
 35 TCAGGAAGTTTCTGTATTGGCAGAACAAAGCCCAGAGAGGAGCAGGGCTTTCTCAACGCCACCCAGCAA
 GTGGACACAGAGCCCGGCCCTGGATGACACCTCCAGGGTTCTGAACCCTGGACCTCGCTTTATGCAAGGA
 GCTGGCCCCACATTTCCATGAATCGGGGAAACAGCACAGAAGGTTGGCCTGTGGCAGGGCAAGGGTTAA
 AGGGGTGACATTGAGGGATGCCCTCAGAGTCAAAGTCCCTGACCAAGAGGAATAGAGTAGAAAACACAGA
 GACAGAGGGTGAGATCACGCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGACATAGAGGTGGAA
 40 ATATACAGAGAAAGATAAATGCAGAGACCAAGGCAGGGAGTGTGCGGGGAAGTAAAGAGGGTGTCTGAA
 GAAAGAAGGATCTGTTCACTCTTACCAGTCTGTCTCGAATGATTTGCATAAAATGAGGAGGTGCCTGTC
 CACACCCCCAATTCTCTCTCAGGCCCCAGAGCCTGAGACCTCACCATGCCCCATCAGAGATGCAAAAA
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 CCTACCCCATGTGCTGTCTGATTTTGCAGATGGGGACAACCTGGGGCCTCCCGGAACCTCTGCCACCCTGGG
 45 GAAGTTGGGGGAGGGCCTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCCCTAAGAATCG
 TTGAGGACCAAAGTTGCTTTTGTGCTGACACGTGTTGCTTTTCTCTTTGCTTTTATTGTTTCAGAGAAAA
 TCAAGTTGACTGTGTCAAGTAACACCCCAACCCCTTACCCCGTCCAGCCATAGTGGCTCTCTGGAGACAC
 AGGTACAGGCGGAGGGTCCCTGATCATCCCCAACACACAGCCAGGGGACTTGACCCCTGTCCACCC
 CTGTCTCGTGCTCCCTCAGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCTCCACACAACT
 50 CTTAGCATGTGATTGCAGATGTGAAATCAAAACGTTGTTTGTGTTTTGTTTTGATTCTACCCCGT
 CGGTCCAGTGTCTGCACAGACGCTTCATTTCTCTGTAAATATGTGACTTGAACAAATGTTTAACACAA
 ACGAGAAGTGGTCATGAATGCATGGTGTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAA
 ATATTTTATTAACAGCAGACATTAAAAAAGAAAAACCACACACA

(SEQ ID NO: 5057 (SOURCE NCBI Reference Sequence NM_001080421.3)).

50 [00173] In various embodiments, an UNC13A mRNA transcript comprises the sequence
 provided as SEQ ID NO: 5058.

55 GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
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 60 CACCAAGGACCCACCTTCCACCGCATCCTCTGGACACGCGCTTTGAGCTACCCTTAGACATTCTGTAA
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 5 GCCCACCACCCCTGGGCTCCCGGGAGTCTTACAGTGACTCCATGCACAGTTACGAGGAGTCTCTGAGCC
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 10 GAGGAGGAGGAGGAGGTGCCGTGACGATTTGGGCAGCTATGCCAGCGTGAAGACGTAGCTGTGGCTGAGC
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 CAGATCCCTGAGGCTGAGCCACCAAGGACGAGGAGAGTTTCAGGCCGAGAGAGGATGAGGAAGGCCAGG
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 15 GCAGGAGGCCCGGGGAGAAGGAGAGATGTCTAAATCCCTATGGTTCAAAGGCGGCCAGGGGGCGGTCTC
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 20 GCATGCGCTGCACCGAGTGCGGTGTCAAGTGCCACGAGAAGTGCCAGGACCTGCTCAACGCCGACTGCCT
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 25 GACCCCTATGTACCGTCCAGGTGCGGAAGACCAAGAAACGGACAAAAACCATCTATGGGAACCTCAACC
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 35 CTTCGCCAGCCAGCAGCCCGGAGAGACTCCAGGACCTCAAAATCCACTGTGGACCTTCTCACCAGCATCACC
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 45 TCCGTGGTGGATGTTTTCTCCCAACTCAACCAGAGCTTTGAAATCATCAAGAACTCGAGTGTCCCGACC
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 50 TGCTACCAGCTTCCAGCCGCACATTGAAGAGTGTGTCAAACAGATGGGTGACATCCTTAGCCAGGTTAAG
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 55 CAGACGGAACCCAGATGATCTTCAATGCAGCCAAGGAGCTGGGTGAGCTGTCCAACTCAAGGATCACAT
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 60 ATCGGCCCAGGGCTTGGGTGTAGAAGACCTGTGGGTGAAGTCTCTGTCCATGTTGAGCTGTTCACTCAT
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 CGACTTCCGGCCGTTTCATCGAGGTCAACATCTGTTGGGCCAGCTCAGCGACAAGAAACGCAAGTTTGC
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5 GCGGGTCCCGAGTGCTATGAGCTGCAGGTGTGCGTCAAGGACTACTGCTTCGCGCGCGAGGACCGCACGG
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 10 CTTAGCGCGGGCGGTGCGCCGAGCGGCACTGCGCCTGCGCGGAGGGCGCTGGGCGGGGAGGGACGGGGCT
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 30 TGGGATCTGCTTTTCCACATGTGTGTATGGCACGCTTTTCTGCTGGATTGGGAAGGACAAGATTTTGC
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 35 TACGCAGTCCTGAGGAGTTTACTTTTATTCTAAGACAGTTGGGGAGCTCCAGGAGCTGTTTTAAGTTGG
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 50 GTCTTTCTGTTCAAGACCTCCGTGTGTGTGTGTGTGTGTTAGGGTTCCCCAGCAATGGCCCAGGCATGT
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 55 GACCCCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGTCTACGCCAGTGGAAATTAT
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 60 CCCGCCCTTGGATGACACCTCCAGGGTTCTGAACCTGGACCTCGCTTTATGCAAGGAGCTGGCCCCACA
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5 GCTGTCGATTTTGCAGATGGGGACAACCTGGGGCCTCCCGGAACTCTGCCACCCTGGGGAAGTTGGGGGA
GGGCCCTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCTAAGAATCGTTGAGGACCAAA
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10 GAGGGTCCCCTGATCATCCCAACCACACAGCCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTGCT
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(SEQ ID NO: 5058 (SOURCE NCBI Reference Sequence NM_001387021.1)).

[00174] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 5059.

15 GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
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25 AGCAACAGCATCCCGCCGCCCTATTATACTACGTCAACCCCAACGCCTCAGTCCACCAATATTCTGTTC
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35 AGGGGCAGGACTCCATGTCCAGGGCCAAGGCCAACTGGCTGCGTGCCCTCAACAAGGTGCGGATGCAGCT
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 5 TTCAAGGTGAAATGGCTCTACAATGAGTATGTGACGGAACCTCCCGCCTTCAAGGACCGCTGCCTGAGT
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(SEQ ID NO: 5060 (SOURCE NCBI Reference Sequence NM_001387023.1)).

[00176] In various embodiments, an UNC13A mRNA transcript comprises the sequence
 60 provided as SEQ ID NO: 5061.

5 CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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 30 CCAAGGTTCAGGTGCCATACCCTCTGTGCCCTCCCTTAGGCCTGTGTGCCCATGGAAGGGTGGGCTG
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 35 ACTCTAGGGGGGAGAAAGAGAAATGAGAGAAAGAGAATGAGAGAGAGAGAAACACAAACACAGTGACACAG
 TGAGAGCTTAGTCTCCAAGACCTATTCAATTGATTCAAACACCCAAGCCACAGGATACCTCAGATGGCCC
 TCTTGCCAGCTGGAAGCTTTTCTCCAATGAGCAAAGTTACAGTGACCTGGCTGGAGTTACCTGGTGCAC
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 40 AGCTGAGTAGTGGGTTTTCTGGAGGATAGAACATCAGATGGGGAGGCTTTCCGAGGTGAAGAATGAGAGG
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 CTGTTGAAACAACGAGAAGGGTGGCACGGCTGGAGCTGAGCCAGCAAGGGGGATCGTGAGGAGCCTTGGG
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 45 CTGTTTTGTGAAGACTAAAACAGTGAGGAGAGGTGGAGGTGCTTTGGGGACACTGAAATGGATTCTTGG
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 50 CAGCCTGGGCAACAGAACAATACTCCATTCCCTCCCCCTACCCCCACAAAAAATAAATCCTGCC
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 55 GTTGTAGCCAGGGATAAGCTTATGTGACTGTTATATGGACTGAGGAGCAGATGTGAATTCGAACCATGA
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5 AGCAGGGCTTTCTCAACGCCACCCAGCAAGTGGACACAGAGCCCGGCCTTGGATGACACCTCCAGGGTT
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 20 AGTCCGGGGAGGCTTCCCTCCACACAACCTCTTAGCATGTGATTGCAGATGTGAAATCAAACGTTGTTT
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 TATGTGACTTGGAAACAAATGTTTAACACAAACGAGAAGTGGTCATGAATGCATGGTGTGAGATGTTTTG
 CACTATTCTGACTTTTTTGGTCTCTGTAAAAATATTTTATTAACAGCAGACATTAAAAAAGAAAAACCAC
 ACACAGCCTTGGA
 20 (SEQ ID NO: 5061 (SOURCE NCBI Reference Sequence XM_011527810.2)).

[00177] In various embodiments, an UNC13A mRNA transcript comprises the sequence
 provided as SEQ ID NO: 5062.

25 CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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 GAGCAGGATTTTCATGTTTCGAGATTAACCGTCTGGATTGTTGGGACTGACGGTGGAGGTGTGGAATAAGGGT
 30 TCATCTGGGACACAATGGTGGGCACTGTGTGGATCCCACTGAGGACCATCCGCCAGTCCAATGAGGAGGG
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 40 GAGGACCTGGAGGACTTCTGGAGGAGGAGGAGCTGCCTGAAGATGAGGAGGAGCTGGAGGAGGAGGAGG
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 45 CTCCATGTCCAGGGCCAAGGCCAAGTGGCTGCGTGCCTTCAACAAGGTGCGGATGCAGCTGCAGGAGGCC
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 ACAGCATGCCAGACATCCGCAAGAGGAAACCTATCCCACTCGTGAGCGACTTGGCCATGTCCCTGGTCCA
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 50 GGACGGCCACCACGCCACCTACTGCTACGAGTGCGAGGGGCTGCTGTGGGGCATCGCGAGGCAGGGCAT
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 55 GCCAAGATCAGCATCACCGTGGTCTGCGCCAGGGCTTGACGGCAAAGGACAAGACAGGATCCAGTGACC
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 15 GGTGCCCTGGAGCGAGACAAGAAGGATGGGTTCAGCAGACCTCAGAGCATGCCCTATTCTCCTGCTCCG
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 35 GGGCTGGCCGTGCTGCAGCTGCGTGAGCTGGGCCAGCGCGGGAGCGCCGCTGCTGGTGGCTGGCCGTGCGC
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20 GATGCCATGGGACTGGGGTTTCTCTGTCCAGCTCTGTTTCTCCAGACTGGGGTCTGAGGACTCTCAGG
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25 GTATTGGCAACAAGCCAGAGAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAAGTGGACACAGAGC
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40 TGCAGATGTGAATCAAAACGTTGTTGTTTTTTGTTTTGTTTGAATTCTACCCCGTCCGTCCAGTGTCT
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AGCAGACATTAAGAAAAGAAAACACACACAGCCTTGA

(SEQ ID NO: 5062 (SOURCE (NCBI Reference Sequence XM_017026502.1))).

45 [00178] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 5063.

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
CCAGCCCAGCGGCCGCTGAGCCGACCCGACAGAGCCGGCCGGCCGCTCCGGCCACCTGCGAGCTCG
50 GAGACATGTCTCTGCTTTGCGTTGGAGTCAAAAAGCCAAGTTTGATGGTGCCAAGAGAAATCAACAC
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55 CCCCTTAGTCCACCGCATCCTCTGGACACGCGTTTGAAGTACCCTTAGACATTCTGAGAGGAGGCTC
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5 (SEQ ID NO: 5063 (SOURCE NCBI Reference Sequence XM_011527811.2)).

[00179] In various embodiments, a UNC13A transcript is a pre-mRNA UNC13A transcript. In various embodiments, a UNC13A pre-mRNA transcript comprises a sequence provided as SEQ ID NO: 5064.

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 AGCTACTCCAGAGGCTGAGGGGTACGAGAATCGCTTGAACCCAGGAGGCACAGGTTGCAGTGAGCCATGA
 TTGTACCACGGCACTCCAGCCTGGGCGACAGAGCAAGACTCTGCCTCAAAAAAATAAAAAAAGT
 55 CTGTTACGGGGGTAGATGGATGGTGGTGGTTAGCAAGGTTAGAGTTGGGGTCACTCCGGGGTAGATCCTT
 GGGTCGAGTGTGAGCCTCACAGAGCACTGGGGCAGGGCAATGTTGTTGGATGTTCTTAGGAGACAGAAGT
 GCAGAAGAAAGTAGTCCAGCTACCTGGGAGGCTGGGGCAGGAAGATCGCTTGAGCTCAGGAGTTTAAAG
 CTGCAATGAGCTATGATTGTGCACTGCACTCCAGCCTGGGTGACCGACATAGCGAGACCCTGTCTTTAA
 AAAAAAATAAATATGGGCCAGGCGCGGTGGCTGACGCTTGTAAATCCAAACACTTTGGGAGGCCAAGGC
 60 AACTGGATCACTTAGGTTAGGAGTTTCAGACAGCAGTGGCCAACATGGTGAGACCCCCCCCGCCACC
 CCTCTGTACTAAAAACAAAAAATCAGCCCGTGTGGTGGTGCATGCCTGTAATCCAGCTACTAGG
 GAGGCTGAGGCAGAAGATCGTTTGAACCCGGGAGACAGAGGTTGCAGTGAGCCGCGATTGTGCCACTGC

5 GCCATGGGACTGGGGGTTTCTCTGTCCAGCTCTGTTTCTCCCAGACTGGGGTCTGAGGACTCTCAGGACC
 CCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGTCTACGCCTAGTGAATTATGTAT
 TGGGGCAGGGTCAGTGTGAGAAACACATCCGCATGCATGTCTGTCCATGTCTGTCCGTACCAACCTTCC
 CCTTCCACACGGACCTGGGCACATAGGAGGTGTCTGAGCCTGACACATGGGACAGAGAGTGGACATGGCT
 10 GAGACACGGACAGAGAAAAAGACAAGGAGTCCAGGGGGCTGAAAGCCTTTTGAAATCAGGAAGTTCTGTGA
 TTGGCAGAACAAAGCCCAGAGAGGAGCAGGGCTTTCCCTCAACGCCACCCAGCAAGTGGACACAGAGCCCG
 GCCTTGGATGACACCTCCAGGGTTCTGAACCCTGGACCTCGCTTTATGCAAGGAGCTGGCCCCACATTTT
 CATGAATCGGGGAAACAGCACAAGAAGTTGGCCTGTGGCAGGGCAAGGGTTAAAGGGGTGACATTGAGG
 15 GATGCCTCAGAGTCAAAGTCCCCTGACCAAGAGGAATAGAGTAGAAAAACACAGAGACAGAGGGTGAGATC
 ACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAGGTGGAATATACAGAGAAAGAT
 AAATGCAGAGACCAAGGCAGGGAGTGTGGGGGAAGTAAAGAGGGTGTCTGAAGAAAGAAGGATCTGTT
 CACTCTTACCAGTCTGTCTCGAATGATTTGCATAAAATGAGGAGGTGCCTGTCCACACCCCCAATTCTCT
 CTCTCAGGCCCCAGAGCCTGAGACCTCACCATGCCCCCATCAGAGATGCAAAAACTAAACACCCCACTA
 20 GAAATCCTTGGGACCTCTCTCGGCTGGGATCTCAGAGCCTTTCTGTCCCCTACCCCTACCCCATGTGCTG
 TCGATTTTGCAGATGGGGACAACCTGGGGCCTCCCGAACTCTGCCACCCCTGGGGAAGTTGGGGGAGGGC
 CTTAGTCCCGGATCACAAACCCGTCTGTCTCCCAAGATCCTTTCTAAGAATCGTTGAGGACCAAGTTG
 TCTTTGCTGACACGTGTGCTTTCTCTTTGCTTTTATTGTTTCAGAGAAAAATCAAGTTGACTGTGTC
 AAGTAACACCCACCCCTTACCCCGTCCAGCCATAGTGGCTCTCTGGAGACACAGGTCAAGGCGGAGG
 25 GTCCCCTGATCATCCCCAACACACAGCCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTGCTCCCT
 CAGACCCCCACAAACCGGCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAACTCTTAGCATGTGATTGC
 AGATGTGAAATCAAAACGTTGTTTGTGTTTTGTTTTGTTTTGATTCTACCCCGTCCGTCCAGTGTCTGCA
 CAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAAACACAAACGAGAAGTGGTCATG
 AATGCATGGTGTGAGATGTTTTGCACTATTCTGACTTTTTTGGTCTCTGTAAAAATATTTTATTAACAGC
 30 AGACATTAAAAAAAGAAAAACACACACAGCCTTGGACACGTGGTTGCCTCCTCTTGCATTCTCTTTATC
 AGCAAAAAAACAAAAACAAAAACCTCAGTACGATTAGCACCTACTAGGTAGGCGCAGACTCAGTAGAAC
 ACATGCTTGGCCATGAACGCGGCTCATCCGCAACTGGAGTCATCCCCATTTTACAGAGAAGGAAACTGA
 AGTACAGAGAGACAAGATCTTGCTCAGATCACATAGCCAGGAAGAGATGGAGCTGGGACTTGAACCTCAGA
 ACATTTGCAACCATTGCTTTTTTTTTTTTTTTTTTGTAGATGAAGTCTCTGTTGCCAGGCTGGAATGCAGT
 35 GGTGCAATCTCAGCTCACTGCAATCTCCACCTCCAGATTCAAGCGATTCTCCTGCCTTAGCCTCCTGAG
 TAGCTGGGATTACAGGCGCCCGCCACCTTGCTGGCTAATTTTGTATTTTGTAGTAGATAGGATTTCA
 CCATGTTGGCCAGGCTGGTGCAGAACCCCTGACCTCAGGTGATCCACTCCCTCGGCCCTCCAAAGTGCTG
 GGATTACAGGCGTGAGCCACCGCACCCGGCCATCTGTTGCCCTTAAGGAAGTTAAGATACAAACACTAGG
 AATACATGCCCTTAATTCAACCCACACCCCATGCTTGTGTTGGTGTGTTGGGTTTTTGGGATCTTCTT
 40 GTTTGTTTGTGTTTTGAGACAGGGTCTTGCTCTGTCAACCAGGATGGAGTTGAGTGTACAATCTCAACTC
 ACTGCATCCTCAACCTCCAGGCTCAGGTGATCTCCACCTCAGCCTCCTGAGTAGTGTGCACCCACCAC
 ACCTGGCTAATTTGTGTATTTTGTAGTGATAGGATGTGCGCCATGTTGCCAGACTGCTCTCGAACTCC
 TCACTTTGGGCAATCCTCTCTCCTCAGCCCTCCAAAGTGTGGGATTACAGGCGTGAGCCACTGTGCCTG
 GCCATGTCTGTTTTAAATGTAGCAGCTGGGGCCAGGCGCAGTGGCTCACGCCTGTAATCCAGCACTTTA
 45 GGAGGCCGAGGCGGGTGGATCACGAGGTGAGGAGATCGAGACCATCCTGGCTAACACGGTGAAACCCCGT
 CTCTACTAAAAGTACCAAAATTAGCCGGGCACGGTGGCAGGCACCTGTAGTTCCAGCTACTCGGGAGGC
 TGAGGCAGGAGAATGGTGTGAACTGGGGAGGCGGAGCTTGCAAGTGAAGCAAGATCACGCCACTGCATTCC
 AGCCTGGGTGACGGAGCGAGACTCCATCTCAAAAAAAGAAAAAAGTAGCAGCTGGGAATCTC
 ATTTCAATAAATCAGATGTGTGAGGAATGAAACTCCATTTTCCAACAGCTGAATTTAATTTCTGTTTTGA
 50 GTTCTCCATCCACGAGGAAGCAGAAATGGAATCTCATTAGCCCAAGTTTCTCGGTAAATTCGGAATTC
 CCCTCCTTATGTCTGGGGTTATTTCTACATTTGAGCGGACAGGACGGGAGCTGCGGGATCCACCACCAGG
 AGTGGGTTTCAAGTGTGCTTTTGGTTGCAAGTAACAGACAGCAGGACTAAAAGTGGGGCCAGAAAGTGGC
 TTACACCAGGAGTTATCCAGCACGCAGCAATCCCGCTCCTGGGGGACTTTTCTCCTTTGAGAACTTGCA
 CGTGGGGGTGTGGTATCTTCTCAAAGAATAGCATATAGCTGGGAAAAGGGGACAAACCGCAGCTGTCTGC
 ATGATGTCTGCAGAGGCAGCCTGCAGGTCTTGAGTGCCCTGCTCATTAGCTGTTTCTGTACCCAAGTG
 55 CATAGGCTACGCACTGTGACTGATGTGGATCTATTTGCCCTCGCTACAAAAGGCTCTCAAGTCTTGTCC
 TTCAGTGTGTGGGACCATCGTGTACCAATGGGGCTTGGGACTGAGGCTCAAGACTGCTTGTCTGGGAA
 ATGTAACCCCTTTGTTCTGGACAGGTAGAAGGAGAGGAATGGTCATCCAGGCCTAATGTAAAGTTTCT
 GCAACCC

(SEQ ID NO: 5064 (SOURCE NCBI Reference Sequence NG_052872.1)).

- 55 [00180] In various embodiments, a UNC13A transcript is a pre-mRNA UNC13A transcript. In
 various embodiments, a UNC13A pre-mRNA transcript comprises a sequence provided as SEQ
 ID NO: 5065. NCBI Reference Sequence NC_000019.10 Reference GRCh38.p13 Primary
 Assembly is SEQ ID NO: 5065.

UNC13A Transcript with a Cryptic Exon

[00181] In some embodiments, an UNC13A AON targets a region of an UNC13A transcript comprising a cryptic exon sequence, the UNC13A mRNA transcript comprising the sequence provided as SEQ ID NO: 5206.

5 TTCTGCCACCATGGGAGAGAAAGTGTTCATGGAGAGTGCAAGGGGTGCGCG
GGGGTCAGAGGTCCCAGGGTCTGGGGCAGCTTACATCATCCATCTGCCTG
TTTATTCAATTAATTCATTCATCTACTCTTTTATCCATCCACACACCCACC
CATCTAACTACCCCAAATTTCACCCATCCACTCTTCCAACCTTTCAGTAA
10 TTCAACCACACATCCATCCATCCATCCATTCATCCATCCCATACATTGAT
CCGCAACTTAATCCACCTACCCAATCATTCAATTCTTTCATACAACCAACC
ATCCATCCACCCATCAATTTATCCAACCATCCATTTTTCGTCTGTCCACC
AGCCACTCACAACCATCCATCTAAATATTCAGAAATTATGAACCCAATTA
TCAATACTTGCAATAGTTCAACCACACATCCTTCCATTCAATCCACCCACC
15 CATTCAATCCATTTGTCCATCTGCCTATCATCCATCCATCCATCCATCCA
TCTACCTATCTACCATCTGACTATCAACAAATTCACCTATCTACTCAAT
CTTCCTTCTAATAACTCAACCACACTTCCATCCATCCCATCCAATACAAC
TTAATCTGTCTATCCCAACATTTTCATCTATCCACCCAGTCAATCATCTATC
CAGCAATCTATCTATCCACTCATCAAGTTATCCATCCATCATTCACTAT
ACTCATCCATCATCTAACAATTACCCCCAAATTCACCCATCCATACATCT
20 ATACTTTCAATAGTTCAATCATATATCCATCCATCTGTCCATCCATCCAT
CATCCATCTAGCCACGAATCTACCCACCAACTCATCCATCTATCCATCCA
TGTAATCACCACATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTC
ATCTGTTCAATCATTCATTCATTCACCAGCATTTATTCAACAACTAGTT
CCTGGGGATAAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACAT
25 ACCCAGACACAAACGGCCCAATCCTGAGTGTTAGGGCTGGAATAGAAG
AAGAACCTGATGATGAGTAGTGAGAGTCAACCTGGAGGCCAAGGTGGGCT
TCCCAGAGGAGGTGACCTGAATCTGGACTTTGATGGATAGGGAGGAGTT
TTCCAGGTAAAGGGAATGGCATGGCGGGCAGTCTCAGAGGGCCAGGAGAG
TGTGGATGGTGTGGCCAGAAAGAGGAGCTGGGCAGGCAGGAATGGTG
30 AGTGGAAGTGGCATGGGAGGGCCGAGCAATGACCCTCAC
(SEQ ID NO: 5206) where underlined = TDP-43 binding site.

[00182] In some embodiments, a cryptic exon sequence within the UNC13A mRNA transcript is provided as SEQ ID NO: 5207.

35 CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCACTCTGTTCA
ATCATTTCATTCATTACCCAGCATTTATTCAACAACTAGTTCTCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACATACCCAGACA
CAAACGGCCCAATCCTGAGTGTTAGGG
(SEQ ID NO: 5207).

[00183] In some embodiments, a cryptic exon sequence within the UNC13A mRNA transcript is provided as SEQ ID NO: 5208.

40 CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCACTCTGTTCA
ATCATTTCATTCATTACCCAGCATTTATTCAACAACTAGTTCTCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAG
(SEQ ID NO: 5208).

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UNC13A Oligonucleotides Targeting Regions of the UNC13A Transcript

[00184] In various embodiments, UNC13A AON disclosed herein are complementary to specific regions of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%)

identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is complementary to a specific region of the UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is at least 85% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 99% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 95% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 95 to 99% complementary to a specific region of the UNC13A transcript.

[00185] In some embodiments, the UNC13A AON (*e.g.*, UNC13A AON) has a segment that has, at most, 7 linked nucleosides. In some embodiments, the UNC13A AON has a segment that has, at most, 6, 5, 4, 3, or 2 linked nucleosides. The segments of the UNC13A AON may be separated from other segments of the UNC13A AON through a spacer. The segment of the UNC13A AON is complementary to a specific region of the UNC13A transcript (for example, a UNC13A transcript) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5063 or an UNC13A pre-mRNA transcript transcribed from SEQ ID NO: 5064 or 5065 or SEQ ID NOs: 5206-5208.

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UNC13A Oligonucleotide Variants

[00186] In various embodiments, UNC13A AONs include different variants, hereafter referred to as UNC13A AON variants. A UNC13A AON variant may be an oligonucleotide sequence of 5 to 100 nucleobases in length, for example, 10 to 40 nucleobases in length, for example, 14 to 40 nucleobases in length, 10 to 30 nucleobases in length, for example, 14 to 30 nucleobases in length, for example, 16 to 28 nucleobases in length, for example, 19 to 23 nucleobases in length, for example, 21 to 23 nucleobases in length, for example, or 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length. A UNC13A AON variant may be an oligonucleotide

sequence complementary to a portion of a UNC13A pre-mRNA sequence or a UNC13A gene sequence.

[00187] In various embodiments, a UNC13A AON variant represents a modified version of a corresponding UNC13A parent oligonucleotide that includes a nucleobase sequence selected from any one of SEQ ID NOs: 1-1264. In some embodiments, a UNC13A AON variant includes a nucleobase sequence that represents a shortened version of a nucleobase sequence of a UNC13A AON selected from any one of SEQ ID NOs: 1-1264. As one example, if a UNC13A parent oligonucleotide includes a 25mer (*e.g.*, 25 oligonucleotide units in length) a variant (*e.g.*, a UNC13A variant) may include a shorter version (*e.g.*, 15mer, 16mer, 17mer, 18mer, 19mer, 20mer, 21mer, or 23mer) of the 25mer UNC13A parent oligonucleotide. In one embodiment, a nucleobase sequence of a UNC13A AON variant differs from a corresponding nucleobase sequence of a UNC13A parent oligonucleotide in that 1, 2, 3, 4, 5, or 6 oligonucleotide units are removed from one or both of the 3' and 5' ends of the nucleobase sequence of the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where two oligonucleotide units were removed from one of the 3' or 5' end of a 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where two oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where four oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and three oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where three oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where five oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where three oligonucleotide units are removed from each of the 3' and 5' ends of the

25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and four oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide.

- 5 In one embodiment, the corresponding UNC13A AON variant may include a 19mer where four oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where six oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

- 10 **[00188]** In one embodiment, the corresponding UNC13A AON variant may include a 18mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and five oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 18mer where five oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 18mer where one oligonucleotide unit is removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and six oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 18mer where six oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and one oligonucleotide unit is removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 18mer where seven oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

- 25 **[00189]** In one embodiment, the corresponding UNC13A AON variant may include a 17mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and six oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 17mer where six oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide.

In one embodiment, the corresponding UNC13A AON variant may include a 17mer where eight oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00190] In one embodiment, the corresponding UNC13A AON variant may include a 16mer

5 where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and seven oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 16mer where seven oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and
10 two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 16mer where nine oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00191] In one embodiment, the corresponding UNC13A AON variant may include a 15mer

15 where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and eight oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where eight oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two
20 oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where ten oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. Example sequences of UNC13A AON variants are shown below in Table 2A and Table 2B.

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Table 2A. Example UNC13A Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
2529	GGAGGGGCCGAGCAATGACCCTC	3793	GAGGGTCATTGCTCGGCCCCCTCC
2530	GGGAGGGGCCGAGCAATGACCCT	3794	AGGGTCATTGCTCGGCCCCCTCCC
2531	TGGGAGGGGCCGAGCAATGACCC	3795	GGGTCATTGCTCGGCCCCCTCCCA
2532	ATGGGAGGGGCCGAGCAATGACC	3796	GGTCATTGCTCGGCCCCCTCCCAT
2533	CATGGGAGGGGCCGAGCAATGAC	3797	GTCATTGCTCGGCCCCCTCCCATG
2534	GCATGGGAGGGGCCGAGCAATGA	3798	TCATTGCTCGGCCCCCTCCCATGC
2535	GGCATGGGAGGGGCCGAGCAATG	3799	CATTGCTCGGCCCCCTCCCATGCC
2536	TGGCATGGGAGGGGCCGAGCAAT	3800	ATTGCTCGGCCCCCTCCCATGCCA

2537	GTGGCATGGGAGGGGCGGAGCAA	3801	TTGCTCGGCCCCCTCCCATGCCAC
2538	AGTGGCATGGGAGGGGCGGAGCA	3802	TGCTCGGCCCCCTCCCATGCCACT
2539	AAGTGGCATGGGAGGGGCGGAGC	3803	GCTCGGCCCCCTCCCATGCCACTT
2540	GAAGTGGCATGGGAGGGGCGGAG	3804	CTCGGCCCCCTCCCATGCCACTTC
2541	GGAAGTGGCATGGGAGGGGCGGA	3805	TCGGCCCCCTCCCATGCCACTTCC
2542	TGGAAGTGGCATGGGAGGGGCGG	3806	CGGCCCCCTCCCATGCCACTTCCA
2543	GTGGAAGTGGCATGGGAGGGGCGC	3807	GGCCCCCTCCCATGCCACTTCCAC
2544	AGTGGAAGTGGCATGGGAGGGGCG	3808	GCCCCCTCCCATGCCACTTCCACT
2545	GAGTGGAAGTGGCATGGGAGGGGG	3809	CCCCCTCCCATGCCACTTCCACTC
2546	TGAGTGGAAGTGGCATGGGAGGGG	3810	CCCTCCCATGCCACTTCCACTCA
2547	GTGAGTGGAAGTGGCATGGGAGGG	3811	CCTCCCATGCCACTTCCACTCAC
2548	GGTGAGTGGAAGTGGCATGGGAGG	3812	CTCCCATGCCACTTCCACTCACC
2549	TGGTGAGTGGAAGTGGCATGGGA	3813	TCCCATGCCACTTCCACTCACCA
2550	ATGGTGAGTGGAAGTGGCATGGG	3814	CCCATGCCACTTCCACTCACCAT
2551	AATGGTGAGTGGAAGTGGCATGG	3815	CCATGCCACTTCCACTCACCATT
2552	GAATGGTGAGTGGAAGTGGCATG	3816	CATGCCACTTCCACTCACCATT
2553	GGAATGGTGAGTGGAAGTGGCAT	3817	ATGCCACTTCCACTCACCATTCC
2554	AGGAATGGTGAGTGGAAGTGGCA	3818	TGCCACTTCCACTCACCATTCCCT
2555	CAGGAATGGTGAGTGGAAGTGGC	3819	GCCACTTCCACTCACCATTCCCTG
2556	GCAGGAATGGTGAGTGGAAGTGG	3820	CCACTTCCACTCACCATTCCCTGC
2557	GGCAGGAATGGTGAGTGGAAGTG	3821	CACTTCCACTCACCATTCCCTGCC
2558	AGGCAGGAATGGTGAGTGGAAGT	3822	ACTTCCACTCACCATTCCCTGCCT
2559	CAGGCAGGAATGGTGAGTGGAAG	3823	CTTCCACTCACCATTCCCTGCCTG
2560	GCAGGCAGGAATGGTGAGTGGA	3824	TTCCACTCACCATTCCCTGCCTGC
2561	GGCAGGCAGGAATGGTGAGTGGA	3825	TCCACTCACCATTCCCTGCCTGCC
2562	GGGCAGGCAGGAATGGTGAGTGG	3826	CCACTCACCATTCCCTGCCTGCCC
2563	TGGGCAGGCAGGAATGGTGAGTG	3827	CACTCACCATTCCCTGCCTGCCCCA
2564	CTGGGCAGGCAGGAATGGTGAGT	3828	ACTCACCATTCCCTGCCTGCCCAG
2565	GCTGGGCAGGCAGGAATGGTGAG	3829	CTCACCATTCCCTGCCTGCCCAGC
2566	AGCTGGGCAGGCAGGAATGGTG	3830	TCACCATTCCCTGCCTGCCCAGCT
2567	GAGCTGGGCAGGCAGGAATGGTG	3831	CACCATTCCCTGCCTGCCCAGCTC
2568	AGAGCTGGGCAGGCAGGAATGGT	3832	ACCATTCCCTGCCTGCCCAGCTCT
2569	AAGAGCTGGGCAGGCAGGAATGG	3833	CCATTCCCTGCCTGCCCAGCTCTT
2570	GAAGAGCTGGGCAGGCAGGAATG	3834	CATTCCCTGCCTGCCCAGCTCTTC
2571	GGAAGAGCTGGGCAGGCAGGAAT	3835	ATTCCTGCCTGCCCAGCTCTTCC
2572	AGGAAGAGCTGGGCAGGCAGGAA	3836	TTCCTGCCTGCCCAGCTCTTCCT
2573	GAGGAAGAGCTGGGCAGGCAGGA	3837	TCCTGCCTGCCCAGCTCTTCCTC
2574	AGAGGAAGAGCTGGGCAGGCAGG	3838	CCTGCCTGCCCAGCTCTTCCTCT
2575	AAGAGGAAGAGCTGGGCAGGCAG	3839	CTGCCTGCCCAGCTCTTCCTCTT
2576	AAAGAGGAAGAGCTGGGCAGGCA	3840	TGCCTGCCCAGCTCTTCCTCTTT
2577	GAAAGAGGAAGAGCTGGGCAGGC	3841	GCCTGCCCAGCTCTTCCTCTTTC
2578	AGAAAGAGGAAGAGCTGGGCAGG	3842	CCTGCCCAGCTCTTCCTCTTTCT
2579	CAGAAAGAGGAAGAGCTGGGCAG	3843	CTGCCCAGCTCTTCCTCTTTCTG

2580	CCAGAAAGAGGAAGAGCTGGGCA	3844	TGCCCAGCTCTTCCTCTTTCTGG
2581	GCCAGAAAGAGGAAGAGCTGGGC	3845	GCCCAGCTCTTCCTCTTTCTGGC
2582	GGCCAGAAAGAGGAAGAGCTGGG	3846	CCCAGCTCTTCCTCTTTCTGGCC
2583	TGGCCAGAAAGAGGAAGAGCTGG	3847	CCAGCTCTTCCTCTTTCTGGCCA
2584	GTGGCCAGAAAGAGGAAGAGCTG	3848	CAGCTCTTCCTCTTTCTGGCCAC
2585	TGTGGCCAGAAAGAGGAAGAGCT	3849	AGCTCTTCCTCTTTCTGGCCACA
2586	GTGTGGCCAGAAAGAGGAAGAGC	3850	GCTCTTCCTCTTTCTGGCCACAC
2587	GGTGTGGCCAGAAAGAGGAAGAG	3851	CTCTTCCTCTTTCTGGCCACACC
2588	TGGTGTGGCCAGAAAGAGGAAGA	3852	TCTTCCTCTTTCTGGCCACACCA
2589	ATGGTGTGGCCAGAAAGAGGAAG	3853	CTTCCTCTTTCTGGCCACACCAT
2590	GATGGTGTGGCCAGAAAGAGGAA	3854	TTCTCTTTCTGGCCACACCATC
2591	GGATGGTGTGGCCAGAAAGAGGA	3855	TCCTCTTTCTGGCCACACCATCC
2592	TGGATGGTGTGGCCAGAAAGAGG	3856	CCTCTTTCTGGCCACACCATCCA
2593	GTGGATGGTGTGGCCAGAAAGAG	3857	CTCTTTCTGGCCACACCATCCAC
2594	TGTGGATGGTGTGGCCAGAAAGA	3858	TCTTTCTGGCCACACCATCCACA
2595	GTGTGGATGGTGTGGCCAGAAAG	3859	CTTTCTGGCCACACCATCCACAC
2596	AGTGTGGATGGTGTGGCCAGAAA	3860	TTTCTGGCCACACCATCCACACT
2597	GAGTGTGGATGGTGTGGCCAGAA	3861	TTCTGGCCACACCATCCACACTC
2598	AGAGTGTGGATGGTGTGGCCAGA	3862	TCTGGCCACACCATCCACACTCT
2599	GAGAGTGTGGATGGTGTGGCCAG	3863	CTGGCCACACCATCCACACTCTC
2600	GGAGAGTGTGGATGGTGTGGCCA	3864	TGGCCACACCATCCACACTCTCC
2601	AGGAGAGTGTGGATGGTGTGGCC	3865	GGCCACACCATCCACACTCTCCT
2602	CAGGAGAGTGTGGATGGTGTGGC	3866	GCCACACCATCCACACTCTCCTG
2603	CCAGGAGAGTGTGGATGGTGTGG	3867	CCACACCATCCACACTCTCCTGG
2604	GCCAGGAGAGTGTGGATGGTGTG	3868	CACACCATCCACACTCTCCTGGC
2605	GGCCAGGAGAGTGTGGATGGTGT	3869	ACACCATCCACACTCTCCTGGCC
2606	GGGCCAGGAGAGTGTGGATGGTG	3870	CACCATCCACACTCTCCTGGCCC
2607	AGGGCCAGGAGAGTGTGGATGGT	3871	ACCATCCACACTCTCCTGGCCCT
2608	GAGGGCCAGGAGAGTGTGGATGG	3872	CCATCCACACTCTCCTGGCCCTC
2609	AGAGGGCCAGGAGAGTGTGGATG	3873	CATCCACACTCTCCTGGCCCTCT
2610	CAGAGGGCCAGGAGAGTGTGGAT	3874	ATCCACACTCTCCTGGCCCTCTG
2611	TCAGAGGGCCAGGAGAGTGTGGA	3875	TCCACACTCTCCTGGCCCTCTGA
2612	CTCAGAGGGCCAGGAGAGTGTGG	3876	CCACACTCTCCTGGCCCTCTGAG
2613	TCTCAGAGGGCCAGGAGAGTGTG	3877	CACACTCTCCTGGCCCTCTGAGA
2614	GTCTCAGAGGGCCAGGAGAGTGT	3878	ACACTCTCCTGGCCCTCTGAGAC
2615	AGTCTCAGAGGGCCAGGAGAGTG	3879	CACTCTCCTGGCCCTCTGAGACT
2616	CAGTCTCAGAGGGCCAGGAGAGT	3880	ACTCTCCTGGCCCTCTGAGACTG
2617	GCAGTCTCAGAGGGCCAGGAGAG	3881	CTCTCCTGGCCCTCTGAGACTGC
2618	GGCAGTCTCAGAGGGCCAGGAGA	3882	TCTCCTGGCCCTCTGAGACTGCC
2619	GGGCAGTCTCAGAGGGCCAGGAG	3883	CTCCTGGCCCTCTGAGACTGCCC
2620	CGGGCAGTCTCAGAGGGCCAGGA	3884	TCCTGGCCCTCTGAGACTGCCCC
2621	GCGGGCAGTCTCAGAGGGCCAGG	3885	CCTGGCCCTCTGAGACTGCCCCG
2622	GGCGGGCAGTCTCAGAGGGCCAG	3886	CTGGCCCTCTGAGACTGCCCCGC

2623	TGGCGGGCAGTCTCAGAGGGCCA	3887	TGGCCCTCTGAGACTGCCCCGCCA
2624	ATGGCGGGCAGTCTCAGAGGGCC	3888	GGCCCTCTGAGACTGCCCCGCCAT
2625	CATGGCGGGCAGTCTCAGAGGGC	3889	GCCCTCTGAGACTGCCCCGCCATG
2626	GCATGGCGGGCAGTCTCAGAGGG	3890	CCCTCTGAGACTGCCCCGCCATGC
2627	GGCATGGCGGGCAGTCTCAGAGG	3891	CCTCTGAGACTGCCCCGCCATGCC
2628	TGGCATGGCGGGCAGTCTCAGAG	3892	CTCTGAGACTGCCCCGCCATGCCA
2629	ATGGCATGGCGGGCAGTCTCAGA	3893	TCTGAGACTGCCCCGCCATGCCAT
2630	AATGGCATGGCGGGCAGTCTCAG	3894	CTGAGACTGCCCCGCCATGCCATT
2631	GAATGGCATGGCGGGCAGTCTCA	3895	TGAGACTGCCCCGCCATGCCATTCT
2632	GGAATGGCATGGCGGGCAGTCTC	3896	GAGACTGCCCCGCCATGCCATTCC
2633	GGGAATGGCATGGCGGGCAGTCT	3897	AGACTGCCCCGCCATGCCATTCCC
2634	AGGGAATGGCATGGCGGGCAGTCT	3898	GACTGCCCCGCCATGCCATTCCCT
2635	AAGGGAATGGCATGGCGGGCAGT	3899	ACTGCCCCGCCATGCCATTCCCTT
2636	AAAGGGAATGGCATGGCGGGCAG	3900	CTGCCCCGCCATGCCATTCCCTTT
2637	TAAAGGGAATGGCATGGCGGGCA	3901	TGCCCCGCCATGCCATTCCCTTTA
2638	GTAAAGGGAATGGCATGGCGGGC	3902	GCCCCGCCATGCCATTCCCTTTAC
2639	GGTAAAGGGAATGGCATGGCGGG	3903	CCCGCCATGCCATTCCCTTTACC
2640	AGGTAAAGGGAATGGCATGGCGG	3904	CCGCCATGCCATTCCCTTTACCT
2641	CAGGTAAAGGGAATGGCATGGCG	3905	CGCCATGCCATTCCCTTTACCTG
2642	CCAGGTAAAGGGAATGGCATGGC	3906	GCCATGCCATTCCCTTTACCTGG
2643	TCCAGGTAAAGGGAATGGCATGG	3907	CCATGCCATTCCCTTTACCTGGA
2644	TTCCAGGTAAAGGGAATGGCATG	3908	CATGCCATTCCCTTTACCTGGAA
2645	TTTCCAGGTAAAGGGAATGGCAT	3909	ATGCCATTCCCTTTACCTGGAAA
2646	TTTTCCAGGTAAAGGGAATGGCA	3910	TGCCATTCCCTTTACCTGGAAAA
2647	GTTTTCCAGGTAAAGGGAATGGC	3911	GCCATTCCCTTTACCTGGAAAAC
2648	AGTTTTCCAGGTAAAGGGAATGG	3912	CCATTCCCTTTACCTGGAAAACCT
2649	GAGTTTTCCAGGTAAAGGGAATG	3913	CATTCCCTTTACCTGGAAAACCTC
2650	GGAGTTTTCCAGGTAAAGGGAAT	3914	ATTCCCTTTACCTGGAAAACCTCC
2651	AGGAGTTTTCCAGGTAAAGGGAA	3915	TTCCCTTTACCTGGAAAACCTCCT
2652	GAGGAGTTTTCCAGGTAAAGGGA	3916	TCCCTTTACCTGGAAAACCTCCTC
2653	GGAGGAGTTTTCCAGGTAAAGGG	3917	CCCTTTACCTGGAAAACCTCCTCC
2654	GGGAGGAGTTTTCCAGGTAAAGG	3918	CCTTTACCTGGAAAACCTCCTCCC
2655	AGGGAGGAGTTTTCCAGGTAAAG	3919	CTTTACCTGGAAAACCTCCTCCCT
2656	TAGGGAGGAGTTTTCCAGGTAAA	3920	TTTACCTGGAAAACCTCCTCCCTA
2657	ATAGGGAGGAGTTTTCCAGGTAA	3921	TTACCTGGAAAACCTCCTCCCTAT
2658	GATAGGGAGGAGTTTTCCAGGTAA	3922	TACCTGGAAAACCTCCTCCCTATC
2659	GGATAGGGAGGAGTTTTCCAGGT	3923	ACCTGGAAAACCTCCTCCCTATCC
2660	TGGATAGGGAGGAGTTTTCCAGG	3924	CCTGGAAAACCTCCTCCCTATCCA
2661	ATGGATAGGGAGGAGTTTTCCAG	3925	CTGGAAAACCTCCTCCCTATCCAT
2662	GATGGATAGGGAGGAGTTTTCCA	3926	TGGAAAACCTCCTCCCTATCCATC
2663	TGATGGATAGGGAGGAGTTTTCC	3927	GGAAAACCTCCTCCCTATCCATCA
2664	TTGATGGATAGGGAGGAGTTTTTC	3928	GAAAACCTCCTCCCTATCCATCAA
2665	TTTGATGGATAGGGAGGAGTTTTT	3929	AAAACCTCCTCCCTATCCATCAAA

2666	CTTTGATGGATAGGGAGGAGTTT	3930	AAACTCCTCCCTATCCATCAAAG
2667	ACTTTGATGGATAGGGAGGAGTT	3931	AACTCCTCCCTATCCATCAAAGT
2668	GACTTTGATGGATAGGGAGGAGT	3932	ACTCCTCCCTATCCATCAAAGTC
2669	GGACTTTGATGGATAGGGAGGAG	3933	CTCCTCCCTATCCATCAAAGTCC
2670	TGGACTTTGATGGATAGGGAGGA	3934	TCCTCCCTATCCATCAAAGTCCA
2671	CTGGACTTTGATGGATAGGGAGG	3935	CCTCCCTATCCATCAAAGTCCAG
2672	TCTGGACTTTGATGGATAGGGAG	3936	CTCCCTATCCATCAAAGTCCAGA
2673	ATCTGGACTTTGATGGATAGGGA	3937	TCCCTATCCATCAAAGTCCAGAT
2674	AATCTGGACTTTGATGGATAGGG	3938	CCCTATCCATCAAAGTCCAGATT
2675	GAATCTGGACTTTGATGGATAGG	3939	CCTATCCATCAAAGTCCAGATTC
2676	TGAATCTGGACTTTGATGGATAG	3940	CTATCCATCAAAGTCCAGATTCA
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2678	CCTGAATCTGGACTTTGATGGAT	3942	ATCCATCAAAGTCCAGATTTCAGG
2679	CCCTGAATCTGGACTTTGATGGA	3943	TCCATCAAAGTCCAGATTTCAGGG
2680	ACCCTGAATCTGGACTTTGATGG	3944	CCATCAAAGTCCAGATTTCAGGGT
2681	GACCCTGAATCTGGACTTTGATG	3945	CATCAAAGTCCAGATTTCAGGGTC
2682	TGACCCTGAATCTGGACTTTGAT	3946	ATCAAAGTCCAGATTTCAGGGTCA
2683	GTGACCCTGAATCTGGACTTTGA	3947	TCAAAGTCCAGATTTCAGGGTCAC
2684	GGTGACCCTGAATCTGGACTTTG	3948	CAAAGTCCAGATTTCAGGGTCACC
2685	AGGTGACCCTGAATCTGGACTTT	3949	AAAGTCCAGATTTCAGGGTCACCT
2686	GAGGTGACCCTGAATCTGGACTT	3950	AAGTCCAGATTTCAGGGTCACCTC
2687	GGAGGTGACCCTGAATCTGGACT	3951	AGTCCAGATTTCAGGGTCACCTCC
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2689	GAGGAGGTGACCCTGAATCTGGA	3953	TCCAGATTTCAGGGTCACCTCCTC
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2696	CTTCCCAGAGGAGGTGACCCTGA	3960	TCAGGGTCACCTCCTCTGGGAAG
2697	GCTTCCCAGAGGAGGTGACCCTG	3961	CAGGGTCACCTCCTCTGGGAAGC
2698	GGCTTCCCAGAGGAGGTGACCCT	3962	AGGGTCACCTCCTCTGGGAAGCC
2699	GGGCTTCCCAGAGGAGGTGACCC	3963	GGGTCACCTCCTCTGGGAAGCCC
2700	TGGGCTTCCCAGAGGAGGTGACC	3964	GGTCACCTCCTCTGGGAAGCCCA
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2702	GGTGGGCTTCCCAGAGGAGGTGA	3966	TCACCTCCTCTGGGAAGCCCACC
2703	AGGTGGGCTTCCCAGAGGAGGTG	3967	CACCTCCTCTGGGAAGCCCACCT
2704	AAGGTGGGCTTCCCAGAGGAGGT	3968	ACCTCCTCTGGGAAGCCCACCTT
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2707	GCCAAGGTGGGCTTCCCAGAGGA	3971	TCCTCTGGGAAGCCCACCTTGGC
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2729	AGTAGTGAGAGTCAACCTGGAGG	3993	CCTCCAGGTTGACTCTCACTACT
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2742	GAACCTGATGATGAGTAGTGAGA	4006	TCTCACTACTCATCATCAGGTTT
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2868	CAGCATTTATTCAACAAACTAGT	4132	ACTAGTTTGTGGAATAAATGCTG
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2871	CACCAGCATTTATTCAACAAACT	4135	AGTTTGTGGAATAAATGCTGGTG
2872	TCACCAGCATTTATTCAACAAAC	4136	GTTTGTGGAATAAATGCTGGTGA
2873	TTCACCAGCATTTATTCAACAAA	4137	TTTGTGGAATAAATGCTGGTGAA
2874	ATTCACCAGCATTTATTCAACAA	4138	TTGTGGAATAAATGCTGGTGAAT
2875	CATTCACCAGCATTTATTCAACA	4139	TGTGGAATAAATGCTGGTGAATG
2876	TCATTCACCAGCATTTATTCAAC	4140	GTTGAATAAATGCTGGTGAATGA
2877	TTCATTCACCAGCATTTATTCAA	4141	TTGAATAAATGCTGGTGAATGAA
2878	ATTCATTCACCAGCATTTATTCA	4142	TGAATAAATGCTGGTGAATGAAT
2879	CATTCATTCACCAGCATTTATTC	4143	GAATAAATGCTGGTGAATGAATG
2880	TCATTCATTCACCAGCATTTATT	4144	AATAAATGCTGGTGAATGAATGA

2881	TTCATTCATTCACCAGCATTAT	4145	ATAAATGCTGGTGAATGAATGAA
2882	ATTCATTCATTCACCAGCATTTA	4146	TAAATGCTGGTGAATGAATGAAT
2883	CATTCATTCATTCACCAGCATTT	4147	AAATGCTGGTGAATGAATGAATG
2884	TCATTCATTCATTCACCAGCATT	4148	AATGCTGGTGAATGAATGAATGA
2885	ATCATTCATTCATTCACCAGCAT	4149	ATGCTGGTGAATGAATGAATGAT
2886	AATCATTCATTCATTCACCAGCA	4150	TGCTGGTGAATGAATGAATGATT
2887	CAATCATTCATTCATTCACCAGC	4151	GCTGGTGAATGAATGAATGATTG
2888	TCAATCATTCATTCATTCACCAG	4152	CTGGTGAATGAATGAATGATTGA
2889	TTCAATCATTCATTCATTCACCA	4153	TGGTGAATGAATGAATGATTGAA
2890	GTTCAATCATTCATTCATTCACC	4154	GGTGAATGAATGAATGATTGAAC
2891	TGTTCAATCATTCATTCATTCAC	4155	GTGAATGAATGAATGATTGAACA
2892	CTGTTCAATCATTCATTCATTCA	4156	TGAATGAATGAATGATTGAACAG
2893	TCTGTTCAATCATTCATTCATTC	4157	GAATGAATGAATGATTGAACAGA
2894	ATCTGTTCAATCATTCATTCATT	4158	AATGAATGAATGATTGAACAGAT
2895	CATCTGTTCAATCATTCATTCAT	4159	ATGAATGAATGATTGAACAGATG
2896	TCATCTGTTCAATCATTCATTCA	4160	TGAATGAATGATTGAACAGATGA
2897	TTCATCTGTTCAATCATTCATTC	4161	GAATGAATGATTGAACAGATGAA
2898	ATTCATCTGTTCAATCATTCATT	4162	AATGAATGATTGAACAGATGAAT
2899	CATTCATCTGTTCAATCATTCAT	4163	ATGAATGATTGAACAGATGAATG
2900	TCATTCATCTGTTCAATCATTC	4164	TGAATGATTGAACAGATGAATGA
2901	CTCATTCATCTGTTCAATCATTC	4165	GAATGATTGAACAGATGAATGAG
2902	ACTCATTCATCTGTTCAATCATT	4166	AATGATTGAACAGATGAATGAGT
2903	CACTCATTCATCTGTTCAATCAT	4167	ATGATTGAACAGATGAATGAGTG
2904	TCACTCATTCATCTGTTCAATCA	4168	TGATTGAACAGATGAATGAGTGA
2905	ATCACTCATTCATCTGTTCAATC	4169	GATTGAACAGATGAATGAGTGAT
2906	CATCACTCATTCATCTGTTCAAT	4170	ATTGAACAGATGAATGAGTGATG
2907	TCATCACTCATTCATCTGTTCAA	4171	TTGAACAGATGAATGAGTGATGA
2908	CTCATCACTCATTCATCTGTTCA	4172	TGAACAGATGAATGAGTGATGAG
2909	ACTCATCACTCATTCATCTGTTTC	4173	GAACAGATGAATGAGTGATGAGT
2910	TACTCATCACTCATTCATCTGTT	4174	AACAGATGAATGAGTGATGAGTA
2911	CTACTCATCACTCATTCATCTGT	4175	ACAGATGAATGAGTGATGAGTAG
2912	TCTACTCATCACTCATTCATCTG	4176	CAGATGAATGAGTGATGAGTAGA
2913	ATCTACTCATCACTCATTCATCT	4177	AGATGAATGAGTGATGAGTAGAT
2914	TATCTACTCATCACTCATTCATC	4178	GATGAATGAGTGATGAGTAGATA
2915	TTATCTACTCATCACTCATTCAT	4179	ATGAATGAGTGATGAGTAGATAA
2916	TTTATCTACTCATCACTCATTC	4180	TGAATGAGTGATGAGTAGATAAAA
2917	TTTTATCTACTCATCACTCATTC	4181	GAATGAGTGATGAGTAGATAAAAA
2918	CTTTTATCTACTCATCACTCATT	4182	AATGAGTGATGAGTAGATAAAAAG
2919	CCTTTTATCTACTCATCACTCAT	4183	ATGAGTGATGAGTAGATAAAAAGG
2920	TCCTTTTATCTACTCATCACTCA	4184	TGAGTGATGAGTAGATAAAAAGGA
2921	ATCCTTTTATCTACTCATCACTC	4185	GAGTGATGAGTAGATAAAAAGGAT
2922	CATCCTTTTATCTACTCATCACT	4186	AGTGATGAGTAGATAAAAAGGATG
2923	CCATCCTTTTATCTACTCATCAC	4187	GTGATGAGTAGATAAAAAGGATGG

2924	TCCATCCTTTTATCTACTCATCA	4188	TGATGAGTAGATAAAAAGGATGGA
2925	ATCCATCCTTTTATCTACTCATC	4189	GATGAGTAGATAAAAAGGATGGAT
2926	CATCCATCCTTTTATCTACTCAT	4190	ATGAGTAGATAAAAAGGATGGATG
2927	CCATCCATCCTTTTATCTACTCA	4191	TGAGTAGATAAAAAGGATGGATGG
2928	TCCATCCATCCTTTTATCTACTC	4192	GAGTAGATAAAAAGGATGGATGGA
2929	CTCCATCCATCCTTTTATCTACT	4193	AGTAGATAAAAAGGATGGATGGAG
2930	TCTCCATCCATCCTTTTATCTAC	4194	GTAGATAAAAAGGATGGATGGAGA
2931	CTCTCCATCCATCCTTTTATCTA	4195	TAGATAAAAAGGATGGATGGAGAG
2932	TCTCTCCATCCATCCTTTTATCT	4196	AGATAAAAAGGATGGATGGAGAGA
2933	ATCTCTCCATCCATCCTTTTATC	4197	GATAAAAAGGATGGATGGAGAGAT
2934	CATCTCTCCATCCATCCTTTTAT	4198	ATAAAAAGGATGGATGGAGAGATG
2935	CCATCTCTCCATCCATCCTTTTA	4199	TAAAAGGATGGATGGAGAGATGG
2936	CCCATCTCTCCATCCATCCTTTT	4200	AAAAGGATGGATGGAGAGATGGG
2937	ACCCATCTCTCCATCCATCCTTT	4201	AAAGGATGGATGGAGAGATGGGT
2938	CACCCATCTCTCCATCCATCCTT	4202	AAGGATGGATGGAGAGATGGGTG
2939	TCACCCATCTCTCCATCCATCCT	4203	AGGATGGATGGAGAGATGGGTGA
2940	CTCACCCATCTCTCCATCCATCC	4204	GGATGGATGGAGAGATGGGTGAG
2941	ACTCACCCATCTCTCCATCCATC	4205	GATGGATGGAGAGATGGGTGAGT
2942	TACTCACCCATCTCTCCATCCAT	4206	ATGGATGGAGAGATGGGTGAGTA
2943	GTACTCACCCATCTCTCCATCCA	4207	TGGATGGAGAGATGGGTGAGTAC
2944	TGTACTCACCCATCTCTCCATCC	4208	GGATGGAGAGATGGGTGAGTACA
2945	ATGTACTCACCCATCTCTCCATC	4209	GATGGAGAGATGGGTGAGTACAT
2946	CATGTACTCACCCATCTCTCCAT	4210	ATGGAGAGATGGGTGAGTACATG
2947	CCATGTACTCACCCATCTCTCCA	4211	TGGAGAGATGGGTGAGTACATGG
2948	TCCATGTACTCACCCATCTCTCC	4212	GGAGAGATGGGTGAGTACATGGA
2949	ATCCATGTACTCACCCATCTCTC	4213	GAGAGATGGGTGAGTACATGGAT
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2952	TCCATCCATGTACTCACCCATCT	4216	AGATGGGTGAGTACATGGATGGA
2953	ATCCATCCATGTACTCACCCATC	4217	GATGGGTGAGTACATGGATGGAT
2954	TATCCATCCATGTACTCACCCAT	4218	ATGGGTGAGTACATGGATGGATA
2955	CTATCCATCCATGTACTCACCCA	4219	TGGGTGAGTACATGGATGGATAG
2956	TCTATCCATCCATGTACTCACCC	4220	GGGTGAGTACATGGATGGATAGA
2957	ATCTATCCATCCATGTACTCACC	4221	GGTGAGTACATGGATGGATAGAT
2958	CATCTATCCATCCATGTACTCAC	4222	GTGAGTACATGGATGGATAGATG
2959	CCATCTATCCATCCATGTACTCA	4223	TGAGTACATGGATGGATAGATGG
2960	TCCATCTATCCATCCATGTACTC	4224	GAGTACATGGATGGATAGATGGA
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2962	CATCCATCTATCCATCCATGTAC	4226	GTACATGGATGGATAGATGGATG
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2964	CTCATCCATCTATCCATCCATGT	4228	ACATGGATGGATAGATGGATGAG
2965	ACTCATCCATCTATCCATCCATG	4229	CATGGATGGATAGATGGATGAGT
2966	AACTCATCCATCTATCCATCCAT	4230	ATGGATGGATAGATGGATGAGTT

2967	CAACTCATCCATCTATCCATCCA	4231	TGGATGGATAGATGGATGAGTTG
2968	CCAACTCATCCATCTATCCATCC	4232	GGATGGATAGATGGATGAGTTGG
2969	ACCAACTCATCCATCTATCCATC	4233	GATGGATAGATGGATGAGTTGGT
2970	CACCAACTCATCCATCTATCCAT	4234	ATGGATAGATGGATGAGTTGGTG
2971	CCACCAACTCATCCATCTATCCA	4235	TGGATAGATGGATGAGTTGGTGG
2972	CCCACCAACTCATCCATCTATCC	4236	GGATAGATGGATGAGTTGGTGGG
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2975	CTACCCACCAACTCATCCATCTA	4239	TAGATGGATGAGTTGGTGGGTAG
2976	TCTACCCACCAACTCATCCATCT	4240	AGATGGATGAGTTGGTGGGTAGA
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2978	AATCTACCCACCAACTCATCCAT	4242	ATGGATGAGTTGGTGGGTAGATT
2979	GAATCTACCCACCAACTCATCCA	4243	TGGATGAGTTGGTGGGTAGATTC
2980	CGAATCTACCCACCAACTCATCC	4244	GGATGAGTTGGTGGGTAGATTCCG
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2990	CATCTAGCCACGAATCTACCCAC	4254	GTGGGTAGATTCTGTGGCTAGATG
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2992	TCCATCTAGCCACGAATCTACCC	4256	GGGTAGATTCTGTGGCTAGATGGA
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2997	CATCATCCATCTAGCCACGAATC	4261	GATTCTGTGGCTAGATGGATGATG
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3003	TCCATCCATCATCCATCTAGCCA	4267	TGGCTAGATGGATGATGGATGGA
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3015	TCCATCTGTCCATCCATCCATCA	4279	TGATGGATGGATGGACAGATGGA
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3017	CATCCATCTGTCCATCCATCCAT	4281	ATGGATGGATGGACAGATGGATG
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3136	TATCTATCCACTCATCAAGTTAT	4400	ATAACTTGATGAGTGATAGATA
3137	CTATCTATCCACTCATCAAGTTA	4401	TAACCTTGATGAGTGATAGATAG
3138	TCTATCTATCCACTCATCAAGTT	4402	AACTTGATGAGTGATAGATAGA

3139	ATCTATCTATCCACTCATCAAGT	4403	ACTTGATGAGTGGATAGATAGAT
3140	AATCTATCTATCCACTCATCAAG	4404	CTTGATGAGTGGATAGATAGATT
3141	CAATCTATCTATCCACTCATCAA	4405	TTGATGAGTGGATAGATAGATTG
3142	GCAATCTATCTATCCACTCATCA	4406	TGATGAGTGGATAGATAGATTGC
3143	AGCAATCTATCTATCCACTCATC	4407	GATGAGTGGATAGATAGATTGCT
3144	CAGCAATCTATCTATCCACTCAT	4408	ATGAGTGGATAGATAGATTGCTG
3145	CCAGCAATCTATCTATCCACTCA	4409	TGAGTGGATAGATAGATTGCTGG
3146	TCCAGCAATCTATCTATCCACTC	4410	GAGTGGATAGATAGATTGCTGGA
3147	ATCCAGCAATCTATCTATCCACT	4411	AGTGGATAGATAGATTGCTGGAT
3148	TATCCAGCAATCTATCTATCCAC	4412	GTGGATAGATAGATTGCTGGATA
3149	CTATCCAGCAATCTATCTATCCA	4413	TGGATAGATAGATTGCTGGATAG
3150	TCTATCCAGCAATCTATCTATCC	4414	GGATAGATAGATTGCTGGATAGA
3151	ATCTATCCAGCAATCTATCTATC	4415	GATAGATAGATTGCTGGATAGAT
3152	CATCTATCCAGCAATCTATCTAT	4416	ATAGATAGATTGCTGGATAGATG
3153	TCATCTATCCAGCAATCTATCTA	4417	TAGATAGATTGCTGGATAGATGA
3154	ATCATCTATCCAGCAATCTATCT	4418	AGATAGATTGCTGGATAGATGAT
3155	AATCATCTATCCAGCAATCTATC	4419	GATAGATTGCTGGATAGATGATT
3156	CAATCATCTATCCAGCAATCTAT	4420	ATAGATTGCTGGATAGATGATTG
3157	TCAATCATCTATCCAGCAATCTA	4421	TAGATTGCTGGATAGATGATTGA
3158	GTCAATCATCTATCCAGCAATCT	4422	AGATTGCTGGATAGATGATTGAC
3159	AGTCAATCATCTATCCAGCAATC	4423	GATTGCTGGATAGATGATTGACT
3160	CAGTCAATCATCTATCCAGCAAT	4424	ATTGCTGGATAGATGATTGACTG
3161	CCAGTCAATCATCTATCCAGCAA	4425	TTGCTGGATAGATGATTGACTGG
3162	CCCAGTCAATCATCTATCCAGCA	4426	TGCTGGATAGATGATTGACTGGG
3163	ACCCAGTCAATCATCTATCCAGC	4427	GCTGGATAGATGATTGACTGGGT
3164	CACCCAGTCAATCATCTATCCAG	4428	CTGGATAGATGATTGACTGGGTG
3165	CCACCCAGTCAATCATCTATCCA	4429	TGGATAGATGATTGACTGGGTGG
3166	TCCACCCAGTCAATCATCTATCC	4430	GGATAGATGATTGACTGGGTGGA
3167	ATCCACCCAGTCAATCATCTATC	4431	GATAGATGATTGACTGGGTGGAT
3168	TATCCACCCAGTCAATCATCTAT	4432	ATAGATGATTGACTGGGTGGATA
3169	CTATCCACCCAGTCAATCATCTA	4433	TAGATGATTGACTGGGTGGATAG
3170	TCTATCCACCCAGTCAATCATCT	4434	AGATGATTGACTGGGTGGATAGA
3171	ATCTATCCACCCAGTCAATCATC	4435	GATGATTGACTGGGTGGATAGAT
3172	CATCTATCCACCCAGTCAATCAT	4436	ATGATTGACTGGGTGGATAGATG
3173	TCATCTATCCACCCAGTCAATCA	4437	TGATTGACTGGGTGGATAGATGA
3174	TTCATCTATCCACCCAGTCAATC	4438	GATTGACTGGGTGGATAGATGAA
3175	TTTCATCTATCCACCCAGTCAAT	4439	ATTGACTGGGTGGATAGATGAAA
3176	ATTTTCATCTATCCACCCAGTCAA	4440	TTGACTGGGTGGATAGATGAAAT
3177	CATTTTCATCTATCCACCCAGTCA	4441	TGACTGGGTGGATAGATGAAATG
3178	ACATTTTCATCTATCCACCCAGTC	4442	GACTGGGTGGATAGATGAAATGT
3179	AACATTTTCATCTATCCACCCAGT	4443	ACTGGGTGGATAGATGAAATGTT
3180	CAACATTTTCATCTATCCACCCAG	4444	CTGGGTGGATAGATGAAATGTTG
3181	CCAACATTTTCATCTATCCACCCA	4445	TGGGTGGATAGATGAAATGTTGG

3182	TCCAACATTTTCATCTATCCACCC	4446	GGGTGGATAGATGAAATGTTGGA
3183	ATCCAACATTTTCATCTATCCACC	4447	GGTGGATAGATGAAATGTTGGAT
3184	CATCCAACATTTTCATCTATCCAC	4448	GTGGATAGATGAAATGTTGGATG
3185	TCATCCAACATTTTCATCTATCCA	4449	TGGATAGATGAAATGTTGGATGA
3186	CTCATCCAACATTTTCATCTATCC	4450	GGATAGATGAAATGTTGGATGAG
3187	GCTCATCCAACATTTTCATCTATC	4451	GATAGATGAAATGTTGGATGAGC
3188	TGCTCATCCAACATTTTCATCTAT	4452	ATAGATGAAATGTTGGATGAGCA
3189	CTGCTCATCCAACATTTTCATCTA	4453	TAGATGAAATGTTGGATGAGCAG
3190	TCTGCTCATCCAACATTTTCATCT	4454	AGATGAAATGTTGGATGAGCAGA
3191	ATCTGCTCATCCAACATTTTCATC	4455	GATGAAATGTTGGATGAGCAGAT
3192	AATCTGCTCATCCAACATTTTCAT	4456	ATGAAATGTTGGATGAGCAGATT
3193	TAATCTGCTCATCCAACATTTCA	4457	TGAAATGTTGGATGAGCAGATTA
3194	TTAATCTGCTCATCCAACATTTTC	4458	GAAATGTTGGATGAGCAGATTAA
3195	CTTAATCTGCTCATCCAACATTT	4459	AAATGTTGGATGAGCAGATTAAAG
3196	ACTTAATCTGCTCATCCAACATT	4460	AATGTTGGATGAGCAGATTAAAGT
3197	AACCTAATCTGCTCATCCAACAT	4461	ATGTTGGATGAGCAGATTAAAGTT
3198	CAACTTAATCTGCTCATCCAACA	4462	TGTTGGATGAGCAGATTAAAGTTG
3199	ACAACCTTAATCTGCTCATCCAAC	4463	GTTGGATGAGCAGATTAAAGTTGT
3200	TACAACCTTAATCTGCTCATCCAA	4464	TTGGATGAGCAGATTAAAGTTGTA
3201	ATACAACCTTAATCTGCTCATCCA	4465	TGGATGAGCAGATTAAAGTTGTAT
3202	AATACAACCTTAATCTGCTCATCC	4466	GGATGAGCAGATTAAAGTTGTATT
3203	CAATACAACCTTAATCTGCTCATC	4467	GATGAGCAGATTAAAGTTGTATTG
3204	CCAATACAACCTTAATCTGCTCAT	4468	ATGAGCAGATTAAAGTTGTATTGG
3205	TCCAATACAACCTTAATCTGCTCA	4469	TGAGCAGATTAAAGTTGTATTGGA
3206	ATCCAATACAACCTTAATCTGCTC	4470	GAGCAGATTAAAGTTGTATTGGAT
3207	CATCCAATACAACCTTAATCTGCT	4471	AGCAGATTAAAGTTGTATTGGATG
3208	CCATCCAATACAACCTTAATCTGC	4472	GCAGATTAAAGTTGTATTGGATGG
3209	CCCATCCAATACAACCTTAATCTG	4473	CAGATTAAAGTTGTATTGGATGGG
3210	TCCCATCCAATACAACCTTAATCT	4474	AGATTAAAGTTGTATTGGATGGGA
3211	ATCCCATCCAATACAACCTTAATC	4475	GATTAAAGTTGTATTGGATGGGAT
3212	CATCCCATCCAATACAACCTTAAT	4476	ATTAAGTTGTATTGGATGGGATG
3213	CCATCCCATCCAATACAACCTTAA	4477	TTAAGTTGTATTGGATGGGATGG
3214	TCCATCCCATCCAATACAACCTTA	4478	TAAGTTGTATTGGATGGGATGGA
3215	ATCCATCCCATCCAATACAACCTT	4479	AAGTTGTATTGGATGGGATGGAT
3216	CATCCATCCCATCCAATACAACCT	4480	AGTTGTATTGGATGGGATGGATG
3217	CCATCCATCCCATCCAATACAAC	4481	GTTGTATTGGATGGGATGGATGG
3218	TCCATCCATCCCATCCAATACAA	4482	TTGTATTGGATGGGATGGATGGA
3219	TTCCATCCATCCCATCCAATACA	4483	TGTATTGGATGGGATGGATGGAA
3220	CTTCCATCCATCCCATCCAATAC	4484	GTATTGGATGGGATGGATGGAAAG
3221	ACTTCCATCCATCCCATCCAATA	4485	TATTGGATGGGATGGATGGAAAGT
3222	CACTTCCATCCATCCCATCCAAT	4486	ATTGGATGGGATGGATGGAAAGTG
3223	ACACTTCCATCCATCCCATCCAA	4487	TTGGATGGGATGGATGGAAAGTGT
3224	CACACTTCCATCCATCCCATCCA	4488	TGGATGGGATGGATGGAAAGTGTG

3225	CCACACTTCCATCCATCCCATCC	4489	GGATGGGATGGATGGAAGTGTGG
3226	ACCACACTTCCATCCATCCCATC	4490	GATGGGATGGATGGAAGTGTGGT
3227	AACCACACTTCCATCCATCCCAT	4491	ATGGGATGGATGGAAGTGTGGTT
3228	CAACCACACTTCCATCCATCCCA	4492	TGGGATGGATGGAAGTGTGGTTG
3229	TCAACCACACTTCCATCCATCCC	4493	GGGATGGATGGAAGTGTGGTTGA
3230	CTCAACCACACTTCCATCCATCC	4494	GGATGGATGGAAGTGTGGTTGAG
3231	ACTCAACCACACTTCCATCCATC	4495	GATGGATGGAAGTGTGGTTGAGT
3232	AACTCAACCACACTTCCATCCAT	4496	ATGGATGGAAGTGTGGTTGAGTT
3233	TA ACTCAACCACACTTCCATCCA	4497	TGGATGGAAGTGTGGTTGAGTTA
3234	ATAACTCAACCACACTTCCATCC	4498	GGATGGAAGTGTGGTTGAGTTAT
3235	AATAACTCAACCACACTTCCATC	4499	GATGGAAGTGTGGTTGAGTTATT
3236	TAATAACTCAACCACACTTCCAT	4500	ATGGAAGTGTGGTTGAGTTATTA
3237	CTAATAACTCAACCACACTTCCA	4501	TGGAAGTGTGGTTGAGTTATTAG
3238	TCTAATAACTCAACCACACTTCC	4502	GGAAGTGTGGTTGAGTTATTAGA
3239	TTCTAATAACTCAACCACACTTC	4503	GAAGTGTGGTTGAGTTATTAGAA
3240	CTTCTAATAACTCAACCACACTT	4504	AAGTGTGGTTGAGTTATTAGAAG
3241	CCTTCTAATAACTCAACCACACT	4505	AGTGTGGTTGAGTTATTAGAAGG
3242	TCCTTCTAATAACTCAACCACAC	4506	GTGTGGTTGAGTTATTAGAAGGA
3243	TTCTTCTAATAACTCAACCACA	4507	TGTGGTTGAGTTATTAGAAGGAA
3244	CTTCCTTCTAATAACTCAACCAC	4508	GTGGTTGAGTTATTAGAAGGAAG
3245	TCTTCCTTCTAATAACTCAACCA	4509	TGGTTGAGTTATTAGAAGGAAGA
3246	ATCTTCCTTCTAATAACTCAACC	4510	GGTTGAGTTATTAGAAGGAAGAT
3247	AATCTTCCTTCTAATAACTCAAC	4511	GTTGAGTTATTAGAAGGAAGATT
3248	CAATCTTCCTTCTAATAACTCAA	4512	TTGAGTTATTAGAAGGAAGATTG
3249	TCAATCTTCCTTCTAATAACTCA	4513	TGAGTTATTAGAAGGAAGATTGA
3250	CTCAATCTTCCTTCTAATAACTC	4514	GAGTTATTAGAAGGAAGATTGAG
3251	ACTCAATCTTCCTTCTAATAACT	4515	AGTTATTAGAAGGAAGATTGAGT
3252	TACTCAATCTTCCTTCTAATAAC	4516	GTTATTAGAAGGAAGATTGAGTA
3253	CTACTCAATCTTCCTTCTAATAA	4517	TTATTAGAAGGAAGATTGAGTAG
3254	TCTACTCAATCTTCCTTCTAATA	4518	TATTAGAAGGAAGATTGAGTAGA
3255	ATCTACTCAATCTTCCTTCTAAT	4519	ATTAGAAGGAAGATTGAGTAGAT
3256	TATCTACTCAATCTTCCTTCTAA	4520	TTAGAAGGAAGATTGAGTAGATA
3257	CTATCTACTCAATCTTCCTTCTA	4521	TAGAAGGAAGATTGAGTAGATAG
3258	CCTATCTACTCAATCTTCCTTCT	4522	AGAAGGAAGATTGAGTAGATAGG
3259	ACCTATCTACTCAATCTTCCTTC	4523	GAAGGAAGATTGAGTAGATAGGT
3260	CACCTATCTACTCAATCTTCCTT	4524	AAGGAAGATTGAGTAGATAGGTG
3261	TCACCTATCTACTCAATCTTCCT	4525	AGGAAGATTGAGTAGATAGGTGA
3262	TTACCTATCTACTCAATCTTCC	4526	GGAAGATTGAGTAGATAGGTGAA
3263	ATTCACCTATCTACTCAATCTTC	4527	GAAGATTGAGTAGATAGGTGAAT
3264	AATTCACCTATCTACTCAATCTT	4528	AAGATTGAGTAGATAGGTGAATT
3265	AAATTCACCTATCTACTCAATCT	4529	AGATTGAGTAGATAGGTGAATTT
3266	CAAATTCACCTATCTACTCAATC	4530	GATTGAGTAGATAGGTGAATTTG
3267	ACAAATTCACCTATCTACTCAAT	4531	ATTGAGTAGATAGGTGAATTTGT

3268	AACAAATTCACCTATCTACTCAA	4532	TTGAGTAGATAGGTGAATTTGTT
3269	CAACAAATTCACCTATCTACTCA	4533	TGAGTAGATAGGTGAATTTGTTG
3270	TCAACAAATTCACCTATCTACTC	4534	GAGTAGATAGGTGAATTTGTTGA
3271	ATCAACAAATTCACCTATCTACT	4535	AGTAGATAGGTGAATTTGTTGAT
3272	TATCAACAAATTCACCTATCTAC	4536	GTAGATAGGTGAATTTGTTGATA
3273	CTATCAACAAATTCACCTATCTA	4537	TAGATAGGTGAATTTGTTGATAG
3274	ACTATCAACAAATTCACCTATCT	4538	AGATAGGTGAATTTGTTGATAGT
3275	GACTATCAACAAATTCACCTATC	4539	GATAGGTGAATTTGTTGATAGTC
3276	TGACTATCAACAAATTCACCTAT	4540	ATAGGTGAATTTGTTGATAGTCA
3277	CTGACTATCAACAAATTCACCTA	4541	TAGGTGAATTTGTTGATAGTCAG
3278	TCTGACTATCAACAAATTCACCT	4542	AGGTGAATTTGTTGATAGTCAGA
3279	ATCTGACTATCAACAAATTCACC	4543	GGTGAATTTGTTGATAGTCAGAT
3280	CATCTGACTATCAACAAATTCAC	4544	GTGAATTTGTTGATAGTCAGATG
3281	CCATCTGACTATCAACAAATTC	4545	TGAATTTGTTGATAGTCAGATGG
3282	CCCATCTGACTATCAACAAATTC	4546	GAATTTGTTGATAGTCAGATGGG
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3284	TACCCATCTGACTATCAACAAAT	4548	ATTTGTTGATAGTCAGATGGGTA
3285	CTACCCATCTGACTATCAACAAA	4549	TTTGTGATAGTCAGATGGGTAG
3286	TCTACCCATCTGACTATCAACAA	4550	TTGTGATAGTCAGATGGGTAGA
3287	ATCTACCCATCTGACTATCAACA	4551	TGTTGATAGTCAGATGGGTAGAT
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3289	CTATCTACCCATCTGACTATCAA	4553	TTGATAGTCAGATGGGTAGATAG
3290	CCTATCTACCCATCTGACTATCA	4554	TGATAGTCAGATGGGTAGATAGG
3291	ACCTATCTACCCATCTGACTATC	4555	GATAGTCAGATGGGTAGATAGGT
3292	TACCTATCTACCCATCTGACTAT	4556	ATAGTCAGATGGGTAGATAGGTA
3293	CTACCTATCTACCCATCTGACTA	4557	TAGTCAGATGGGTAGATAGGTAG
3294	TCTACCTATCTACCCATCTGACT	4558	AGTCAGATGGGTAGATAGGTAGA
3295	ATCTACCTATCTACCCATCTGAC	4559	GTCAGATGGGTAGATAGGTAGAT
3296	CATCTACCTATCTACCCATCTGA	4560	TCAGATGGGTAGATAGGTAGATG
3297	CCATCTACCTATCTACCCATCTG	4561	CAGATGGGTAGATAGGTAGATGG
3298	TCCATCTACCTATCTACCCATCT	4562	AGATGGGTAGATAGGTAGATGGA
3299	ATCCATCTACCTATCTACCCATC	4563	GATGGGTAGATAGGTAGATGGAT
3300	CATCCATCTACCTATCTACCCAT	4564	ATGGGTAGATAGGTAGATGGATG
3301	CCATCCATCTACCTATCTACCCA	4565	TGGGTAGATAGGTAGATGGATGG
3302	TCCATCCATCTACCTATCTACCC	4566	GGGTAGATAGGTAGATGGATGGA
3303	ATCCATCCATCTACCTATCTACC	4567	GGTAGATAGGTAGATGGATGGAT
3304	CATCCATCCATCTACCTATCTAC	4568	GTAGATAGGTAGATGGATGGATG
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3306	TCCATCCATCCATCTACCTATCT	4570	AGATAGGTAGATGGATGGATGGA
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3308	CATCCATCCATCCATCTACCTAT	4572	ATAGGTAGATGGATGGATGGATG
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3314	TCCATCCATCCATCCATCCATCT	4578	AGATGGATGGATGGATGGATGGA
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3321	CTATACATCCATCCATCCATCCA	4585	TGGATGGATGGATGGATGTATAG
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3324	TGCCTATACATCCATCCATCCAT	4588	ATGGATGGATGGATGTATAGGCA
3325	CTGCCTATACATCCATCCATCCA	4589	TGGATGGATGGATGTATAGGCAG
3326	TCTGCCTATACATCCATCCATCC	4590	GGATGGATGGATGTATAGGCAGA
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3328	CATCTGCCTATACATCCATCCAT	4592	ATGGATGGATGTATAGGCAGATG
3329	CCATCTGCCTATACATCCATCCA	4593	TGGATGGATGTATAGGCAGATGG
3330	TCCATCTGCCTATACATCCATCC	4594	GGATGGATGTATAGGCAGATGGA
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3332	TGTCCATCTGCCTATACATCCAT	4596	ATGGATGTATAGGCAGATGGACA
3333	TTGTCCATCTGCCTATACATCCA	4597	TGGATGTATAGGCAGATGGACAA
3334	TTTGTCCATCTGCCTATACATCC	4598	GGATGTATAGGCAGATGGACAAA
3335	ATTTGTCCATCTGCCTATACATC	4599	GATGTATAGGCAGATGGACAAAT
3336	CATTTGTCCATCTGCCTATACAT	4600	ATGTATAGGCAGATGGACAAATG
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3338	TCCATTTGTCCATCTGCCTATAC	4602	GTATAGGCAGATGGACAAATGGA
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3340	CATCCATTTGTCCATCTGCCTAT	4604	ATAGGCAGATGGACAAATGGATG
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3345	CCATTCATCCATTTGTCCATCTG	4609	CAGATGGACAAATGGATGAATGG
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3348	CACCCATTCATCCATTTGTCCAT	4612	ATGGACAAATGGATGAATGGGTG
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3350	CCCACCCATTCATCCATTTGTCC	4614	GGACAAATGGATGAATGGGTGGG
3351	ACCCACCCATTCATCCATTTGTC	4615	GACAAATGGATGAATGGGTGGGT
3352	CACCCACCCATTCATCCATTTGT	4616	ACAAATGGATGAATGGGTGGGTG
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3354	TCCACCCACCCATTCATCCATTT	4618	AAATGGATGAATGGGTGGGTGGA
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3356	CATCCACCCACCCATTCATCCAT	4620	ATGGATGAATGGGTGGGTGGATG
3357	TCATCCACCCACCCATTCATCCA	4621	TGGATGAATGGGTGGGTGGATGA
3358	TTCATCCACCCACCCATTCATCC	4622	GGATGAATGGGTGGGTGGATGAA
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3365	CCTTCCATTCATCCACCCACCCA	4629	TGGGTGGGTGGATGAATGGAAGG
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3370	CACATCCTTCCATTCATCCACCC	4634	GGGTGGATGAATGGAAGGATGTG
3371	ACACATCCTTCCATTCATCCACC	4635	GGTGGATGAATGGAAGGATGTGT
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3373	CCACACATCCTTCCATTCATCCA	4637	TGGATGAATGGAAGGATGTGTGG
3374	ACCACACATCCTTCCATTCATCC	4638	GGATGAATGGAAGGATGTGTGGT
3375	AACCACACATCCTTCCATTCATC	4639	GATGAATGGAAGGATGTGTGGTT
3376	CAACCACACATCCTTCCATTCAT	4640	ATGAATGGAAGGATGTGTGGTTG
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3380	AGTTCAACCACACATCCTTCCAT	4644	ATGGAAGGATGTGTGGTTGAACT
3381	TAGTTCAACCACACATCCTTCCA	4645	TGGAAGGATGTGTGGTTGAACTA
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3383	AATAGTTCAACCACACATCCTTTC	4647	GAAGGATGTGTGGTTGAACTATT
3384	CAATAGTTCAACCACACATCCTT	4648	AAGGATGTGTGGTTGAACTATTG
3385	GCAATAGTTCAACCACACATCCT	4649	AGGATGTGTGGTTGAACTATTGC
3386	TGCAATAGTTCAACCACACATCC	4650	GGATGTGTGGTTGAACTATTGCA
3387	TTGCAATAGTTCAACCACACATC	4651	GATGTGTGGTTGAACTATTGCAA
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3389	ACTTGCAATAGTTCAACCACACA	4653	TGTGTGGTTGAACTATTGCAAGT
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3391	ATACTTGCAATAGTTCAACCACA	4655	TGTGGTTGAACTATTGCAAGTAT
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3393	CAATACTTGCAATAGTTCAACCA	4657	TGGTTGAACTATTGCAAGTATTG
3394	TCAATACTTGCAATAGTTCAACC	4658	GGTTGAACTATTGCAAGTATTGA
3395	ATCAATACTTGCAATAGTTCAAC	4659	GTTGAACTATTGCAAGTATTGAT
3396	TATCAATACTTGCAATAGTTCAA	4660	TTGAACTATTGCAAGTATTGATA

3397	TTATCAATACTTGCAATAGTTCA	4661	TGAACTATTGCAAGTATTGATAA
3398	ATTATCAATACTTGCAATAGTTC	4662	GAAGTATTGCAAGTATTGATAAT
3399	AATTATCAATACTTGCAATAGTT	4663	AACTATTGCAAGTATTGATAAATT
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3402	CCCAATTATCAATACTTGCAATA	4666	TATTGCAAGTATTGATAAATTGGG
3403	ACCCAATTATCAATACTTGCAAT	4667	ATTGCAAGTATTGATAAATTGGGT
3404	AACCCAATTATCAATACTTGCAA	4668	TTGCAAGTATTGATAAATTGGGTT
3405	GAACCCAATTATCAATACTTGCA	4669	TGCAAGTATTGATAAATTGGGTTC
3406	TGAACCCAATTATCAATACTTGC	4670	GCAAGTATTGATAAATTGGGTTC
3407	ATGAACCCAATTATCAATACTTG	4671	CAAGTATTGATAAATTGGGTTCAT
3408	TATGAACCCAATTATCAATACTT	4672	AAGTATTGATAAATTGGGTTCATA
3409	TTATGAACCCAATTATCAATACT	4673	AGTATTGATAAATTGGGTTCATAA
3410	ATTATGAACCCAATTATCAATAC	4674	GTATTGATAAATTGGGTTCATAAT
3411	AATTATGAACCCAATTATCAATA	4675	TATTGATAAATTGGGTTCATAATT
3412	AAATTATGAACCCAATTATCAAT	4676	ATTGATAAATTGGGTTCATAATTT
3413	GAAATTATGAACCCAATTATCAA	4677	TTGATAAATTGGGTTCATAATTTCT
3414	AGAAATTATGAACCCAATTATCA	4678	TGATAAATTGGGTTCATAATTTCT
3415	CAGAAATTATGAACCCAATTATC	4679	GATAAATTGGGTTCATAATTTCTG
3416	TCAGAAATTATGAACCCAATTAT	4680	ATAAATTGGGTTCATAATTTCTGA
3417	TTCAGAAATTATGAACCCAATTA	4681	TAATTGGGTTCATAATTTCTGAA
3418	ATTCAGAAATTATGAACCCAATT	4682	AATTGGGTTCATAATTTCTGAAT
3419	TATTCAGAAATTATGAACCCAAT	4683	ATTGGGTTCATAATTTCTGAATA
3420	ATATTCAGAAATTATGAACCCAA	4684	TTGGGTTCATAATTTCTGAATAT
3421	AATATTCAGAAATTATGAACCCA	4685	TGGGTTCATAATTTCTGAATATT
3422	AAATATTCAGAAATTATGAACCC	4686	GGGTTCATAATTTCTGAATATTT
3423	TAAATATTCAGAAATTATGAACC	4687	GGTTCATAATTTCTGAATATTTA
3424	CTAAATATTCAGAAATTATGAAC	4688	GTTTCATAATTTCTGAATATTTAG
3425	TCTAAATATTCAGAAATTATGAA	4689	TTCATAATTTCTGAATATTTAGA
3426	ATCTAAATATTCAGAAATTATGA	4690	TCATAATTTCTGAATATTTAGAT
3427	CATCTAAATATTCAGAAATTATG	4691	CATAATTTCTGAATATTTAGATG
3428	CCATCTAAATATTCAGAAATTAT	4692	ATAATTTCTGAATATTTAGATGG
3429	TCCATCTAAATATTCAGAAATTA	4693	TAATTTCTGAATATTTAGATGGA
3430	ATCCATCTAAATATTCAGAAATT	4694	AATTTCTGAATATTTAGATGGAT
3431	CATCCATCTAAATATTCAGAAAT	4695	ATTTCTGAATATTTAGATGGATG
3432	CCATCCATCTAAATATTCAGAAA	4696	TTTCTGAATATTTAGATGGATGG
3433	ACCATCCATCTAAATATTCAGAA	4697	TTCTGAATATTTAGATGGATGGT
3434	AACCATCCATCTAAATATTCAGA	4698	TCTGAATATTTAGATGGATGGTT
3435	CAACCATCCATCTAAATATTCAG	4699	CTGAATATTTAGATGGATGGTTG
3436	ACAACCATCCATCTAAATATTC	4700	TGAATATTTAGATGGATGGTTGT
3437	CACAACCATCCATCTAAATATTC	4701	GAATATTTAGATGGATGGTTGTG
3438	TCACAACCATCCATCTAAATATT	4702	AATATTTAGATGGATGGTTGTGA
3439	CTCACAACCATCCATCTAAATAT	4703	ATATTTAGATGGATGGTTGTGAG

3440	ACTCACAACCATCCATCTAAATA	4704	TATTTAGATGGATGGTTGTGAGT
3441	CACTCACAACCATCCATCTAAAT	4705	ATTTAGATGGATGGTTGTGAGTG
3442	CCACTCACAACCATCCATCTAAA	4706	TTTAGATGGATGGTTGTGAGTGG
3443	GCCACTCACAACCATCCATCTAA	4707	TTAGATGGATGGTTGTGAGTGGC
3444	AGCCACTCACAACCATCCATCTA	4708	TAGATGGATGGTTGTGAGTGGCT
3445	CAGCCACTCACAACCATCCATCT	4709	AGATGGATGGTTGTGAGTGGCTG
3446	CCAGCCACTCACAACCATCCATC	4710	GATGGATGGTTGTGAGTGGCTGG
3447	ACCAGCCACTCACAACCATCCAT	4711	ATGGATGGTTGTGAGTGGCTGGT
3448	CACCAGCCACTCACAACCATCCA	4712	TGGATGGTTGTGAGTGGCTGGTG
3449	CCACCAGCCACTCACAACCATCC	4713	GGATGGTTGTGAGTGGCTGGTGG
3450	TCCACCAGCCACTCACAACCATC	4714	GATGGTTGTGAGTGGCTGGTGGA
3451	GTCCACCAGCCACTCACAACCAT	4715	ATGGTTGTGAGTGGCTGGTGGAC
3452	TGTCCACCAGCCACTCACAACCA	4716	TGGTTGTGAGTGGCTGGTGGACA
3453	CTGTCCACCAGCCACTCACAACC	4717	GGTTGTGAGTGGCTGGTGGACAG
3454	TCTGTCCACCAGCCACTCACAAC	4718	GTTGTGAGTGGCTGGTGGACAGA
3455	GTCTGTCCACCAGCCACTCACAA	4719	TTGTGAGTGGCTGGTGGACAGAC
3456	CGTCTGTCCACCAGCCACTCACA	4720	TGTGAGTGGCTGGTGGACAGACG
3457	TCGTCTGTCCACCAGCCACTCAC	4721	GTGAGTGGCTGGTGGACAGACGA
3458	TTCGTCTGTCCACCAGCCACTCA	4722	TGAGTGGCTGGTGGACAGACGAA
3459	TTTCGTCTGTCCACCAGCCACTC	4723	GAGTGGCTGGTGGACAGACGAAA
3460	TTTTCGTCTGTCCACCAGCCACT	4724	AGTGGCTGGTGGACAGACGAAAA
3461	TTTTTCGTCTGTCCACCAGCCAC	4725	GTGGCTGGTGGACAGACGAAAAA
3462	ATTTTTCGTCTGTCCACCAGCCA	4726	TGGCTGGTGGACAGACGAAAAAT
3463	CATTTTTCGTCTGTCCACCAGCC	4727	GGCTGGTGGACAGACGAAAAATG
3464	CCATTTTTCGTCTGTCCACCAGC	4728	GCTGGTGGACAGACGAAAAATGG
3465	TCCATTTTTCGTCTGTCCACCAG	4729	CTGGTGGACAGACGAAAAATGGA
3466	ATCCATTTTTCGTCTGTCCACCA	4730	TGGTGGACAGACGAAAAATGGAT
3467	CATCCATTTTTCGTCTGTCCACC	4731	GGTGGACAGACGAAAAATGGATG
3468	CCATCCATTTTTCGTCTGTCCAC	4732	GTGGACAGACGAAAAATGGATGG
3469	ACCATCCATTTTTCGTCTGTCCA	4733	TGGACAGACGAAAAATGGATGGT
3470	AACCATCCATTTTTCGTCTGTCC	4734	GGACAGACGAAAAATGGATGGTT
3471	CAACCATCCATTTTTCGTCTGTC	4735	GACAGACGAAAAATGGATGGTTG
3472	CCAACCATCCATTTTTCGTCTGT	4736	ACAGACGAAAAATGGATGGTTGG
3473	TCCAACCATCCATTTTTCGTCTG	4737	CAGACGAAAAATGGATGGTTGGA
3474	ATCCAACCATCCATTTTTCGTCT	4738	AGACGAAAAATGGATGGTTGGAT
3475	TATCCAACCATCCATTTTTCGTC	4739	GACGAAAAATGGATGGTTGGATA
3476	TTATCCAACCATCCATTTTTCGT	4740	ACGAAAAATGGATGGTTGGATAA
3477	TTTATCCAACCATCCATTTTTCG	4741	CGAAAAATGGATGGTTGGATAAA
3478	ATTTATCCAACCATCCATTTTTC	4742	GAAAAATGGATGGTTGGATAAAT
3479	AATTTATCCAACCATCCATTTT	4743	AAAAATGGATGGTTGGATAAATT
3480	CAATTTATCCAACCATCCATTTT	4744	AAAATGGATGGTTGGATAAATTG
3481	TCAATTTATCCAACCATCCATTT	4745	AAATGGATGGTTGGATAAATTGA
3482	ATCAATTTATCCAACCATCCATT	4746	AATGGATGGTTGGATAAATTGAT

3483	CATCAATTTATCCAACCATCCAT	4747	ATGGATGGTTGGATAAATTGATG
3484	CCATCAATTTATCCAACCATCCA	4748	TGGATGGTTGGATAAATTGATGG
3485	CCCATCAATTTATCCAACCATCC	4749	GGATGGTTGGATAAATTGATGGG
3486	ACCCATCAATTTATCCAACCATC	4750	GATGGTTGGATAAATTGATGGGT
3487	CACCCATCAATTTATCCAACCAT	4751	ATGGTTGGATAAATTGATGGGTG
3488	CCACCCATCAATTTATCCAACCA	4752	TGGTTGGATAAATTGATGGGTGG
3489	TCCACCCATCAATTTATCCAACC	4753	GGTTGGATAAATTGATGGGTGGA
3490	ATCCACCCATCAATTTATCCAAC	4754	GTTGGATAAATTGATGGGTGGAT
3491	CATCCACCCATCAATTTATCCAA	4755	TTGGATAAATTGATGGGTGGATG
3492	CCATCCACCCATCAATTTATCCA	4756	TGGATAAATTGATGGGTGGATGG
3493	TCCATCCACCCATCAATTTATCC	4757	GGATAAATTGATGGGTGGATGGA
3494	ATCCATCCACCCATCAATTTATC	4758	GATAAATTGATGGGTGGATGGAT
3495	CATCCATCCACCCATCAATTTAT	4759	ATAAATTGATGGGTGGATGGATG
3496	CCATCCATCCACCCATCAATTTA	4760	TAAATTGATGGGTGGATGGATGG
3497	ACCATCCATCCACCCATCAATTT	4761	AAATTGATGGGTGGATGGATGGT
3498	AACCATCCATCCACCCATCAATT	4762	AATTGATGGGTGGATGGATGGTT
3499	CAACCATCCATCCACCCATCAAT	4763	ATTGATGGGTGGATGGATGGTTG
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3501	ACCAACCATCCATCCACCCATCA	4765	TGATGGGTGGATGGATGGTTGGT
3502	AACCAACCATCCATCCACCCATC	4766	GATGGGTGGATGGATGGTTGGTT
3503	CAACCAACCATCCATCCACCCAT	4767	ATGGGTGGATGGATGGTTGGTTG
3504	ACAACCAACCATCCATCCACCCA	4768	TGGGTGGATGGATGGTTGGTTGT
3505	TACAACCAACCATCCATCCACCC	4769	GGGTGGATGGATGGTTGGTTGTA
3506	ATACAACCAACCATCCATCCACC	4770	GGTGGATGGATGGTTGGTTGTAT
3507	CATACAACCAACCATCCATCCAC	4771	GTGGATGGATGGTTGGTTGTATG
3508	TCATACAACCAACCATCCATCCA	4772	TGGATGGATGGTTGGTTGTATGA
3509	TTCATACAACCAACCATCCATCC	4773	GGATGGATGGTTGGTTGTATGAA
3510	TTTCATACAACCAACCATCCATC	4774	GATGGATGGTTGGTTGTATGAAA
3511	CTTTCATACAACCAACCATCCAT	4775	ATGGATGGTTGGTTGTATGAAAG
3512	TCTTTCATACAACCAACCATCCA	4776	TGGATGGTTGGTTGTATGAAAGA
3513	TTCTTTCATACAACCAACCATCC	4777	GGATGGTTGGTTGTATGAAAGAA
3514	ATTCTTTCATACAACCAACCATC	4778	GATGGTTGGTTGTATGAAAGAAT
3515	CATTCTTTCATACAACCAACCAT	4779	ATGGTTGGTTGTATGAAAGAATG
3516	TCATTCTTTCATACAACCAACCA	4780	TGGTTGGTTGTATGAAAGAATGA
3517	TTCATTCTTTCATACAACCAACC	4781	GGTTGGTTGTATGAAAGAATGAA
3518	ATTCATTCTTTCATACAACCAAC	4782	GTTGGTTGTATGAAAGAATGAAT
3519	CATTCAATTCTTTCATACAACCAA	4783	TTGGTTGTATGAAAGAATGAATG
3520	TCATTCAATTCTTTCATACAACCA	4784	TGGTTGTATGAAAGAATGAATGA
3521	ATCATTCAATTCTTTCATACAACC	4785	GGTTGTATGAAAGAATGAATGAT
3522	AATCATTCAATTCTTTCATACAAC	4786	GTTGTATGAAAGAATGAATGATT
3523	CAATCATTCAATTCTTTCATACAA	4787	TTGTATGAAAGAATGAATGATTG
3524	CCAATCATTCAATTCTTTCATACA	4788	TGTATGAAAGAATGAATGATTGG
3525	CCCAATCATTCAATTCTTTCATAC	4789	GTATGAAAGAATGAATGATTGGG

3526	ACCCAATCATTCAATTCCTTCATA	4790	TATGAAAGAATGAATGATTGGGT
3527	TACCCAATCATTCAATTCCTTCAT	4791	ATGAAAGAATGAATGATTGGGTA
3528	CTACCCAATCATTCAATTCCTTCA	4792	TGAAAGAATGAATGATTGGGTAG
3529	CCTACCCAATCATTCAATTCCTTC	4793	GAAAGAATGAATGATTGGGTAGG
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3536	TAATCCACCTACCCAATCATTCA	4800	TGAATGATTGGGTAGGTGGATTA
3537	TTAATCCACCTACCCAATCATTCA	4801	GAATGATTGGGTAGGTGGATTAA
3538	CTTAATCCACCTACCCAATCATT	4802	AATGATTGGGTAGGTGGATTAAAG
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3541	CAACTTAATCCACCTACCCAATC	4805	GATTGGGTAGGTGGATTAAAGTTG
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3544	CCGCAACTTAATCCACCTACCCA	4808	TGGGTAGGTGGATTAAAGTTGCGG
3545	TCCGCAACTTAATCCACCTACCC	4809	GGGTAGGTGGATTAAAGTTGCGGA
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3547	GATCCGCAACTTAATCCACCTAC	4811	GTAGGTGGATTAAAGTTGCGGATC
3548	TGATCCGCAACTTAATCCACCTA	4812	TAGGTGGATTAAAGTTGCGGATCA
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3551	CATTGATCCGCAACTTAATCCAC	4815	GTGGATTAAAGTTGCGGATCAATG
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3553	TACATTGATCCGCAACTTAATCC	4817	GGATTAAAGTTGCGGATCAATGTA
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3556	CCATACATTGATCCGCAACTTAA	4820	TTAAGTTGCGGATCAATGTATGG
3557	CCCATACATTGATCCGCAACTTA	4821	TAAGTTGCGGATCAATGTATGGG
3558	TCCCATACATTGATCCGCAACTT	4822	AAGTTGCGGATCAATGTATGGGA
3559	ATCCCATACATTGATCCGCAACT	4823	AGTTGCGGATCAATGTATGGGAT
3560	CATCCCATACATTGATCCGCAAC	4824	GTTGCGGATCAATGTATGGGATG
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3562	TCCATCCCATACATTGATCCGCA	4826	TGCGGATCAATGTATGGGATGGA
3563	ATCCATCCCATACATTGATCCGC	4827	GCGGATCAATGTATGGGATGGAT
3564	CATCCATCCCATACATTGATCCG	4828	CGGATCAATGTATGGGATGGATG
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3574	TCCATCCATTCATCCATCCCATA	4838	TATGGGATGGATGAATGGATGGA
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3576	CATCCATCCATTCATCCATCCCA	4840	TGGGATGGATGAATGGATGGATG
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3578	TCCATCCATCCATTCATCCATCC	4842	GGATGGATGAATGGATGGATGGA
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3587	ACACATCCATCCATCCATCCATT	4851	AATGGATGGATGGATGGATGTGT
3588	CACACATCCATCCATCCATCCAT	4852	ATGGATGGATGGATGGATGTGTG
3589	CCACACATCCATCCATCCATCCA	4853	TGGATGGATGGATGGATGTGTGG
3590	ACCACACATCCATCCATCCATCC	4854	GGATGGATGGATGGATGTGTGGT
3591	AACCACACATCCATCCATCCATC	4855	GATGGATGGATGGATGTGTGGTT
3592	CAACCACACATCCATCCATCCAT	4856	ATGGATGGATGGATGTGTGGTTG
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3604	CTTTCAGTAATTCAACCACACAT	4868	ATGTGTGGTTGAATTACTGAAAG
3605	CCTTTCAGTAATTCAACCACACA	4869	TGTGTGGTTGAATTACTGAAAGG
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3607	AACCTTTCAGTAATTCAACCACA	4871	TGTGGTTGAATTACTGAAAGGTT
3608	CAACCTTTCAGTAATTCAACCAC	4872	GTGGTTGAATTACTGAAAGGTTG
3609	CCAACCTTTCAGTAATTCAACCA	4873	TGGTTGAATTACTGAAAGGTTGG
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3619	ATCCACTCTTCCAACCTTTTCAGT	4883	ACTGAAAGGTTGGAAGAGTGGAT
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3621	CCATCCACTCTTCCAACCTTTTCA	4885	TGAAAGGTTGGAAGAGTGGATGG
3622	CCCATCCACTCTTCCAACCTTTTC	4886	GAAAGGTTGGAAGAGTGGATGGG
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3638	ACTACCCCAAATTTACCCATCC	4902	GGATGGGTGAAATTTGGGGTAGT
3639	AACTACCCCAAATTTACCCATC	4903	GATGGGTGAAATTTGGGGTAGTT
3640	TAACCTACCCCAAATTTACCCAT	4904	ATGGGTGAAATTTGGGGTAGTTA
3641	CTAACTACCCCAAATTTACCCA	4905	TGGGTGAAATTTGGGGTAGTTAG
3642	TCTAACTACCCCAAATTTACCC	4906	GGGTGAAATTTGGGGTAGTTAGA
3643	ATCTAACTACCCCAAATTTACCC	4907	GGTGAAATTTGGGGTAGTTAGAT
3644	CATCTAACTACCCCAAATTTAC	4908	GTGAAATTTGGGGTAGTTAGATG
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3646	CCCATCTAACTACCCCAAATTTTC	4910	GAAATTTGGGGTAGTTAGATGGG
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3648	CACCCATCTAACTACCCCAAATT	4912	AATTTGGGGTAGTTAGATGGGTG
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3653	ACACCCACCCATCTAACTACCCC	4917	GGGGTAGTTAGATGGGTGGGTGT
3654	CACACCCACCCATCTAACTACCC	4918	GGGTAGTTAGATGGGTGGGTGTG

3655	ACACACCCACCCATCTAACTACC	4919	GGTAGTTAGATGGGTGGGTGTGT
3656	CACACACCCACCCATCTAACTAC	4920	GTAGTTAGATGGGTGGGTGTGTG
3657	CCACACACCCACCCATCTAACTA	4921	TAGTTAGATGGGTGGGTGTGTGG
3658	TCCACACACCCACCCATCTAACT	4922	AGTTAGATGGGTGGGTGTGTGGA
3659	ATCCACACACCCACCCATCTAAC	4923	GTTAGATGGGTGGGTGTGTGGAT
3660	CATCCACACACCCACCCATCTAA	4924	TTAGATGGGTGGGTGTGTGGATG
3661	CCATCCACACACCCACCCATCTA	4925	TAGATGGGTGGGTGTGTGGATGG
3662	TCCATCCACACACCCACCCATCT	4926	AGATGGGTGGGTGTGTGGATGGA
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3664	TATCCATCCACACACCCACCCAT	4928	ATGGGTGGGTGTGTGGATGGATA
3665	TTATCCATCCACACACCCACCCA	4929	TGGGTGGGTGTGTGGATGGATAA
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3667	TTTTATCCATCCACACACCCACC	4931	GGTGGGTGTGTGGATGGATAAAA
3668	CTTTTATCCATCCACACACCCAC	4932	GTGGGTGTGTGGATGGATAAAAG
3669	TCTTTTATCCATCCACACACCCA	4933	TGGGTGTGTGGATGGATAAAAGA
3670	CTCTTTTATCCATCCACACACCC	4934	GGGTGTGTGGATGGATAAAAGAG
3671	ACTCTTTTATCCATCCACACACC	4935	GGTGTGTGGATGGATAAAAGAGT
3672	TACTCTTTTATCCATCCACACAC	4936	GTGTGTGGATGGATAAAAGAGTA
3673	CTACTCTTTTATCCATCCACACA	4937	TGTGTGGATGGATAAAAGAGTAG
3674	TCTACTCTTTTATCCATCCACAC	4938	GTGTGGATGGATAAAAGAGTAGA
3675	ATCTACTCTTTTATCCATCCACA	4939	TGTGGATGGATAAAAGAGTAGAT
3676	CATCTACTCTTTTATCCATCCAC	4940	GTGGATGGATAAAAGAGTAGATG
3677	TCATCTACTCTTTTATCCATCCA	4941	TGGATGGATAAAAGAGTAGATGA
3678	TTCATCTACTCTTTTATCCATCC	4942	GGATGGATAAAAGAGTAGATGAA
3679	ATTCATCTACTCTTTTATCCATC	4943	GATGGATAAAAGAGTAGATGAAT
3680	CATTCATCTACTCTTTTATCCAT	4944	ATGGATAAAAGAGTAGATGAATG
3681	TCATTCATCTACTCTTTTATCCA	4945	TGGATAAAAGAGTAGATGAATGA
3682	TTCATTCATCTACTCTTTTATCC	4946	GGATAAAAGAGTAGATGAATGAA
3683	ATTCATTCATCTACTCTTTTATC	4947	GATAAAAGAGTAGATGAATGAAT
3684	AATTCATTCATCTACTCTTTTAT	4948	ATAAAAGAGTAGATGAATGAATT
3685	TAATTCATTCATCTACTCTTTTA	4949	TAAAAGAGTAGATGAATGAATTA
3686	TTAATTCATTCATCTACTCTTTT	4950	AAAAGAGTAGATGAATGAATTA
3687	ATTAATTCATTCATCTACTCTTT	4951	AAAGAGTAGATGAATGAATTAAT
3688	CATTAATTCATTCATCTACTCTT	4952	AAGAGTAGATGAATGAATTAATG
3689	TCATTAATTCATTCATCTACTCT	4953	AGAGTAGATGAATGAATTAATGA
3690	TTCATTAATTCATTCATCTACTC	4954	GAGTAGATGAATGAATTAATGAA
3691	ATTCATTAATTCATTCATCTACT	4955	AGTAGATGAATGAATTAATGAAT
3692	TATTCATTAATTCATTCATCTAC	4956	GTAGATGAATGAATTAATGAATA
3693	TTATTCATTAATTCATTCATCTA	4957	TAGATGAATGAATTAATGAATAA
3694	TTTATTCATTAATTCATTCATCT	4958	AGATGAATGAATTAATGAATAAA
3695	GTTTATTCATTAATTCATTCATC	4959	GATGAATGAATTAATGAATAAAC
3696	TGTTTATTCATTAATTCATTCAT	4960	ATGAATGAATTAATGAATAAACA
3697	CTGTTTATTCATTAATTCATTCA	4961	TGAATGAATTAATGAATAAACAG

3698	CCTGTTTATTCATTAATTCATTC	4962	GAATGAATTAATGAATAAACAGG
3699	GCCTGTTTATTCATTAATTCATT	4963	AATGAATTAATGAATAAACAGGC
3700	TGCCTGTTTATTCATTAATTCAT	4964	ATGAATTAATGAATAAACAGGCA
3701	CTGCCTGTTTATTCATTAATTCA	4965	TGAATTAATGAATAAACAGGCAG
3702	TCTGCCTGTTTATTCATTAATTC	4966	GAATTAATGAATAAACAGGCAGA
3703	ATCTGCCTGTTTATTCATTAATT	4967	AATTAATGAATAAACAGGCAGAT
3704	CATCTGCCTGTTTATTCATTAAT	4968	ATTAATGAATAAACAGGCAGATG
3705	CCATCTGCCTGTTTATTCATTAA	4969	TTAATGAATAAACAGGCAGATGG
3706	TCCATCTGCCTGTTTATTCATTA	4970	TAATGAATAAACAGGCAGATGGA
3707	ATCCATCTGCCTGTTTATTCATT	4971	AATGAATAAACAGGCAGATGGAT
3708	CATCCATCTGCCTGTTTATTCAT	4972	ATGAATAAACAGGCAGATGGATG
3709	TCATCCATCTGCCTGTTTATTC	4973	TGAATAAACAGGCAGATGGATGA
3710	ATCATCCATCTGCCTGTTTATTC	4974	GAATAAACAGGCAGATGGATGAT
3711	CATCATCCATCTGCCTGTTTATT	4975	AATAAACAGGCAGATGGATGATG
3712	ACATCATCCATCTGCCTGTTTAT	4976	ATAAACAGGCAGATGGATGATGT
3713	TACATCATCCATCTGCCTGTTTA	4977	TAAACAGGCAGATGGATGATGTA
3714	TTACATCATCCATCTGCCTGTTT	4978	AAACAGGCAGATGGATGATGTAA
3715	CTTACATCATCCATCTGCCTGTT	4979	AACAGGCAGATGGATGATGTAAG
3716	GCTTACATCATCCATCTGCCTGTT	4980	ACAGGCAGATGGATGATGTAAGC
3717	AGCTTACATCATCCATCTGCCTG	4981	CAGGCAGATGGATGATGTAAGCT
3718	CAGCTTACATCATCCATCTGCCT	4982	AGGCAGATGGATGATGTAAGCTG
3719	GCAGCTTACATCATCCATCTGCC	4983	GGCAGATGGATGATGTAAGCTGC
3720	GGCAGCTTACATCATCCATCTGC	4984	GCAGATGGATGATGTAAGCTGCC
3721	GGGCAGCTTACATCATCCATCTG	4985	CAGATGGATGATGTAAGCTGCCC
3722	GGGGCAGCTTACATCATCCATCT	4986	AGATGGATGATGTAAGCTGCCCC
3723	TGGGGCAGCTTACATCATCCATC	4987	GATGGATGATGTAAGCTGCCCCA
3724	CTGGGGCAGCTTACATCATCCAT	4988	ATGGATGATGTAAGCTGCCCCAG
3725	TCTGGGGCAGCTTACATCATCCA	4989	TGGATGATGTAAGCTGCCCCAGA
3726	GTCTGGGGCAGCTTACATCATCC	4990	GGATGATGTAAGCTGCCCCAGAC
3727	GGTCTGGGGCAGCTTACATCATC	4991	GATGATGTAAGCTGCCCCAGACC
3728	GGGTCTGGGGCAGCTTACATCAT	4992	ATGATGTAAGCTGCCCCAGACCC
3729	AGGGTCTGGGGCAGCTTACATCA	4993	TGATGTAAGCTGCCCCAGACCCT
3730	CAGGGTCTGGGGCAGCTTACATC	4994	GATGTAAGCTGCCCCAGACCCTG
3731	CCAGGGTCTGGGGCAGCTTACAT	4995	ATGTAAGCTGCCCCAGACCCTGG
3732	CCCAGGGTCTGGGGCAGCTTACA	4996	TGTAAGCTGCCCCAGACCCTGGG
3733	TCCCAGGGTCTGGGGCAGCTTAC	4997	GTAAGCTGCCCCAGACCCTGGGA
3734	GTCCCAGGGTCTGGGGCAGCTTA	4998	TAAGCTGCCCCAGACCCTGGGAC
3735	GGTCCCAGGGTCTGGGGCAGCTT	4999	AAGCTGCCCCAGACCCTGGGACC
3736	AGGTCCCAGGGTCTGGGGCAGCT	5000	AGCTGCCCCAGACCCTGGGACCT
3737	GAGGTCCCAGGGTCTGGGGCAGC	5001	GCTGCCCCAGACCCTGGGACCTC
3738	AGAGGTCCCAGGGTCTGGGGCAG	5002	CTGCCCCAGACCCTGGGACCTCT
3739	CAGAGGTCCCAGGGTCTGGGGCA	5003	TGCCCCAGACCCTGGGACCTCTG
3740	TCAGAGGTCCCAGGGTCTGGGGC	5004	GCCCCAGACCCTGGGACCTCTGA

3741	GTCAGAGGTCCCAGGGTCTGGGG	5005	CCCCAGACCCTGGGACCTCTGAC
3742	GGTCAGAGGTCCCAGGGTCTGGG	5006	CCCAGACCCTGGGACCTCTGACC
3743	GGGTTCAGAGGTCCCAGGGTCTGG	5007	CCAGACCCTGGGACCTCTGACCC
3744	GGGGTCAGAGGTCCCAGGGTCTG	5008	CAGACCCTGGGACCTCTGACCCC
3745	GGGGGTTCAGAGGTCCCAGGGTCT	5009	AGACCCTGGGACCTCTGACCCCC
3746	CGGGGGTCAGAGGTCCCAGGGTC	5010	GACCCTGGGACCTCTGACCCCCG
3747	CCGGGGGTTCAGAGGTCCCAGGGT	5011	ACCCTGGGACCTCTGACCCCCGG
3748	GCCGGGGGTTCAGAGGTCCCAGGG	5012	CCCTGGGACCTCTGACCCCCGGC
3749	CGCCGGGGGTTCAGAGGTCCCAGG	5013	CCTGGGACCTCTGACCCCCGGCG
3750	TCGCCGGGGGTTCAGAGGTCCCAG	5014	CTGGGACCTCTGACCCCCGGCGA
3751	GTCGCCGGGGGTTCAGAGGTCCCA	5015	TGGGACCTCTGACCCCCGGCGAC
3752	GGTCGCCGGGGGTTCAGAGGTCCC	5016	GGGACCTCTGACCCCCGGCGACC
3753	GGGTTCGCCGGGGGTTCAGAGGTCC	5017	GGACCTCTGACCCCCGGCGACCC
3754	GGGGTTCGCCGGGGGTTCAGAGGTC	5018	GACCTCTGACCCCCGGCGACCCC
3755	AGGGGTTCGCCGGGGGTTCAGAGGT	5019	ACCTCTGACCCCCGGCGACCCCT
3756	AAGGGGTTCGCCGGGGGTTCAGAGG	5020	CCTCTGACCCCCGGCGACCCCTT
3757	CAAGGGGTTCGCCGGGGGTTCAGAG	5021	CTCTGACCCCCGGCGACCCCTTG
3758	GCAAGGGGTTCGCCGGGGGTTCAGA	5022	TCTGACCCCCGGCGACCCCTTGC
3759	TGCAAGGGGTTCGCCGGGGGTTCAG	5023	CTGACCCCCGGCGACCCCTTGCA
3760	GTGCAAGGGGTTCGCCGGGGGTCA	5024	TGACCCCCGGCGACCCCTTGAC
3761	AGTGCAAGGGGTTCGCCGGGGGTTC	5025	GACCCCCGGCGACCCCTTGCACT
3762	GAGTGCAAGGGGTTCGCCGGGGGT	5026	ACCCCCGGCGACCCCTTGCACTC
3763	AGAGTGCAAGGGGTTCGCCGGGGG	5027	CCCCGGCGACCCCTTGCACTCT
3764	GAGAGTGCAAGGGGTTCGCCGGGG	5028	CCCCGGCGACCCCTTGCACTCTC
3765	GGAGAGTGCAAGGGGTTCGCCGGG	5029	CCCGGCGACCCCTTGCACTCTCC
3766	TGGAGAGTGCAAGGGGTTCGCCGG	5030	CCGGCGACCCCTTGCACTCTCCA
3767	ATGGAGAGTGCAAGGGGTTCGCCG	5031	CGGCGACCCCTTGCACTCTCCAT
3768	CATGGAGAGTGCAAGGGGTTCGCC	5032	GGCGACCCCTTGCACTCTCCATG
3769	TCATGGAGAGTGCAAGGGGTTCGC	5033	GCGACCCCTTGCACTCTCCATGA
3770	GTCATGGAGAGTGCAAGGGGTTCG	5034	CGACCCCTTGCACTCTCCATGAC
3771	TGTCATGGAGAGTGCAAGGGGTTC	5035	GACCCCTTGCACTCTCCATGACA
3772	GTGTCATGGAGAGTGCAAGGGGT	5036	ACCCCTTGCACTCTCCATGACAC
3773	AGTGTCATGGAGAGTGCAAGGGG	5037	CCCCTTGCACTCTCCATGACACT
3774	AAGTGTCATGGAGAGTGCAAGGG	5038	CCCTTGCACTCTCCATGACACTT
3775	AAAGTGTCATGGAGAGTGCAAGG	5039	CCTTGCACTCTCCATGACACTTT
3776	GAAAGTGTCATGGAGAGTGCAAG	5040	CTTGCACTCTCCATGACACTTTC
3777	AGAAAGTGTCATGGAGAGTGCAA	5041	TTGCACTCTCCATGACACTTTCT
3778	GAGAAAGTGTCATGGAGAGTGCA	5042	TGCACTCTCCATGACACTTTCTC
3779	AGAGAAAGTGTCATGGAGAGTGC	5043	GCACTCTCCATGACACTTTCTCT
3780	GAGAGAAAGTGTCATGGAGAGTG	5044	CACTCTCCATGACACTTTCTCTC
3781	GGAGAGAAAGTGTCATGGAGAGT	5045	ACTCTCCATGACACTTTCTCTCC
3782	GGGAGAGAAAGTGTCATGGAGAG	5046	CTCTCCATGACACTTTCTCTCCC
3783	TGGGAGAGAAAGTGTCATGGAGA	5047	TCTCCATGACACTTTCTCTCCCA

3784	ATGGGAGAGAAAGTGTTCATGGAG	5048	CTCCATGACACTTTCTCTCCCAT
3785	CATGGGAGAGAAAGTGTTCATGGA	5049	TCCATGACACTTTCTCTCCCATG
3786	CCATGGGAGAGAAAGTGTTCATGG	5050	CCATGACACTTTCTCTCCCATGG
3787	ACCATGGGAGAGAAAGTGTTCATG	5051	CATGACACTTTCTCTCCCATGGT
3788	CACCATGGGAGAGAAAGTGTTCAT	5052	ATGACACTTTCTCTCCCATGGTG
3789	CCACCATGGGAGAGAAAGTGTCA	5053	TGACACTTTCTCTCCCATGGTGG
3790	GCCACCATGGGAGAGAAAGTGTG	5054	GACACTTTCTCTCCCATGGTGGC
3791	TGCCACCATGGGAGAGAAAGTGT	5055	ACACTTTCTCTCCCATGGTGCCA
3792	CTGCCACCATGGGAGAGAAAGTG	5056	CACTTTCTCTCCCATGGTGCCAG

- * At least one nucleoside linkage of the nucleobase sequence is selected from 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.

Table 2B. Example UNC13A Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
5209	TCTTTCCAGGAAACCCAGGCA	5222	TGCCTGGGTTTCCTGGAAAGA
5210	CTTTCCAGGAAACCCAGGCA	5223	TGCCTGGGTTTCCTGGAAAG
5211	TCTTTCCAGGAAACCCAGGC	5224	GCCTGGGTTTCCTGGAAAGA
5212	TTTCCAGGAAACCCAGGCA	5225	TGCCTGGGTTTCCTGGAAA
5213	TCTTTCCAGGAAACCCAGG	5226	CCTGGGTTTCCTGGAAAGA
5214	TTCCAGGAAACCCAGGCA	5227	TGCCTGGGTTTCCTGGAA
5215	TCTTTCCAGGAAACCCAG	5228	CTGGGTTTCCTGGAAAGA
5216	TCCAGGAAACCCAGGCA	5229	TGCCTGGGTTTCCTGGA
5217	TCTTTCCAGGAAACCCA	5230	TGGGTTTCCTGGAAAGA
5218	CCAGGAAACCCAGGCA	5231	TGCCTGGGTTTCCTGG
5219	TCTTTCCAGGAAACCC	5232	GGGTTTCCTGGAAAGA
5220	CAGGAAACCCAGGCA	5233	TGCCTGGGTTTCCTG
5221	TCTTTCCAGGAAACC	5234	GGTTTCCTGGAAAGA

* At least one nucleoside linkage of the nucleobase sequence is selected from 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
5 thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00192] In various embodiments, each of the nucleosides of antisense oligonucleotides shown in Table 2B are modified nucleosides with 2'-O-(2-methoxyethyl) (2'MOE) sugar moieties, and each "C" is replaced with a 5-methylcytosine (5-MeC). Additionally, each of the internucleoside
10 linkages between the nucleosides are phosphorothioate internucleoside linkages.

Antisense Oligonucleotides with One or more Locked Nucleic Acids (LNAs)

[00193] In various embodiments, antisense oligonucleotides disclosed herein (*e.g.*, UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more locked
15 nucleic acids (LNAs). In particular embodiments, an antisense oligonucleotide includes one LNA. In particular embodiments, an antisense oligonucleotide includes two LNAs. In particular embodiments, an antisense oligonucleotide includes three LNAs. Generally, a LNA refers to nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit,
20 thereby forming a bicyclic sugar.

[00194] In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 4th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 7th position of the antisense oligonucleotide. In some embodiments, an antisense
25 oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 9th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 12th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 15th position of the antisense oligonucleotide. In some embodiments, an antisense
30 oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 17th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a LNA at a 20th position of the antisense oligonucleotide.

[00195] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise two LNAs located at two different positions of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a fourth position of the antisense oligonucleotide and a second LNA at a 20th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 7th position of the antisense oligonucleotide and a second LNA at a 15th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 7th position of the antisense oligonucleotide and a second LNA at a 17th position of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 9th position of the antisense oligonucleotide and a second LNA at a 17th position of the antisense oligonucleotide.

[00196] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise three LNAs located at three different positions of the antisense oligonucleotide. In some embodiments, an antisense oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 4th position of the antisense oligonucleotide, a second LNA at a 12th position of the antisense oligonucleotide, and a third LNA at a 20th position of the antisense oligonucleotide.

Antisense Oligonucleotides with One or more Spacers

[00197] In various embodiments, antisense oligonucleotides comprise one or more spacers. In particular embodiments, an antisense oligonucleotide includes one spacer. In particular embodiments, an antisense oligonucleotide includes two spacers. In particular embodiments, an antisense oligonucleotide includes three spacers. Generally, a spacer refers to a nucleoside-replacement group lacking a nucleotide base and wherein the nucleoside sugar moiety is replaced by a non-sugar substitute group. The non-sugar substitute group is not capable of linking to a nucleobase, but is capable of linking with the 3' and 5' positions of nucleosides adjacent to the spacer through an internucleoside linking group.

[00198] In certain embodiments, an oligonucleotide with one or more spacers, such as disclosed herein, may be an oligonucleotide with 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length,

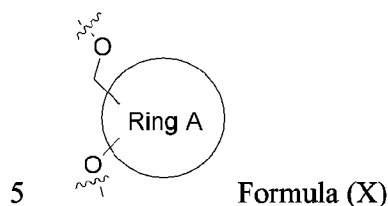
or 18, 19, 20, 21, 22, 23, 24, or 25 oligonucleotide units in length. As used herein, an “oligonucleotide unit” refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide. [00199] In particular embodiments, oligonucleotides with one or more spacers are 25

5 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18, at
10 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 embodiments, the oligonucleotides with one or more spacers are at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 20 oligonucleotide units in length. In
15 various embodiments, the oligonucleotides with one or more spacers are at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 24
20 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 25 oligonucleotide units in length.

[00200] In various embodiments, a UNC13A AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of 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
25 Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of 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 embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID
30 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 embodiments, a UNC13A AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of 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 embodiments, a

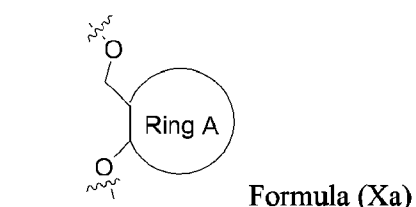
UNC13A AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

[00201] In some embodiments, the spacer is of Formula (X):



wherein ring A is as defined herein.

[00202] In some embodiments, the spacer is of Formula (Xa):

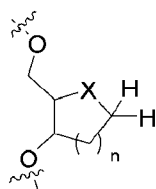


wherein ring A is as defined herein and the -CH₂-O- group is on a ring A atom adjacent to the -O- group.

[00203] As generally defined herein, ring A of formulae (X) and (Xa), is an optionally substituted 4-8 member monocyclic cycloalkyl group (*e.g.* ring A is cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl) or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N (*e.g.* ring A is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl). In some embodiments, ring A is tetrahydrofuranyl. In some embodiments, ring A is tetrahydropyranyl. In some embodiments, ring A is pyrrolidinyl. In some embodiments, ring A is cyclopentyl. In some embodiments, the monocyclic cycloalkyl or monocyclic heterocyclyl is not further substituted. In some embodiments, the cycloalkyl or heterocyclyl is further substituted with 0, 1, 2 or 3 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH₂)OMe, -O(CH₂)₂OMe and CN.

[00204] In some embodiments, tetrahydrofuranyl is substituted with 1 or 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH₂)OMe, -O(CH₂)₂OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH₂)OMe, -O(CH₂)₂OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 1 substituent selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH₂)OMe, -O(CH₂)₂OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with -O(CH₂)₂OMe.

[00205] In some embodiments, the spacer is represented by Formula (I), wherein:

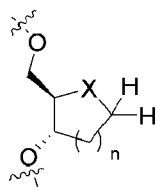


Formula (I)

X is selected from -CH₂- and -O-; and

n is 0, 1, 2 or 3.

5 **[00206]** In some embodiments, the spacer is represented by Formula (I'), wherein:

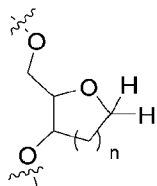


Formula (I')

X is selected from -CH₂- and -O-; and

n is 0, 1, 2 or 3.

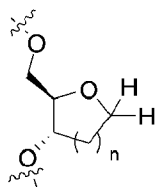
[00207] In some embodiments, the spacer is represented by Formula (Ia), wherein:



Formula (Ia)

and n is 0, 1, 2 or 3.

[00208] In some embodiments, the spacer is represented by Formula (Ia'), wherein:



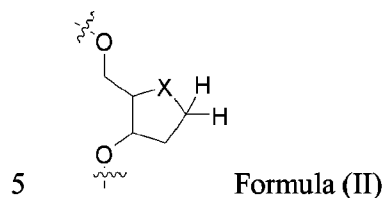
Formula (Ia')

and n is 0, 1, 2 or 3.

15 **[00209]** As generally defined herein, X is selected from -CH₂- and -O-. In some embodiments, X is -CH₂-. In other embodiments, X is -O-.

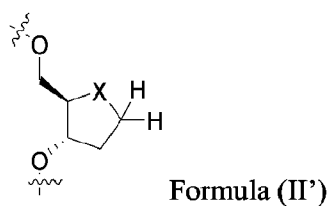
[00210] As generally defined herein, n is 0, 1, 2 or 3. In some embodiments, n is 0. In some embodiments, n is 1 or 2. In some embodiments, n is 1. In other embodiments, n is 2. In certain embodiments, n is 3.

[00211] In some embodiments, the spacer is represented by Formula (II), wherein:



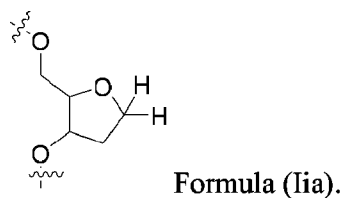
X is selected from -CH₂- and -O-.

[00212] In some embodiments, the spacer is represented by Formula (II'), wherein:

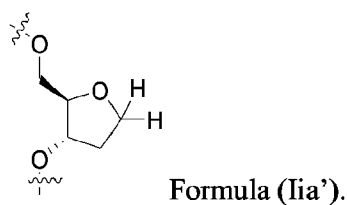


X is selected from -CH₂- and -O-.

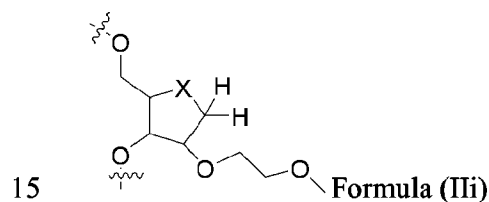
10 **[00213]** In some embodiments, the spacer is represented by Formula (Iia), wherein:



[00214] In some embodiments, the spacer is represented by Formula (Iia'), wherein:

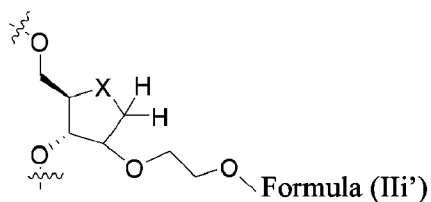


[00215] In some embodiments, the spacer is represented by Formula (IIi), wherein:



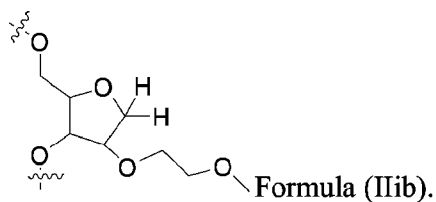
X is selected from -CH₂- and -O-.

[00216] In some embodiments, the spacer is represented by Formula (IIi'), wherein:

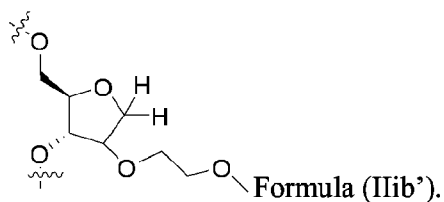


X is selected from -CH₂- and -O-.

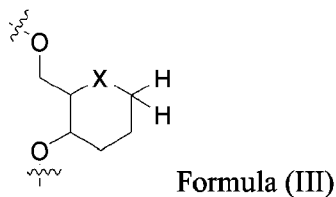
5 [00217] In some embodiments, the spacer is represented by Formula (IIib), wherein:



[00218] In some embodiments, the spacer is represented by Formula (IIib'), wherein:

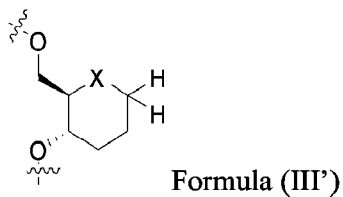


[00219] In some embodiments, the spacer is represented by Formula (III), wherein:



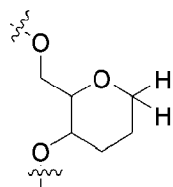
X is selected from -CH₂- and -O-.

[00220] In some embodiments, the spacer is represented by Formula (III'), wherein:



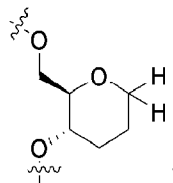
X is selected from -CH₂- and -O-.

[00221] In some embodiments, the spacer is represented by Formula (IIIa), wherein:



Formula (IIIa).

[00222] In some embodiments, the spacer is represented by Formula (IIIa'), wherein:



Formula (IIIa').

- 5 **[00223]** In some embodiments, the open positions of Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') (*i.e.*, the positions not specifically depicted as bearing exclusively hydrogen atoms, including the -CH₂- group of X) are further substituted with 0-3 substituents independently selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH₂)OMe, -O(CH₂)₂OMe and CN. In some embodiments, Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') are not further substituted.
- 10

[00224] As described further below, a UNC13A oligonucleotide with one or more spacers is described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A variant oligonucleotide. In various embodiments, a UNC13A oligonucleotide with a spacer differs from a UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide in that the spacer replaces a nucleoside in the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. As used hereafter, the "position" of the UNC13A oligonucleotide refers to a particular location as counted from the 5' end of the UNC13A oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. In particular embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide.

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[00225] In various embodiments, a UNC13A oligonucleotide includes one spacer that replaces a nucleoside in the UNC13A oligonucleotide (*e.g.*, one spacer replaces one nucleoside of the UNC13A oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the UNC13A oligonucleotide. In particular

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embodiments, the spacer replaces a nucleoside at position 10 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 12 and 16 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide.

[00226] In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example, the UNC13A oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at position 12. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the UNC13A oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the UNC13A oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00227] In various embodiments, a UNC13A oligonucleotide includes two spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., two spacers replace two separate nucleosides of the UNC13A oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00228] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16

and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20, positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the UNC13A oligonucleotide.

[00229] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 14 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A parent oligonucleotide and the second spacer replaces a nucleoside at position 16 of the UNC13A parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 22 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide.

[00230] In various embodiments, a UNC13A oligonucleotide includes three spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., three spacers replace three separate nucleosides of the UNC13A oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 21 and 24 of the UNC13A oligonucleotide. In some embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the UNC13A oligonucleotide.

[00231] In various embodiments, the three spacers in a UNC13A oligonucleotide are positioned such that each of the four segments of the UNC13A oligonucleotide are at most 7 linked

nucleosides in length. For example, a UNC13A oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and
5 connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00232] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six,
10 seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are
15 positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00233] In various embodiments, the one or more spacers are positioned in the oligonucleotide to
20 control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one
25 embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each
30 immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a

guanine group, or five spacers that each immediately succeed a guanine group. In various embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

5 [00234] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

10 [00235] In various embodiments, the UNC13A oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the UNC13A oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at
15 least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more
20 spacers are positioned in the UNC13A oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the UNC13A oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00236] In various embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) at least
25 two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00237] In various embodiments, the inclusion of one or more spacers in the UNC13A
30 oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full

length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a
5 corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a corresponding UNC13A parent oligonucleotide.

[00238] Tables 3A, 3B, 4, and 5 document example UNC13A oligonucleotides with one or more
10 spacers and their relation to corresponding UNC13A parent oligonucleotides. Each UNC13A oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as “X_spA” (for a UNC13A AON with one spacer), “X_spA_spB” (for a UNC13A AON with two spacers), or “X_spA_spB_spC” (for a UNC13A AON with three spacers). Here, “X” refers to the length of the UNC13A AON, “A” refers to the position in the
15 UNC13A AON where the first spacer is located, “B” refers to the position in the UNC13A AON where the second spacer is located, and if present, “C” refers to the position in the UNC13A AON where the third spacer is located.

[00239] In various embodiments, UNC13A oligonucleotides include one spacer. In various embodiments, the UNC13A oligonucleotides are oligonucleotide variants, such as any one of a
20 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00240] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the
30 oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide. Example UNC13A AONs with one spacer are documented below in Table 3A.

Table 3A: Identification of UNC13A AONs with one spacer. Here, each UNC13A AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	Relation to UNC13A oligonucleotide variant		Sequence* (where X indicates a nucleoside of the UNC13A parent oligonucleotide and S _y indicates presence of a Spacer where y denotes the position) (5' → 3')
UNC13A parent oligonucleotide	N/A		XXXXXXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
UNC13A Oligonucleotide (25mer) with Spacer at position 15 (UNC13A AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer		XXXXXXXXXXXXXXXXXXS ₁₅ XXXXXXXXXX
UNC13A oligonucleotide variant (23mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Oligonucleotide (23mer) with Spacer at position 12 (UNC13A AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer		XXXXXXXXXXXXXS ₁₂ XXXXXXXXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Oligonucleotide (21mer) with Spacer at position 11 (UNC13A AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer		XXXXXXXXXXXXXS ₁₁ XXXXXXXXXXXXX
UNC13A oligonucleotide variant (19mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Oligonucleotide (19mer) with Spacer at position 10 (UNC13A AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer		XXXXXXXXXXXXXS ₁₀ XXXXXXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from 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 phosphorodiamidate linkage, 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.

5 **[00241]** In various embodiments, UNC13A oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example UNC13A AONs with two spacers are documented below in Table 3B.

Table 3B: Identification of UNC13A AONs with two spacers. Here, each UNC13A AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	Relation to UNC13A parent oligonucleotide		Sequence* (where X indicates a nucleoside of the UNC13A parent oligonucleotide and S _y indicates presence of a Spacer where y denotes the position) (5' → 3')
UNC13A parent oligonucleotide	N/A		XXXXXXXXXXXXXXXXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 22 (UNC13A AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer		XXXXXXXXXXS ₁₁ XXXXXXXXXXS ₂₂ XXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14 (UNC13A AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer		XXXXXXS ₇ XXXXXXS ₁₄ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 19 (UNC13A AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers		XXXXXXXS ₈ XXXXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 14 (UNC13A AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers		XXXXXXXS ₈ XXXXXXS ₁₄ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 14 (UNC13A AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers		XXXXXXXXXS ₉ XXXXXS ₁₄ XXXXXXXXXX

(UNC13A AON 25_sp9sp14)			
UNC13A Oligonucleotide with Spacers at positions 10 and 14 (UNC13A AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXS ₁₄ XXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 14 (UNC13A AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers		XXXXXXXXXXS ₁₁ XXS ₁₄ XXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 15 (UNC13A AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers		XXXXXXXS ₈ XXXXXXS ₁₅ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 15 (UNC13A AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers		XXXXXXXXXS ₉ XXXXXS ₁₅ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 15 (UNC13A AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers		XXXXXXXXXS ₁₀ XXXXS ₁₅ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 15 (UNC13A AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXS ₁₅ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 16 (UNC13A AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXXS ₈ XXXXXXS ₁₆ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 16 (UNC13A AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers		XXXXXXXXXS ₉ XXXXXS ₁₆ XXXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 10 and 16 (UNC13A AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXS ₁₆ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 16 (UNC13A AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXS ₁₆ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 17 (UNC13A AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers		XXXXXXXS ₈ XXXXXXXXXS ₁₇ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 17 (UNC13A AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers		XXXXXXXXXS ₉ XXXXXXXXXS ₁₇ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 17 (UNC13A AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXS ₁₇ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 17 (UNC13A AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXS ₁₇ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 18 (UNC13A AON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers		XXXXXXXS ₈ XXXXXXXXXS ₁₈ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 18 (UNC13A AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers		XXXXXXXXXS ₉ XXXXXXXXXS ₁₈ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 18 (UNC13A AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXS ₁₈ XXXXXXX

positions 10 and 18 (UNC13A AON 25_sp10sp18)	substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 11 and 18 (UNC13A AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXXXXS ₁₈ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 19 (UNC13A AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers		XXXXXXXXXS ₉ XXXXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 19 (UNC13A AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 19 (UNC13A AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 20 (UNC13A AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers		XXXXXXXXXS ₉ XXXXXXXXXXS ₂₀ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 20 (UNC13A AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXXXXXXS ₂₀ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 20 (UNC13A AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXXXXS ₂₀ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 21 (UNC13A AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers		XXXXXXXXXXS ₁₀ XXXXXXXXXXS ₂₁ XXXXXX

UNC13A Oligonucleotide with Spacers at positions 11 and 21 (UNC13A AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers		XXXXXXXXXXS ₁₁ XXXXXXXXXXS ₂₁ XXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 15 (UNC13A AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers		XXXS ₄ XXXXXXXXXXS ₁₅ XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 19 (UNC13A AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers		XXXXXXS ₇ XXXXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 18 (UNC13A AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers		XXXXXXS ₇ XXXXXXXXXXS ₁₈ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 21 (UNC13A AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers		XXXXXXXXXS ₉ XXXXXXXXXXS ₂₁ XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from 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 phosphorodiamidate linkage, 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.

- 10 [00242] In various embodiments, UNC13A oligonucleotides include three spacers. The inclusion of three spacers divides up the UNC13A oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the UNC13A oligonucleotide

such that each of the segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. Example UNC13A AONs with three spacers are documented below in Table 4.

Table 4: Identification of UNC13A AONs or AON variants with three spacers. Here, each

5 UNC13A AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	Relation to UNC13A parent oligonucleotide		Sequence* (where X indicates a nucleoside of the UNC13A parent oligonucleotide and S _y indicates presence of a Spacer where y denotes the position) (5' → 3')
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 24 (UNC13A AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers		XXXXXXXXS ₈ XXXXXXXXS ₁₆ XXXXXXXXS ₂₄ X
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 23 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers		XXXXXXXXS ₈ XXXXXXXXS ₁₆ XXXXXXXXS ₂₃ XX
UNC13A Oligonucleotide with Spacers at positions 2 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers		XS ₂ XXXXXXXXS ₁₀ XXXXXXXXS ₁₈ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 3 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 3 and 10 and 18 are substituted with spacers		XXS ₃ XXXXXXXXS ₁₀ XXXXXXXXS ₁₈ XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 12 and 19 (UNC13A AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers		XXXS ₄ XXXXXXXXS ₁₂ XXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at	Nucleosides at positions 8 and 13 and 18		XXXXXXXXS ₈ XXXXX ₁₃ XXXXX ₁₈ XXXXXXX

positions 8 and 13 and 18 (UNC13A AON 25_sp8sp13sp18)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 5 and 13 and 21 (UNC13A AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers		XXXXS ₅ XXXXXXXXS ₁₃ XXXXXXXXS ₂₁ XXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 13 and 19 (UNC13A AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers		XXXXXS ₇ XXXXXS ₁₃ XXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 6 and 13 and 20 (UNC13A AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers		XXXXXS ₆ XXXXXS ₁₃ XXXXXS ₂₀ XXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 19 (UNC13A AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers		XXXXXXXXS ₈ XXS ₁₁ XXXXXXXXS ₁₉ XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 16 (UNC13A AON 23_sp8sp11sp16)	Nucleosides at positions 8 and 11 and 16 are substituted with spacers		XXXXXXXXS ₈ XXS ₁₁ XXXXS ₁₆ XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14 and 22 (UNC13A AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers		XXXXXS ₇ XXXXXS ₁₄ XXXXXS ₂₂ XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from 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 phosphorodiamidate (e.g., comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a

5 thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00243] In various embodiments, UNC13A AONs with one or more spacers are reduced in length in comparison to the UNC13A AONs described above in Tables 3B and 4. For example, such UNC13A AONs may be UNC13A oligonucleotide variants with one or more spacers. In

10 various embodiments, the UNC13A oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, UNC13A oligonucleotide variants include two spacers such that the UNC13A oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7

15 linked nucleosides. Example UNC13A oligonucleotide variants with one or more spacers are shown below in Table 5.

Table 5: Example UNC13A AON variants with two spacers. Here, each UNC13A AON variant has 3 segments, where at least one segment has at most 7 linked nucleosides.

Sequence name	Relation to UNC13A oligonucleotide variant		Sequence* (where X indicates a nucleoside of the UNC13A oligonucleotide variant and S _y indicates presence of a Spacer where y denotes the position) (5' → 3')
UNC13A oligonucleotide variant (23mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (UNC13A AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXXS ₈ XXXXXXXS ₁₆ XXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A		XXXXXXXXXXXXXXXXXXXXX (21mer)

UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (UNC13A AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers		XXXXS ₅ XXXXXXS ₁₂ XXXXXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (UNC13A AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXXXS ₈ XXXXXXXXS ₁₆ XXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (UNC13A AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers		XXXXXS ₆ XXXXXXXXS ₁₄ XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A AON variant 21_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers		XXXXXXXXS ₈ XXXXXS ₁₄ XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A AON variant 21_sp8sp14)	Nucleosides at positions 6 and 20 are substituted with spacers		XXXXXS ₆ XXXXXXXXXXXXXXXXXS ₂₀ X
UNC13A oligonucleotide variant (19mer)	N/A		XXXXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Variant Oligonucleotide	Nucleosides at positions 5 and 12 are		XXXXS ₅ XXXXXXS ₁₂ XXXXXXX

(19mer) with Spacers at positions 5 and 12 (UNC13A AON variant 19_sp5sp12)	substituted with spacers		
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (UNC13A AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers		XXXXXXXXS ₈ XXXXXXXXS ₁₅ XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from 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 phosphorodiamidate linkage, 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.

- 10 **[00244]** In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more spacers as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and three LNAs.

- 15 **[00245]** In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be

located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00246] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if

5 counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense
10 oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a
15 second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00247] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located
20 at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th
25 position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense
30 oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

Performance of UNC13A Oligonucleotides

[00248] Generally, UNC13A oligonucleotides and/or UNC13A parent oligonucleotides (*e.g.*, UNC13A oligonucleotides with sequences of any of SEQ ID NOs: 1-1264, SEQ ID NO: 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) target UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065

5 or SEQ ID NOs: 5206-5208 in order to increase, restore, rescue, or stabilize levels of expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein (*e.g.*, full length UNC13A). In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A mRNA. In various

10 embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of mis-spliced UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A protein. In

15 some embodiments, the percent increase of the full length UNC13A protein is an increase in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length UNC13A protein followed by increase of the full length UNC13A protein using a UNC13A AON.

20 **[00249]** In some embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In some embodiments, the percent rescue of full length UNC13A refers to the % of full length UNC13A following depletion using a TDP43 antisense oligonucleotide and a treatment using UNC13A AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment

25 or cells that were treated with a vehicle solution).

[00250] In various embodiments, UNC13A AONs can exhibit at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon. In various

30 embodiments, UNC13A AONs can exhibit at least a 100% reduction of an UNC13A transcript with a cryptic exon. In various embodiments, reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide. In various embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

Modifications

[00251] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those
5 nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

10 **[00252]** Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased activity.

15 **[00253]** Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

20 **[00254]** The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the
25 presence of nucleases.

[00255] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and
30 phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[00256] In certain embodiments, antisense compounds targeted to a UNC13A nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain

embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a UNC13A nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Modified Sugar Moieties

[00257] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or C(R₁)(R₂) (R, R₁ and R₂ are each independently H, C₁-C₁₂ alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (*see* PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with further substitution at the 2'-position (*see* published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (*see* PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[00258] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or 5), 4'-S, 2'-F, 2'-OCH₃, 2'-OCH₂CH₃, 2'-OCH₂CH₂F and 2'-O(CH₂)₂OCH₃ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C₁-C₁₀ alkyl, OCF₃, OCH₂F, O(CH₂)₂S CH₃, O(CH₂)₂—O—N(R_m)(R_n), O—CH₂—C(=O)—N(R_m)(R_n), and O—CH₂—C(=O)—N(R₁)—(CH₂)₂—N(R_m)(R_n), where each R₁, R_m and R_n is, independently, H or substituted or unsubstituted C₁-C₁₀ alkyl.

[00259] Additional examples of modified sugar moieties include 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 (*e.g.*, tcDNA).

[00260] As used herein, “bicyclic nucleosides” refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH₂)—O-2' (LNA); 4'-(CH₂)—S-2'; 4'-(CH₂)₂—O-2' (ENA); 4'-CH(CH₃)—O-2' and 4'-CH(CH₂OCH₃)—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-C(CH₃)(CH₃)—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH₂—N(OCH₃)-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH₂—O—N(CH₃)-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'-CH₂—N(R)—O-2', wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH₂—C(H)(CH₃)-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH₂—C(=CH₂)-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[00261] Further reports related to bicyclic nucleosides can also be found in published literature (see for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Elayadi et al., Curr. Opinion Invest. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; and Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Ser. No. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on Mar. 25, 1999 as WO 99/14226).

[00262] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —[C(R_a)(R_b)]_n—, —C(R_a)=C(R_b)—, —C(R_a)=N—,

—C(=O)— , $\text{—C(=NR}_a\text{)—}$, —C(=S)— , —O— , $\text{—Si(R}_a\text{)}_2\text{—}$, $\text{—S(=O)}_x\text{—}$, and $\text{—N(R}_a\text{)—}$;

wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

- 5 each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , $COOJ_1$, acyl ($C(=O)\text{—H}$), substituted acyl, CN, sulfonyl ($S(=O)_2\text{—}$), or sulfoxyl ($S(=O)\text{—}J_1$); and

each J_1 and J_2 is, independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($C(=O)\text{—H}$), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl or a protecting group.

- 15 **[00263]** In certain embodiments, the bridge of a bicyclic sugar moiety is $\text{—[C(R}_a\text{)(R}_b\text{)]}_n\text{—}$, $\text{—[—[C(R}_a\text{)(R}_b\text{)]}_n\text{—O—}$, $\text{—C(R}_a\text{R}_b\text{)—N(R)—O—}$ or $\text{—C(R}_a\text{R}_b\text{)—O—N(R)—}$. In certain embodiments, the bridge is 4'- $\text{CH}_2\text{—}2'$, 4'- $(\text{CH}_2)_2\text{—}2'$, 4'- $(\text{CH}_2)_3\text{—}2'$, 4'- $\text{CH}_2\text{—O—}2'$, 4'- $(\text{CH}_2)_2\text{—O—}2'$, 4'- $\text{CH}_2\text{—O—N(R)—}2'$ and 4'- $\text{CH}_2\text{—N(R)—O—}2'$ - wherein each R is, independently, H, a protecting group or C_1 - C_{12} alkyl, each R_a and R_b is, independently, H, a protecting group,
- 20 hydroxyl, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5 - C_7 alicyclic radical, substituted C_5 - C_7 alicyclic radical, halogen, OJ_1 , NJ_1J_2 , SJ_1 , N_3 , $COOJ_1$, acyl ($C(=O)\text{—H}$), substituted acyl, CN, sulfonyl ($S(=O)_2\text{—}J_1$), or sulfoxyl ($S(=O)\text{—}J_1$); each J_1 and J_2 is,
- 25 independently, H, C_1 - C_{12} alkyl, substituted C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkenyl, C_2 - C_{12} alkynyl, substituted C_2 - C_{12} alkynyl, C_5 - C_{20} aryl, substituted C_5 - C_{20} aryl, acyl ($C(=O)\text{—H}$), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1 - C_{12} aminoalkyl, substituted C_1 - C_{12} aminoalkyl or a protecting group; and R is H, C_1 - C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

- 30 **[00264]** In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α -L configuration or in the β -D configuration. Previously, α -L-methyleneoxy (4'- $\text{CH}_2\text{—O—}2'$) BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00265] In certain embodiments, bicyclic nucleosides include, but are not limited to, α -L-methyleneoxy (4'-CH₂—O-2') BNA, β -D-methyleneoxy (4'-CH₂—O-2') BNA, ethyleneoxy (4'-(CH₂)₂—O-2) BNA, aminooxy (4'-CH₂—O—N(R)-2') BNA, oxyamino (4'-CH₂—N(R)—O-2') BNA, methyl(methyleneoxy) (4'-CH(CH₃)—O-2') BNA, methylene-thio (4'-CH₂—S-2') BNA, methylene-amino (4'-CH₂—N(R)-2') BNA, methyl carbocyclic (4'-CH₂—CH(CH₃)-2') BNA, and propylene carbocyclic (4'-(CH₂)₃-2') BNA; wherein R is H, C₁-C₁₂ alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00266] The present disclosure provide, in some embodiments, methods for treating, ameliorating, or preventing a neurological disease and/or a neuropathy further include methods of administering, to a patient, a pharmaceutically acceptable composition, for example, a pharmaceutically acceptable formulation that includes one or more UNC13A oligonucleotides. UNC13A oligonucleotides can increase, restore, or stabilize UNC13A activity, for example, UNC13A activity, and/or levels of UNC13A expression, for example, UNC13A mRNA and/or protein expression.

[00267] The present disclosure also provides pharmaceutical compositions comprising a UNC13A oligonucleotide formulated together with one or more pharmaceutically or cosmetically acceptable excipients. These formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use, *e.g.*, as part of a composition suitable for applying topically to skin and/or mucous membrane, for example, a composition in the form of a gel, a paste, a wax, a cream, a spray, a liquid, a foam, a lotion, an ointment, a topical solution, a transdermal patch, a powder, a vapor, or a tincture. Although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular UNC13A oligonucleotide being used.

[00268] The present disclosure also provides a pharmaceutical composition comprising a UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a UNC13A AON that includes a sequence of any of SEQ ID NOs: 1-1264, SEQ ID NO: 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).

[00269] The present disclosure also provides methods that include the use of pharmaceutical compositions comprising a UNC13A AON is formulated together with one or more pharmaceutically acceptable excipients. Exemplary compositions provided herein include

compositions comprising a UNC13A AON, and one or more pharmaceutically acceptable excipients. Formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (e.g., subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (e.g., buccal, vaginal, and rectal), or for topical use. The most suitable form of administration in any given case will depend on the clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition that one is trying to prevent in a subject; the state, disorder, disease, or condition one is trying to prevent in a subject; and/or on the nature of the particular compound and/or the composition being used.

Additional Chemically Modified UNC13A Oligonucleotides

[00270] UNC13A AONs described herein, can include chemically modified nucleosides, including modified ribonucleosides and modified deoxyribonucleosides. Chemically modified nucleosides include, but are not limited to, uracine, uridine, 2'-O-(2-methoxyethyl) modifications, for example, 2'-O-(2-methoxyethyl)guanosine, 2'-O-(2-methoxyethyl)adenosine, 2'-O-(2-methoxyethyl)cytosine, and 2'-O-(2-methoxyethyl)thymidine. In certain embodiments, mixed modalities, e.g., a combination of a UNC13A peptide nucleic acid (PNA) and a UNC13A locked nucleic acid (LNA). Chemically modified nucleosides also include, but are not limited to, locked nucleic acids (LNAs), 2'-O-methyl, 2'-fluoro, and 2'-fluoro-β-D-arabinonucleotide (FANA), and Fluoro Cyclohexenyl nucleic acid (F-CeNA) modifications. Chemically modified nucleosides that can be included in UNC13A AONs described herein are described in Johannes and Lucchino, (2018) "Current Challenges in Delivery and Cytosolic Translocation of Therapeutic RNAs" *Nucleic Acid Ther.* 28(3): 178–93; Rettig and Behlke, (2012) "Progress toward in vivo use of siRNAs-II" *Mol Ther* 20:483–512; and Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238–48, the contents of each of which are incorporated by reference herein.

[00271] UNC13A AONs described herein can include chemical modifications that promote stabilization of an oligonucleotide's terminal 5'-phosphate and phosphatase-resistant analogs of 5'-phosphate. Chemical modifications that promote oligonucleotide terminal 5'-phosphate stabilization or which are phosphatase-resistant analogs of 5'-phosphate include, but are not limited to, 5'-methyl phosphonate, 5'-methylenephosphonate, 5'-methylenephosphonate analogs, 5'-E-vinyl phosphonate (5'-E-VP), 5'-phosphorothioate, and 5'-C-methyl analogs. Chemical modifications that promote AON terminal 5'-phosphate stabilization and phosphatase-resistant analogues of 5'-phosphate are described in Khvorova and Watts, (2017) "The chemical evolution

of oligonucleotide therapies of clinical utility” *Nat Biotechnol.*, 35(3):238-48, the contents of which are incorporated by reference herein.

[00272] In some embodiments described herein, UNC13A AONs described herein can include chemically modified nucleosides, for example, 2’ O-methyl ribonucleosides, for example, 2’ O-methyl cytidine, 2’ O-methyl guanosine, 2’ O-methyl uridine, and/or 2’ O-methyl adenosine.

UNC13A AONs described herein can include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methylcytosine, and/or a 5-methylpurine, for example, 5-methylguanine. Chemically modified nucleosides can further include pseudo-uridine or 5’methoxyuridine. UNC13A AONs described herein can include any of the following chemically modified nucleosides: 5-methyl-2’-O-methylcytidine, 5-methyl-2’-O-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl 2’-deoxycytidine.

[00273] UNC13A AONs described herein can include a phosphate backbone where one or more of the oligonucleoside linkages is a phosphate linkage. UNC13A AONs described herein may include a modified oligonucleotide backbone, where one or more of the nucleoside linkages of

the sequence is selected from the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate 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. In some embodiments of UNC13A AONs described herein, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a

phosphorothioate linkage. For example, in some embodiments of UNC13A AONs described herein, one, two, three, or more internucleoside linkages of the oligonucleotide is a phosphorothioate linkage. In preferred embodiments of UNC13A AONs described herein, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. Thus, in some embodiments, all of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 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 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 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 are phosphorothioate linkages.

[00274] In various embodiments, nucleotide linkages of UNC13A AON described herein such as any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs:

5 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 include a mix of phosphodiester and phosphorothioate linkages.

[00275] In some embodiments, nucleoside linkages linking a base at position 3 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXXXX

where “o” represents a phosphodiester bond and “D” represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

15 **[00276]** In some embodiments, one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

20 XXoDXXXXXXXXXXXXXXXXXXXXXXX

where “o” represents a phosphodiester bond and “D” represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00277] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

25 XXDoXXXXXXXXXXXXXXXXXXXXXXX

where “o” represents a phosphodiester bond and “D” represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00278] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein being a phosphodiester bond, the UNC13A AON further includes two spacers. The two spacers can be positioned in the UNC13A AON such that the UNC13A AON includes a segment with at most 7 linked nucleosides. An example 25mer UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XxoDS₁XXXXXXXXXS₂XXXXXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond and “D” represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

5 [00279] An example 25mer UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXS₁XXXXXXXXXS₂XXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond and “D” represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

10 [00280] In some embodiments, nucleoside linkages linking a base at position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 4 can be denoted as:

15 XXXoDoXXXXXXXXXXXXXXXXXXXXX

where “o” represents a phosphodiester bond and “D” represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00281] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 4
20 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXXX

25 where “o” represents a phosphodiester bond and “D” represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00282] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXXX

30 where “o” represents a phosphodiester bond and “D” represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00283] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base

(e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXXXX

5 where “o” represents a phosphodiester bond, “D” represents the base at position 3, and “E” represents the base at position 4. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00284] In various embodiments, UNC13A AON described herein include one or more spacers
10 and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the UNC13A AON are each linked to their
15 respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the 2 bases immediately preceding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00285] In various embodiments, the UNC13A AON may include more than one spacer. In
20 some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A
25 AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds.

[00286] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various
30 embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the UNC13A AON are each linked to their respective adjacent bases through

phosphodiester bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDoSoEoXXXXXXXXXX

where “S” represents a spacer, “o” represents a phosphodiester bond, “D” represents a base immediately preceding the spacer, and “E” represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00287] As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00288] In various embodiments, the UNC13A AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers of the UNC13A AON are linked to respective preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXoDoS₁oEoXXXXXXXXXXXXS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents a base immediately preceding the spacer, and “E” represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00289] As another example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXXS₁XXXXXXXXXXXXoDoS₂oDoXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents a base immediately preceding the spacer, and “E” represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00290] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXoS₁XXXXXXXXXXXXS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00291] As another example, a UNC13A AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXS₁XXXXXXXXXXoS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00292] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be

denoted as:

XXXXXXoS₁XXXXXS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00293] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXS₁XXXXXoS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00294] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer UNC13A AON can be denoted as:

XXxEoDoS₁XXXXXS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents the base immediately preceding S₁ and “E” represents the base immediately preceding “D.” Any nucleobase in the AON can be a nucleobase analog.

[00295] As another example, a 21mer UNC13A AON can be denoted as:

XXXXXS₁XXxEoDoS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents the base immediately preceding S₂ and “E” represents the base immediately preceding “D.” Any nucleobase in the AON can be a nucleobase analog.

[00296] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another

base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer UNC13A AON can be denoted as:

5 XXXEoDS₁XXXXXXoS₂XXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents the base immediately preceding S₁ and “E” represents the base immediately preceding “D.” Here, the base “D” is linked to the first spacer S₁ through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base “D” is linked to
10 base “E” through a phosphodiester bond. The second spacer S₂ is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00297] Another example of such a 21mer UNC13A AON can be denoted as:

15 XXXXXoS₁XXXXEoDS₂XXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents the base immediately preceding S₂ and “E” represents the base immediately preceding “D.” Here, the base “D” is linked to the second spacer S₂ through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base “D” is linked to base “E” through a phosphodiester bond. The first spacer S₁ is linked to an immediately
20 preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00298] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted
25 as:

XXXXXXS₁oXXXXXXXXXXXXS₂XXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00299] As another example, a UNC13A AON includes a second spacer that is linked to the
30 immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXXS₁XXXXXXXXXXXXS₂oXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00300] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXXXXS₁oXXXXXS₂XXXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00301] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXXXXS₁XXXXXS₂oXXXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00302] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A AON have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. An example of such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXoDoS₁oEoXXXXXXXXXXoFoS₂oHoXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, “o” represents a phosphodiester bond, “D” represents a base immediately preceding the first spacer, “E” represents the base immediately succeeding the first spacer, “F” represents a base immediately preceding the second spacer, and “H” represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00303] In various UNC13A AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON

are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

5 [00304] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00305] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

10 XXXXXXXXS₁XXXXoDoEoFoHoXXXS₂XXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, and “o” represents a phosphodiester bond. The bases “D,” “E,” “F,” and “H” represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases
15 is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00306] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a UNC13A AON (e.g., 23mer) can be denoted as:

20 XXXXXXXXS₁XXXoDoEoXXXS₂XXXXXXX

where “S₁” represents a first spacer, “S₂” represents a second spacer, and “o” represents a phosphodiester bond. The bases “D” and “E” represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second
25 spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

30 [00307] In some embodiments, a disclosed UNC13A AON may have at least one modified nucleobase, e.g., 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

[00308] UNC13A AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH

group may be replaced by any one selected from the group consisting of OR, R, R'OR, SH, SR, NH₂, NR₂, N₃, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R' is an alkylene).

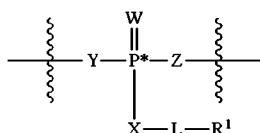
Examples of a modified sugar moiety include a 2'-Ome modified sugar moiety, bicyclic sugar moiety, 2'-O-(2-methoxyethyl) (2'MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-

5 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 (*e.g.*, tcDNA).

[00309] In some embodiments, UNC13A AONs comprise 2'OMe (*e.g.*, a UNC13A AON comprising one or more 2'OMe modified sugar), 2'MOE or MOE (*e.g.*, a UNC13A AON
10 comprising one or more 2'MOE modified sugar), PNA (*e.g.*, a UNC13A AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a UNC13A AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a UNC13A AON comprising one or more cET sugar), cMOE (*e.g.*, a UNC13A AON
15 comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a UNC13A AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a UNC13A AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a UNC13A AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a UNC13A AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a UNC13A AON comprising one or more HNA
20 modified sugar). In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate
25 linkage, morpholino linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00310] In some embodiments, UNC13A AONs with a sequence 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
30 NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00311] For example, a UNC13A AON with a sequence 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 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (---X-L-R^1); wherein: the oligonucleotides of the at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of the at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of the at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



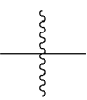
wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently ---O--- , ---S--- , $\text{---N(---L-R}^1\text{)---}$, or L; L is a

covalent bond or an optionally substituted, linear or branched C₁-C₅₀ alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C₁-C₆ alkylene, C₁-C₆ alkenylene, $\text{---C}\equiv\text{C---}$, $\text{---C(R')}_2\text{---}$, ---Cy--- , ---O--- , ---S--- , ---S---S--- , ---N(R')--- , ---C(O)--- , ---C(S)--- , ---C(NR')--- , ---C(O)N(R')--- , $\text{---N(R')C(O)N(R')---}$, ---N(R')C(O)--- , ---N(R')C(O)O--- , ---OC(O)N(R')--- , ---S(O)--- , $\text{---S(O)}_2\text{---}$, $\text{---S(O)}_2\text{N(R')---}$, $\text{---N(R')S(O)}_2\text{---}$, ---SC(O)--- , ---C(O)S--- , ---OC(O)--- , or ---C(O)O--- ; R¹ is halogen, R, or an

optionally substituted C₁-C₁₀ aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C₁-C₆ alkylene, C₁-C₆ alkenylene, $\text{---C}\equiv\text{C---}$, $\text{---C(R')}_2\text{---}$, ---Cy--- , ---O--- , ---S--- , ---S---S--- , ---N(R')--- , ---C(O)--- , ---C(S)--- , ---C(NR')--- , ---C(O)N(R')--- , $\text{---N(R')C(O)N(R')---}$, ---N(R')C(O)--- , ---N(R')C(O)O--- , ---OC(O)N(R')--- , ---S(O)--- , $\text{---S(O)}_2\text{---}$, $\text{---S(O)}_2\text{N(R')---}$, $\text{---N(R')S(O)}_2\text{---}$, ---SC(O)--- , ---C(O)S--- , ---OC(O)--- , or ---C(O)O--- ; each R' is independently ---R--- , ---C(O)R--- , $\text{---CO}_2\text{R---}$, or $\text{---SO}_2\text{R---}$, or: two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R' on the same carbon are taken together with their

intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; ---Cy--- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally substituted group selected from C₁-C₆ aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or

heterocyclyl; and each  independently represents a connection to a nucleoside. In some embodiments, a UNC13A AON with a sequence 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 is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

10 **Motor Neuron Diseases**

[00312] Motor neuron diseases are a group of diseases characterized by loss of function of motor neurons that coordinate voluntary movement of muscles by the brain. Motor neuron diseases may affect upper and/or lower motor neurons, and may have sporadic or familial origins. Motor neuron diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, post-polio syndrome, and ALS with frontotemporal dementia.

[00313] Symptoms of motor neuron diseases include muscle decay or weakening, muscle pain, spasms, slurred speech, difficulty swallowing, loss of muscle control, joint pain, stiff limbs, difficulty breathing, drooling, and complete loss of muscle control, including over basic functions such as breathing, swallowing, eating, speaking, and limb movement. These symptoms are also sometimes accompanied by depression, loss of memory, difficulty with planning, language deficits, altered behavior, and difficulty assessing spatial relationships and/or changes in personality.

[00314] Motor neuron diseases can be assessed and diagnosed by a clinician of skill, for example, a neurologist, using various tools and tests. For example, the presence or risk of developing a motor neuron disease can be assessed or diagnosed using blood and urine tests (for example, tests that assay for the presence of creatinine kinase), magnetic resonance imaging (MRI), electromyography (EMG), nerve conduction study (NCS), spinal tap, lumbar puncture, and/or muscle biopsy. Motor neuron diseases can be diagnosed with the aid of a physical exam and/or a neurological exam to assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

Amyotrophic Lateral Sclerosis

[00315] ALS is a progressive motor neuron disease that disrupts signals to all voluntary muscles. ALS results in atrophy of both upper and lower motor neurons. Symptoms of ALS include weakening and wasting of the bulbar muscles, general and bilateral loss of strength, spasticity, muscle spasms, muscle cramps, fasciculations, slurred speech, and difficulty breathing or loss of ability to breathe. Some individuals with ALS also suffer from cognitive decline. At the molecular level, ALS is characterized by protein and RNA aggregates in the cytoplasm of motor neurons, including aggregates of the RNA-binding protein TDP43.

[00316] ALS is most common in males above 40 years of age, although it can also occur in women and children. Risk of ALS is also heightened in individuals who smoke, are exposed to chemicals such as lead, or who have served in the military. Most instances of ALS are sporadic, while only about 10% of cases are familial. Causes of ALS include sporadic or inherited genetic mutations, high levels of glutamate, protein mishandling. Genetic mutations associated with ALS include mutations in the genes SOD1, C9orf72, TARDBP, FUS, ANG, ATXN2, CHCHD10, CHMP2B, DCTN1, ErbB4, FIG4, HNRPA1, MATR3, NEFH, OPTN, PFN1, PRPH, SETX, SIGMAR1, SMN1, SPG11, SQSTM1, TBK1, TRPM7, TUBA4A, UBQLN2, VAPB, and VCP.

Frontotemporal Dementia

[00317] Frontotemporal dementia (FTD) is a form of dementia that affects the frontal and temporal lobes of the brain. FTD includes frontotemporal lobar degeneration (FTLD). It has an earlier average age of onset than Alzheimer's disease – 40 years of age. Symptoms of FTD include extreme changes in behavior and personality, speech and language problems, and movement-related symptoms such as tremor, rigidity, muscle spasm, weakness, and difficulty swallowing. Subtypes of FTD include behavior variant frontotemporal dementia (bvFTD), characterized by changes in personality and behavior, and primary progressive aphasia (PPA), which affects language skills, speaking, writing and comprehension. FTD is associated with tau protein accumulation (Pick bodies) and altered TDP43 function. About 30% of cases of FTD are familial, and no other risk factors other than family history of the disease are known. Genetic mutations associated with FTD include mutations in the genes C9orf72, Progranulin (GRN), microtubule-associated protein tau (MAPT), UBQLN2, VPC, CHMP2B, TARDBP, FUS, ITM2B, CHCHD10, SQSTM1, PSEN1, PSEN2, CTSF, CYP27A1, TBK1 and TBP.

Amyotrophic lateral sclerosis with frontotemporal dementia

[00318] Amyotrophic lateral sclerosis with frontotemporal dementia (ALS with FTD) is a clinical syndrome in which FTD and ALS occur in the same individual. Interestingly, mutations in C9orf72 are the most common cause of familial forms of ALS and FTD. Additionally, mutations in TBK1, VCP, SQSTM1, UBQLN2 and CHMP2B are also associated with ALS with FTD. Symptoms of ALS with FTD include dramatic changes in personality, as well as muscle weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and degeneration of the spinal cord, motor neurons, and frontal and temporal lobes of the brain. At the molecular level, ALS with FTD is characterized by the accumulation of TDP-43 and/or FUS proteins.

10 TBK1 mutations are associated with ALS, FTD, and ALS with FTD.

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

[00319] Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by accumulation of misfolded TDP-43 protein in the brain, specifically in the limbic system. LATE is a neurological disorder that typically manifests in older patients (e.g., greater than 80 years old). LATE can be a diagnosis for dementia and LATE often mimics the symptoms of Alzheimer's Disease including memory loss, confusion, and mood changes.

15

Methods of Treatment

[00320] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), 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 a patient in need thereof comprising administering a UNC13A AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed UNC13A AON. In some embodiments of the disclosure, an effective amount of a disclosed UNC13A oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein, thereby increase, restore, or stabilize UNC13A activity and/or function.

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[00321] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle

weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS, FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed UNC13A AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

5 [00322] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed UNC13A AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed UNC13A AON. Neurological diseases that can be treated in this manner include motor neuron
10 diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00323] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a UNC13A
15 AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a UNC13A AON disclosed herein.

[00324] Patients treated using an above method may experience an increase, restoration of, or stabilization of UNC13A mRNA expression, which is capable of translation to produce a
20 functional UNC13A protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize UNC13A activity and/or function in a target cell (for example, a motor neuron) after administering a UNC13A oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a UNC13A
25 oligonucleotide may be on, *e.g.*, at least a daily basis. The UNC13A oligonucleotide may be administered orally. In some embodiments, the UNC13A oligonucleotide is administered intrathecally, intrathalamically, or intracisternally. For example, in an embodiment described herein, a UNC13A oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a
30 neurological disease in a patient as a consequence of administering a UNC13A oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as compared to a patient who is not administered a UNC13A oligonucleotide, such as one disclosed herein.

[00325] UNC13A oligonucleotides can be used alone or in combination with each other whereby at least two UNC13A oligonucleotides are used together in a single composition or as part of a treatment regimen. UNC13A oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

5 [00326] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (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
10 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-
15 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
20 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- β -D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET),
25 and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00327] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (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
30 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 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- β -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.

15 **[00328]** In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (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: 5168-20 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 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- β -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.

Treatment and Evaluation

[00329] A patient, as described herein, refers to any animal at risk for, suffering from or
5 diagnosed with a neurological disease, including, but not limited to, mammals, primates, and
humans. In certain embodiments, the patient may be a non-human mammal such as, for
example, a cat, a dog, or a horse. A patient may be an individual diagnosed with a high risk of
developing a neurological disease, someone who has been diagnosed with a neurological disease,
someone who previously suffered from a neurological disease, or an individual evaluated for
10 symptoms or indications of a neurological disease, for example, any of the signs or symptoms
associated with neurological diseases such as: 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),
15 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
20 complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

[00330] "A patient in need," as used herein, refers to a patient suffering from any of the
symptoms or manifestations of a neurological disease, a patient who may suffer from any of the
symptoms or manifestations of a neurological disease, or any patient who might benefit from a
method of the disclosure for treating a neurological disease. A patient in need may include a
25 patient who is diagnosed with a risk of developing a neurological disease, a patient who has
suffered from a neurological disease in the past, or a patient who has previously been treated for
a neurological disease.

[00331] "Effective amount," as used herein, refers to the amount of an agent that is sufficient to
at least partially treat a condition when administered to a patient. The therapeutically effective
30 amount will vary depending on the severity of the condition, the route of administration of the
component, and the age, weight, etc. of the patient being treated. Accordingly, an effective
amount of a disclosed UNC13A oligonucleotide is the amount of the UNC13A oligonucleotide
necessary to treat a neurological disease in a patient such that administration of the agent
prevents a neurological disease from occurring in a subject, prevents neurological disease

progression (e.g., prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, i.e. causes regression of the disease.

[00332] Efficacy of treatment may be evaluated by means of evaluation of gross symptoms

5 associated with a neurological disease, analysis of tissue histology, biochemical assay, imaging methods such as, for example, magnetic resonance imaging, or other known methods. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological
10 disease, a disclosed UNC13A oligonucleotide.

[00333] Efficacy of treatment may also be evaluated at the tissue or cellular level, for example, by means of obtaining a tissue biopsy (e.g., a brain, spinal, muscle, motor neuron tissue biopsy, or olfactory neurosphere cell biopsy) and evaluating gross tissue or cell morphology or staining properties. Biochemical assays that examine protein or RNA expression may also be used to

15 evaluate efficacy of treatment. For instance, one may evaluate levels of a protein or gene product indicative of a neurological disease, in dissociated cells or non-dissociated tissue via immunocytochemical, immunohistochemical, Western blotting, or Northern blotting methods, or methods useful for evaluating RNA levels such as quantitative or semi-quantitative polymerase chain (e.g., digital PCR (DigitalPCR, dPCR, or dePCR), qPCR etc.) reaction. One may also
20 evaluate the presence or level of expression of useful biomarkers (e.g., neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43 or p75 extracellular domain (p75^{ECD})) found in spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, exosome-like cerebrospinal fluid extracellular vesicles (“CSF exosomes”), such as those described in Welton *et al.*, (2017) “Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery
25 in neurological disease; multiple sclerosis” *J Extracell Vesicles.*, 6(1):1-10; and Street *et al.*, (2012) “Identification and proteomic profiling of exosomes in human cerebrospinal fluid” *J Transl. Med.*, 10:5), urine, fecal matter, lymphatic fluid, blood, plasma, or serum to evaluate disease state and efficacy of treatment. One may also evaluate the presence or level of expression of useful biomarkers found in the plasma, neuronal extracellular vesicles/exosomes.
30 Additional measurements of efficacy may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential (CMAP), and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain (p75^{ECD}) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament

heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

5 **[00334]** In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed UNC13A oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results
10 of biochemical or histological analysis of tissue following administration of a disclosed UNC13A oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the
15 UNC13A oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the UNC13A oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient
20 prior to administration of the UNC13A oligonucleotide.

[00335] Validation of UNC13A oligonucleotides may be determined by direct or indirect assessment of UNC13A expression levels or activity. For instance, biochemical assays that measure UNC13A protein or RNA expression may be used to evaluate overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at
25 least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. For instance, one may measure UNC13A protein levels in cells or tissue by Western blot to evaluate overall UNC13A levels. One may also measure UNC13A mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on UNC13A transcripts (for example, a
30 UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. One may also evaluate UNC13A protein levels or levels of another protein indicative of UNC13A signaling activity in dissociated cells, non-dissociated

tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

5 **[00336]** Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or p75^{ECD} found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF

10 exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a

15 sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength

20 duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain (p75^{ECD}) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease

25 status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00337] The disclosure also provides methods of restoring expression of full length UNC13A transcripts in cells of a patient suffering from a neurological disease. Full length UNC13A transcripts may be restored in any cell in which UNC13A expression or activity occurs, including

30 cells of the nervous system (including the central nervous system (*e.g.*, spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal

muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

Pharmaceutical Compositions and Routes of Administration

5 [00338] The present disclosure also provides methods for treating a neurological disease via administration of a pharmaceutical composition comprising a disclosed UNC13A oligonucleotide. In another aspect, the disclosure provides a pharmaceutical composition for use in treating a neurological disease. The pharmaceutical composition may be comprised of a disclosed UNC13A oligonucleotide, and a pharmaceutically acceptable carrier. As used herein the term “pharmaceutical composition” means, for example, a mixture containing a specified
10 amount of a therapeutic compound, *e.g.*, a therapeutically effective amount, of a therapeutic compound in a pharmaceutically acceptable carrier to be administered to a mammal, *e.g.*, a human, in order to treat a neurological disease. In some embodiments, described herein are pharmaceutical compositions comprising a disclosed UNC13A oligonucleotide, and a pharmaceutically acceptable carrier. In another aspect, the disclosure provides use of a disclosed
15 UNC13A oligonucleotide in the manufacture of a medicament for treating a neurological disease. “Medicament,” as used herein, has essentially the same meaning as the term “pharmaceutical composition.”

[00339] As used herein, “pharmaceutically acceptable carrier” means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without
20 excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be “acceptable” in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical
25 administration. The use of such media and agents for pharmaceutically active substances is known in the art. In one embodiment the pharmaceutical composition is administered orally and includes an enteric coating suitable for regulating the site of absorption of the encapsulated substances within the digestive system or gut. For example, an enteric coating can include an ethylacrylate-methacrylic acid copolymer.

30 [00340] In one embodiment, a disclosed UNC13A oligonucleotide and any pharmaceutical composition thereof may be administered by one or several routes, including topically, intrathecally, intrathalamically, intracisternally, intracerebroventricularly, parenterally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. The term parenteral as used herein includes subcutaneous

injections, intrapancreatic administration, intravenous, intracisternal, intracerebroventricular, intrathecal, intrathalamic, intramuscular, intraperitoneal, intrasternal injection or infusion techniques. For example, a disclosed UNC13A oligonucleotide may be administered subcutaneously to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered orally to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered directly to the nervous system, or specific regions or cells of the nervous system (*e.g.*, the brain, brain stem, lower motor neurons, spinal cord, upper motor neurons) via parenteral administration, for example, a disclosed UNC13A oligonucleotide may be administered intrathecally, intrathalamically intracisternally, or intracerebroventricularly.

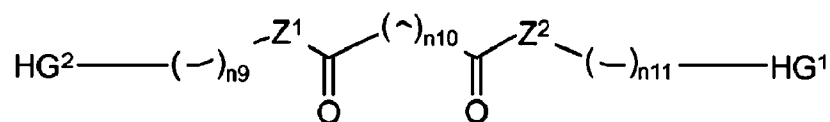
5 [00341] In various embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be exposed to calcium-containing buffers prior to administration. Such calcium-containing buffers can mitigate toxicity adverse effects of the UNC13A oligonucleotide. Further details of exposing an example antisense oligonucleotide to calcium-containing buffers is described in Moazami, et al., Quantifying and Mitigating Motor Phenotypes Induced by Antisense
10 Oligonucleotides in the Central Nervous System, bioRxiv 2021.02.14.431096, which is hereby incorporated by reference in its entirety.

[00342] In some embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be encapsulated in a nanoparticle coating. It is believed that nanoparticle encapsulation prevents AON degradation and enhances cellular uptake. For example, in some embodiments a UNC13A
15 oligonucleotide is encapsulated in a coating of a cationic polymer, for example, a synthetic polymer (*e.g.*, poly-L-lysine, polyamidoamine, a poly(β -amino ester), and polyethyleneimine) or a naturally occurring polymer (*e.g.*, chitosan and a protamine). In some embodiments, a UNC13A oligonucleotide is encapsulated in a lipid or lipid-like material, for example, a cationic lipid, a cationic lipid-like material, or an ionizable lipid that is positively charged only at an
20 acidic pH. An example of a lipid nanoparticle nucleotide therapy includes Exicure's XCUR-FXN, a lipid-nanoparticle spherical nucleic acid (SNA)-based therapeutic candidate. For example, in some embodiments, a UNC13A oligonucleotide is encapsulated in a lipid nanoparticle that includes hydrophobic moieties, *e.g.*, cholesterol and/or a polyethylene glycol (PEG) lipid.

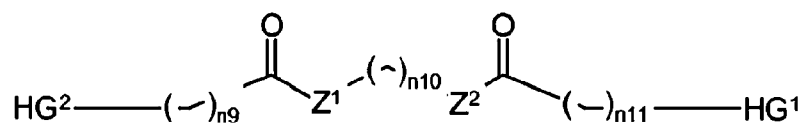
25 [00343] In various embodiments, a pharmaceutical composition comprising a disclosed UNC13A oligonucleotide may further comprise a bolaamphiphilic compound. Example bolaamphiphilic compounds are described in WO2014039493A1, WO2014039500A1, WO2014039502A1, WO2014039503A1, and WO2014039504A1, each of which is hereby incorporated by reference in its entirety. In particular embodiments, a bolaamphiphilic compound is a compound according

to formula I: $\text{HG}^2 \text{L}^1 \text{HG}^1$, or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, isotopic variant, or N-oxide thereof, or a combination thereof; wherein: each HG^1 and HG^2 is independently a hydrophilic head group; and L^1 is alkylene, alkenyl, heteroalkylene, or heteroalkenyl linker; unsubstituted or substituted with C1-C20 alkyl, hydroxyl, or oxo.

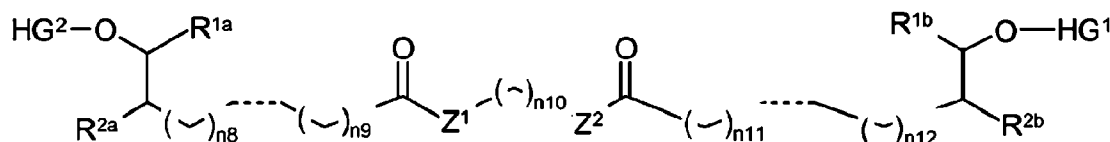
[00344] In one embodiment, with respect to the bolaamphiphilic compound of formula I, the bolaamphiphilic compound is a compound according to formula II, III, IV, V, or VI:



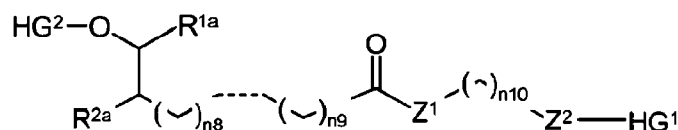
II



III

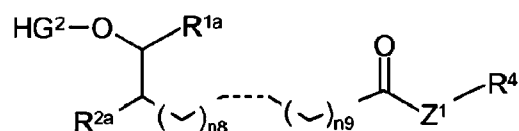


IV



V

; or



VI

[00345] or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, isotopic variant, or N-oxide thereof, or a combination thereof;

wherein:

each HG^1 and HG^2 is independently a hydrophilic head group;

each Z^1 and Z^2 is independently $-C(R^3)_2-$, $-N(R^3)-$ or $-O-$;

each R^{1a} , R^{1b} , R^3 , and R^4 is independently H or C_1 - C_8 alkyl;

5 each R^{2a} and R^{2b} is independently H, C_1 - C_8 alkyl, OH, alkoxy, or $O-HG^1$ or $O-HG^2$; each

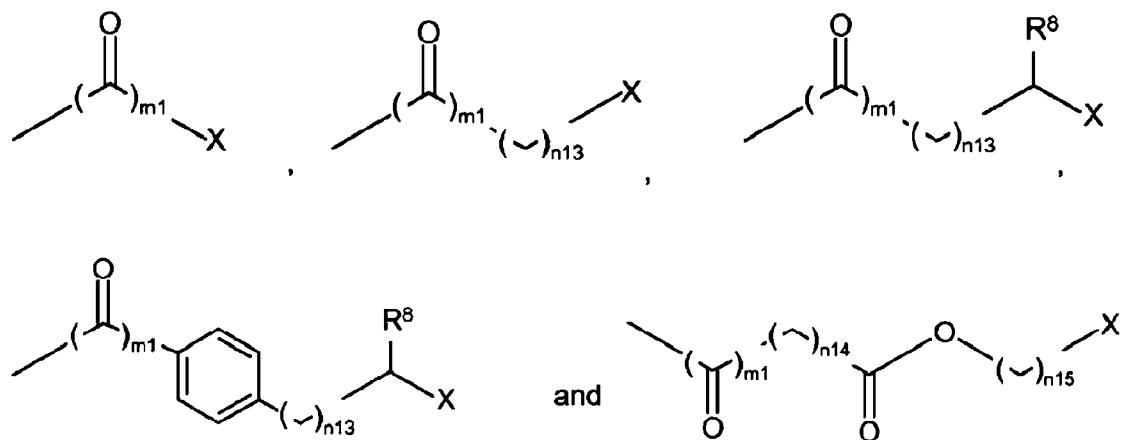
n_8 , n_9 , n_{11} , and n_{12} is independently an integer from 1-20;

n_{10} is an integer from 2-20; and

each dotted bond is independently a single or a double bond.

[00346] In one embodiment, with respect to the bolaamphiphilic compound of formula I,

10 II, III, IV, V, or VI, each HG^1 and HG^2 is independently selected from:



[00347] wherein: X is $-NR^{5a}R^{5b}$, or $-N^+R^{5a}R^{5b}R^{5c}$; each R^{5a} , and R^{5b} is independently H or

15 substituted or unsubstituted C_1 - C_{20} alkyl or R^{5a} and R^{5b} may join together to form an N

containing substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

each R^{5c} is independently substituted or unsubstituted C_1 - C_{20} alkyl; each R^8 is independently H,

substituted or unsubstituted C_1 - C_{20} alkyl, alkoxy, or carboxy; m_1 is 0 or 1; and each n_{13} , n_{14} , and

n_{15} is independently an integer from 1-20.

20 **[00348]** In various embodiments, pharmaceutical compositions disclosed herein comprise

complexes between bolaamphiphiles and pharmacologically or biologically active compounds

(e.g., an UNC13A oligonucleotide disclosed herein). In various embodiments, the

pharmaceutical compositions disclosed herein comprise a bolaamphiphile vesicle complexes

comprising one or more bolaamphiphilic compounds and the biologically active compound is an

25 oligonucleotide (e.g., an UNC13A oligonucleotide disclosed herein).

[00349] Pharmaceutical compositions containing a disclosed UNC13A oligonucleotide, such as those disclosed herein, can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

[00350] Pharmaceutical formulations, in some embodiments, are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Parenteral Administration

[00351] The pharmaceutical compositions of the disclosure can be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intracisternal, intracerebroventricular, intramuscular, subcutaneous, intrathecal, intrathalamic, intralesional, or intraperitoneal routes. The preparation of an aqueous composition, such as an aqueous pharmaceutical composition containing a disclosed UNC13A oligonucleotide, will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

[00352] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including normal saline, artificial cerebrospinal fluid, sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00353] Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a

nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In one embodiment, a disclosed UNC13A

antisense oligonucleotide may be suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethylcellulose and 0.1% (v/v) TWEEN™ 80. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00354] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. Sterile injectable solutions of the disclosure may be prepared by incorporating a disclosed UNC13A antisense oligonucleotide in the required amount of the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter.

[00355] The preparation of more, or highly concentrated solutions for intramuscular injection is also contemplated. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the disclosed oligonucleotide to a small area.

[00356] Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and for example, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose, petrolatum,

polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

Oral Administration

[00357] In some embodiments, contemplated herein are compositions suitable for oral delivery of a disclosed UNC13A oligonucleotide, *e.g.*, tablets that include an enteric coating, *e.g.*, a gastro-resistant coating, such that the compositions may deliver a UNC13A oligonucleotide to, *e.g.*, the gastrointestinal tract of a patient.

[00358] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any SEQ ID NOs: 1-1264, SEQ ID NO: 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 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00359] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 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 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 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 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable filler. For example, a

disclosed UNC13A oligonucleotide and a filler may be blended together, optionally, with other excipients, and formed into granules. In some embodiments, the intragranular phase may be formed using wet granulation, *e.g.*, a liquid (*e.g.*, water) is added to the blended UNC13A oligonucleotide and filler, and then the combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intragranular phase.

[00360] In some embodiments, contemplated formulations include an extra-granular phase, which may include one or more pharmaceutically acceptable excipients, and which may be blended with the intragranular phase to form a disclosed formulation.

[00361] A disclosed formulation may include an intragranular phase that includes a filler. Exemplary fillers include, but are not limited to, cellulose, gelatin, calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, microcrystalline cellulose, pectin, polyacrylates, dextrose, cellulose acetate, hydroxypropylmethyl cellulose, partially pre-gelatinized starch, calcium carbonate, and others including combinations thereof.

[00362] In some embodiments, a disclosed formulation may include an intragranular phase and/or an extragranular phase that includes a binder, which may generally function to hold the ingredients of the pharmaceutical formulation together. Exemplary binders of the disclosure may include, but are not limited to, the following: starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, pre-gelatinized maize starch, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, low substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, sugar alcohols and others including combinations thereof.

[00363] Contemplated formulations, *e.g.*, that include an intragranular phase and/or an extragranular phase, may include a disintegrant such as but not limited to, starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, alginates, corn starch, crosmellose sodium, crosslinked carboxymethyl cellulose, low substituted hydroxypropyl cellulose, acacia, and others including combinations thereof. For example, an intragranular phase and/or an extragranular phase may include a disintegrant.

[00364] In some embodiments, a contemplated formulation includes an intra-granular phase comprising a disclosed UNC13A oligonucleotide and excipients chosen from: mannitol, microcrystalline cellulose, hydroxypropylmethyl cellulose, and sodium starch glycolate or combinations thereof, and an extra-granular phase comprising one or more of: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate or mixtures thereof.

[00365] In some embodiments, a contemplated formulation may include a lubricant, *e.g.* an extra-granular phase may contain a lubricant. Lubricants include but are not limited to talc, silica, fats, stearin, magnesium stearate, calcium phosphate, silicone dioxide, calcium silicate, calcium phosphate, colloidal silicon dioxide, metallic stearates, hydrogenated vegetable oil, corn starch, sodium benzoate, polyethylene glycols, sodium acetate, calcium stearate, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate, talc, and stearic acid.

[00366] In some embodiments, the pharmaceutical formulation comprises an enteric coating. Generally, enteric coatings create a barrier for the oral medication that controls the location at which the drug is absorbed along the digestive track. Enteric coatings may include a polymer that disintegrates at different rates according to pH. Enteric coatings may include for example, cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymers, ethylacrylate-methacrylic acid copolymers, methacrylic acid copolymer type C, polyvinyl acetate-phthalate, and cellulose acetate phthalate.

[00367] Exemplary enteric coatings include Opadry® AMB, Acryl-EZE®, Eudragit® grades. In some embodiments, an enteric coating may comprise about 5% to about 10%, about 5% to about 20%, 8% to about 15%, about 8% to about 20%, about 10% to about 20%, or about 12% to about 20%, or about 18% of a contemplated tablet by weight. For example, enteric coatings may include an ethylacrylate-methacrylic acid copolymer.

[00368] For example, in a contemplated embodiment, a tablet is provided that comprises or consists essentially of about 0.5% to about 70%, *e.g.*, about 0.5% to about 10%, or about 1% to about 20%, by weight of a disclosed UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof. Such a tablet may include for example, about 0.5% to about 60% by weight of mannitol, *e.g.*, about 30% to about 50% by weight mannitol, *e.g.*, about 40% by weight mannitol; and/or about 20% to about 40% by weight of microcrystalline cellulose, or about 10% to about 30% by weight of microcrystalline cellulose. For example, a disclosed tablet may comprise an intragranular phase that includes about 30% to about 60%, *e.g.* about 45% to about 65% by weight, or alternatively, about 5 to about 10% by weight of a disclosed UNC13A oligonucleotide, about 30% to about 50%, or alternatively, about 5% to about 15% by weight mannitol, about 5% to about 15% microcrystalline cellulose, about 0% to about 4%, or about 1% to about 7% hydroxypropylmethylcellulose, and about 0% to about 4%, *e.g.*, about 2% to about 4% sodium starch glycolate by weight.

[00369] In another contemplated embodiment, a pharmaceutical tablet formulation for oral administration of a disclosed UNC13A oligonucleotide comprises an intra-granular phase,

wherein the intra-granular phase includes a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and which may also include an extra-granular phase, that may include a pharmaceutically acceptable excipient such as a disintegrant. The extra-granular phase may include components chosen from microcrystalline cellulose, magnesium stearate, and mixtures thereof. The pharmaceutical composition may also include an enteric coating of about 12% to 20% by weight of the tablet. For example, a pharmaceutically acceptable tablet for oral use may comprise about 0.5% to 10% by weight of a disclosed UNC13A AON, *e.g.*, a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof, about 30% to 50% by weight mannitol, about 10% to 30% by weight microcrystalline cellulose, and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[00370] In another example, a pharmaceutically acceptable tablet for oral use may comprise an intra-granular phase, comprising about 5 to about 10% by weight of a disclosed UNC13A AON, *e.g.*, a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof, about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydroxypropylmethyl cellulose, and about 2% by weight sodium starch glycolate; an extra-granular phase comprising about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, about 0.4% by weight magnesium stearate; and an enteric coating over the tablet comprising an ethylacrylate-methacrylic acid copolymer.

[00371] In some embodiments the pharmaceutical composition may contain an enteric coating comprising about 13% or about 15%, 16%, 17% or 18% by weight, *e.g.*, AcyrLEZE® (*see, e.g.*, PCT Publication No. WO 2010/054826, which is hereby incorporated by reference in its entirety).

[00372] The rate at which the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the UNC13A oligonucleotide releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. In another embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in diluted HCl with a pH of 1.0, where substantially none of the UNC13A oligonucleotide is released after 120 minutes. A contemplated tablet, in another embodiment, may have a dissolution profile, *e.g.*, when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 6.6, of about 10% to

about 30%, or not more than about 50% of the UNC13A oligonucleotide releasing after 30 minutes.

[00373] In some embodiments, methods provided herein may further include administering at least one other agent that is directed to treatment of diseases and disorders disclosed herein. In one embodiment, contemplated other agents may be co-administered (*e.g.*, sequentially or simultaneously).

Dosage and Frequency of Administration

[00374] The dosage or amounts described below refer either to the oligonucleotide or a pharmaceutically acceptable salt thereof.

[00375] In some embodiments, methods described herein include administering at least 1 µg, at least 5 µg, at least 10 µg, at least 20 µg, at least 30 µg, at least 40 µg, at least 50 µg, at least 60 µg, at least 70 µg, at least 80 µg, at least 90 µg, or at least 100 µg of a UNC13A antisense oligonucleotide *e.g.*, a UNC13A oligonucleotide. In some embodiments, methods include administering from 10 mg to 500 mg, from 1 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from 350 mg to 400 mg, from 400 mg to 450 mg, from 450 mg to 500 mg, from 500 mg to 600 mg, from 600 mg to 700 mg, from 700 mg to 800 mg, from 800 mg to 900 mg, from 900 mg to 1 g, from 1 mg to 50 mg, from 20 mg to 40 mg, or from 1 mg to 500 mg of a UNC13A antisense oligonucleotide.

[00376] In some embodiments, methods described herein include administering formulations that include about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, 4.0 g, 4.5 g, or 5.0 g of a disclosed UNC13A oligonucleotide. In some embodiments, a formulation may include about 40 mg, 80 mg, or 160 mg of a disclosed UNC13A oligonucleotide. In some embodiments, a formulation may include at least 100 µg of a disclosed UNC13A oligonucleotide. For example, formulations may include about 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of a disclosed UNC13A oligonucleotide. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health and size of the patient, the *in vivo* potency of the UNC13A oligonucleotide, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly

achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once per day for 7 days. In some embodiments, dosing is once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In some embodiments, dosing is once a month to every three months. In some embodiments, dosing is once every 2 weeks for three dose, then monthly, bimonthly, or every three or four months.

Combination Therapies

[00377] In various embodiments, a UNC13A AON as disclosed herein can be administered in combination with one or more additional therapies. The combination therapy of the disclosed oligonucleotide and the one or more additional therapies can, in some embodiments, be synergistic in treating any 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 Parkinson'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.

[00378] Non-limiting examples of therapies for Parkinson's disease (PD) include: 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, Nuplazid, and embryonic dopamine cell implantation.

[00379] Non-limiting examples of therapies for Alzheimer's disease (AD) include aducanumab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), and lecanemab.

5 [00380] A non-limiting example of a therapy for amyotrophic lateral sclerosis (ALS) is pridopidine.

[00381] Non-limiting examples of therapies for frontotemporal dementia (FTD) include olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote),
10 carbamazepine (Tegretol), and medroxyprogesterone.

[00382] Non-limiting examples of therapies for epilepsy include 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
15 (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (Lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and zonisamide (zonegran).

[00383] Example additional therapies include any of Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor,
20 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, or QRL-101), bioactive scaffolds,
25 anticonvulsants and psychostimulant agents. Additional therapies can further include breathing care, physical therapy, occupational therapy, speech therapy, and nutritional support. Further non-limiting examples of additional therapies include any of deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri,
30 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 (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant

(belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), 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), and zonisamide (zonegran). In various embodiments, an additional therapy can be a second antisense oligonucleotide. As an example, the second antisense oligonucleotide may target a UNC13A transcript (*e.g.*, UNC13A pre-mRNA, mature UNC13A mRNA) to modulate the expression levels of full length UNC13A protein.

15 **[00384]** Non-limiting examples of therapies for spinal cord injury includes bioactive scaffolds, such as bioactive scaffolds with enhanced supramolecular motion. Further details of example bioactive scaffolds as therapies for spinal cord injury is described in Alvarez et al., “Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury.” Science, 374, 848-856 (2021), which is hereby incorporated by reference in its entirety.

20 **[00385]** In various embodiments, the disclosed oligonucleotide and the one or more additional therapies can be conjugated to one another and provided in a conjugated form. Further description regarding conjugates involving the disclosed oligonucleotide is described below. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided concurrently. In various embodiments, the disclosed oligonucleotide and one or more

25 additional therapies are provided simultaneously. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided sequentially.

Conjugates

[00386] In certain embodiments, provided herein are oligomeric compounds, which comprise an oligonucleotide (*e.g.*, UNC13A oligonucleotide) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups include one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends

of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

[00387] Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

Conjugate Groups

[00388] In certain embodiments, a UNC13A AON is covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge, and clearance. In particular embodiments, conjugate groups modify the circulation time (e.g., increase) of the oligonucleotides in the bloodstream such that increased concentrations of the oligonucleotides are delivered to the brain. In particular embodiments, conjugate groups modify the residence time (e.g., increase residence time) of the oligonucleotides in a target organ (e.g., brain) such that increased residence time of the oligonucleotides improves their performance (e.g., efficacy). In particular embodiments, conjugate groups increase the delivery of the oligonucleotide to the brain through the blood brain barrier and/or brain parenchyma (e.g., through receptor mediated transcytosis). In particular embodiments, conjugate groups enable the oligonucleotide to target a specific organ (e.g., the brain). In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. NY. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac -glycerol or triethyl -ammonium 1,2-di-0-

hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937), a tocopherol group (Nishina *et al.*, Molecular Therapy Nucleic Acids, 2015, 4, e220; and Nishina *et al.*, Molecular Therapy, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

Conjugate Moieties

- 10 [00389] Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, dyes, bile acids, and phenylbutyric acid. In
15 particular embodiments, conjugate moieties are selected from a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, lipoic acid, panthothenic acid, polyethylene glycol, an antibody (*e.g.*, an antibody for crossing the blood brain barrier such as anti-transferrin receptor antibody), or a cell-penetrating peptide (*e.g.*, transactivator of transcription (TAT) and penetratine).
- 20 [00390] In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

25 Conjugate Linkers

- [00391] Conjugate moieties are attached to a UNC13A AON through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (*i.e.*, the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbon chain, or an oligomer of
30 repeating units such as ethylene glycol, nucleosides, or amino acid units.
- [00392] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups

selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

[00393] In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a parent compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[00394] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) and 6-aminohexanoic acid (AHX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[00395] In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise 3 linker-nucleosides.

[00396] In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to

the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

[00397] Herein, linker-nucleosides are not considered to be part of the oligonucleotide.

Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide

5 consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

10 **[00398]** In certain embodiments, it is desirable for a conjugate group to be cleaved from the UNC13A AON. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or
15 more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain
20 embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

[00399] In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain
25 embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

[00400] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one
30 another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or

phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxy adenosine.

Terminal Groups

[00401] In certain embodiments, oligomeric compounds comprise one or more terminal groups.

- 5 In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked
- 10 nucleoside is an abasic nucleoside. In various embodiments, terminal groups comprise one or more spacers.

Diagnostic Methods

[00402] The disclosure also provides a method of diagnosing a patient with a neurological

15 disease that relies upon detecting levels of UNC13A expression signal in one or more biological samples of a patient. As used herein, the term "UNC13A expression signal" can refer to any indication of UNC13A gene expression, or gene or gene product activity. UNC13A gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of UNC13A gene expression that can be assessed include, but are not limited to, UNC13A gene or chromatin state,

20 UNC13A gene interaction with cellular components that regulate gene expression, UNC13A gene product expression levels (*e.g.*, expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, or interaction of UNC13A RNA or protein with transcriptional,

25 translational, or post-translational processing machinery.

- [00403] Detection of UNC13A expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or
- 30 cells of a patient. Detection may be achieved by measuring expression signal of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including

blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, plasma, or serum. Methods of detection include assays that measure levels of UNC13A gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (e.g., MRI), or immunostaining methods (e.g., immunohistochemistry or immunocytochemistry).

Modifications in General

[00404] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

[00405] Although the sequence listing accompanying this filing identifies each sequence as either “RNA” or “DNA” as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as “RNA” or “DNA” to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence “ATCGATCG” encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence “AUCGAUCG” and those having some DNA bases and some RNA bases such as “AUCGATCG” and oligomeric compounds having other modified nucleobases, such as “AT^mCGAUCG,” wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position.

[00406] Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided

herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that contain stereocenters that are drawn or described with undefined stereochemistry included all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

[00407] The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^1H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^2H or ^3H in place of ^1H , ^{13}C or ^{14}C in place of ^{12}C , ^{15}N in place of ^{14}N , ^{17}O or ^{18}O in place of ^{16}O , and ^{33}S , ^{34}S , ^{35}S , or ^{36}S in place of ^{32}S . In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool.

EXAMPLES

[00408] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only, and are not to be construed as limiting the scope or content of the disclosure in any way.

Example 1: Design and Selection of UNC13A Oligonucleotides

[00409] UNC13A AONs oligonucleotides that target a UNC13A transcript are designed and tested to identify UNC13A AONs capable of reducing quantity of UNC13A transcripts (e.g., mis-spliced UNC13A transcripts). Such UNC13A AONs include UNC13A parent oligonucleotides represented by any of SEQ ID NOs: 1-1264 or UNC13A oligonucleotide variants represented by SEQ ID NOs: 2529-3792. The UNC13A parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the UNC13A parent oligonucleotides are modified nucleosides with 2'MOE sugar moieties, and each "C" is replaced with a 5-MeC. Additionally, each of the internucleoside linkages between the nucleosides of the UNC13A oligonucleotides are phosphorothioate internucleoside linkages.

[00410] Generally, the length of the UNC13A antisense oligonucleotides are 25 oligonucleotide units in length. However, variants of the UNC13A antisense oligonucleotides were also designed with varying lengths (e.g., 23mers, 21mers, or 19mers). Examples of these variant UNC13A antisense oligonucleotides were designed to include a subset of the sequences of SEQ ID NOs: 2529-3792.

[00411] Table 6A: Example UNC13A AONs (including UNC13A oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence (where <u>S</u> indicates presence of a Spacer)* (5' → 3')	Length
5133	GGGCAGSCAGGAATGGTGS GTGGAA	25
5134	AGGGAGSAGTTTTCCAGGSAAAGGG	25
5135	GCAGCTSGAAGAGACATASCCAGAC	25
5136	TCCACCSGCCACTCACAASCATCCA	25
5137	GAAAGTSTCATGGAGAGTSCAAGGG	25
5138	GGGCAGGCSGGAATGGTGS GTGGAA	25
5139	AGGGAGGASTTTTTCCAGGSAAAGGG	25
5140	GCAGCTGGSAGAGACATASCCAGAC	25
5141	TCCACCAGSCACTCACAASCATCCA	25
5142	GAAAGTGTSATGGAGAGTSCAAGGG	25
5143	GCAGGCASGAATGGTSAGTGGAA	23
5144	GGGCAGGSAGGAATGSTGAGTGG	23
5145	GGCAGGCSGGAATGGSGAGTGGAA	23
5146	GTAAAGGSAATGGCASGGCGGGC	23
5147	AGGTAAASGGAATGGSATGGCGG	23
5148	GGTAAAGSGAATGGCSTGGCGGG	23
5149	AGGAGGTSACCCTGASTCTGGAC	23
5150	AGAGGAGSTGACCCTSAATCTGG	23
5151	GAGGAGGSGACCCTGSATCTGGA	23
5152	ACAAACGSCCCAATCSTGAGTGG	23
5153	ACACAAASGGCCCAASCCTGAGT	23
5154	CACAAACSGCCCAATSCTGAGTG	23
5155	TCTTTCCSGGAAACCSAGGCAGC	23
5156	GTTCTTTSCAGGAAASCCAGGCA	23
5157	TTCTTTCSAGGAAACSCAGGCAG	23
5158	TCCGCAASTTAATCCSCCTACCC	23
5159	GATCCGCSACTTAATSCACCTAC	23
5160	ATCCGCASCTTAATCSACCTACC	23

5161	CCCACCCSTCTAACTSCCCCAA	23
5162	CACCCACSCATCTAASTACCCCA	23
5163	ACCCACCSATCTAACSACCCCAA	23
5164	AAGTGTCTGGAGAGSGCAAGGG	23
5165	GAAAGTGSCATGGAGSGTGCAAG	23
5166	AAAGTGTSATGGAGASTGCAAGG	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as

5 disclosed herein.

[00412] Table 6B: Example UNC13A AONs (including UNC13A oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence (where S indicates presence of a Spacer)* (5' → 3')	Length
5168	AGTTCASCCACACATCCTSCCATTC	25
5169	AGTTCAACSACACATCCTSCCATTC	25
5170	GTTCAACSACACATCSTTCCATT	23
5171	AGTTCAASCACACATSCTTCCAT	23
5172	TTCAACCSCACATCCSTCCATTC	23
5173	CTTGCASTAGTTCAACCASACATCC	25
5174	CTTGCAATSGTTCAACCASACATCC	25
5175	TTGCAATSGTTCAACSACACATC	23
5176	CTTGCAASAGTTCAASCACACAT	23
5177	TGCAATASTTCAACCSCACATCC	23
5178	ACACATSCATCCATCCATSCATTCA	25
5179	ACACATCCSTCCATCCATSCATTCA	25
5180	CACATCCSTCCATCCSTCCATTC	23
5181	ACACATCSATCCATCSATCCATT	23
5182	ACATCCASCCATCCASCCATTCA	23
5183	CAGTAASTCAACCACACASCCATCC	25

5184	CAGTAATTSAACCACACASCCATCC	25
5185	AGTAATTSAACCACASATCCATC	23
5186	CAGTAATSCAACCACSCATCCAT	23
5187	GTAATTCSACCACACSTCCATCC	23
5188	ACCTTTSAGTAATTCAACSACACAT	25
5189	ACCTTTCASTAATTCAACSACACAT	25
5190	CCTTTCASTAATTCASCCACACA	23
5191	ACCTTTCSGTAATTCSACCACAC	23
5192	CTTTCAGSAATTCAASCACACAT	23
5193	CTCTTTSATCCATCCACASACCCAC	25
5194	CTCTTTTASCCATCCACASACCCAC	25
5195	TCTTTTASCCATCCASACACCCA	23
5196	CTCTTTTSTCCATCCSCACACCC	23
5197	CTTTTATSCATCCACSCACCCAC	23
5198	ATCTACSCTTTTATCCATSCACACA	25
5199	ATCTACTCSTTTATCCATSCACACA	25
5200	TCTACTCSTTTATCCSTCCACAC	23
5201	ATCTACTSTTTTATCSATCCACA	23
5202	CTACTCTSTTATCCASCCACACA	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by S is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein.

Example 2: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00413] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 50,000 cells / well.

10 Antisense oligonucleotide (AON) to TDP43 was transfected with Endoportor (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13a transcript. Vehicle control consisted of motor neuron treatment with Endoportor alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00414] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C" is 5-MeC.

[00415] To evaluate UNC13a AON ability to restore full length UNC13A (UNC13A FL) mRNA (also referred to as correctly spliced UNC13A (UNC13A CS) mRNA), antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoport in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoport were washed out and replaced with fresh media alone. After 72 additional hours, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A full length transcript and reference GAPDH quantification.

[00416] Transcript levels (e.g., UNC13A full length transcript or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting UNC13A-FL transcripts using Thermofisher® TaqMan Gene Expression Assay Hs00392638_m1.

[00417] RT-qPCR was performed on Applied Biosystems® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00418] UNC13A-FL (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-FL), the normalized UNC13A-FL signal was further normalized to the vehicle (treated with Endoport alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-\text{deltadeltaCt}}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A FL were normalized using the following formula:

$$(((RQAON - RQTDP43)/(RQendo - RQTDP43)) * 100$$

[00419] Table 7 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons. UNC13A AONs (e.g., UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to increase or restore full-length UNC13A mRNA (i.e., mRNA from which full-length UNC13A protein is translated) levels. In some cases, UNC13A AONs with spacers increased full-length UNC13A mRNA ("UNC13A FL"), also referred to herein as correctly spliced UNC13A

(UNC13A CS). In some cases, UNC13A AONs without spacers increased full-length UNC13A mRNA or correctly spliced UNC13A mRNA (UNC13A CS)). Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00420] As shown in Table 7, a 500 nM dose of SEQ ID NO: 5326

5 (ACACAAASGGCCCAASCCTGAGT with two spacers) rescued full length UNC13A mRNA to 55.69%. Comparatively, a 500 nM dose of SEQ ID NO: 5325 (ACACAAACGGCCCAATCCTGAGT with no spacers) rescued full length UNC13A mRNA to 41.87%. This indicates that the addition of spacers of SEQ ID NO: 5326 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5325).

[00421] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5352

(GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 55.88%. A 500 nM dose of SEQ ID NO: 5352 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 66.62%. Comparatively, a 200 nM dose of SEQ ID NO: 3547 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 43.88%. A 500 nM dose of SEQ ID NO: 5351 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 66.98%. This indicates that at 200 nM and 500 nM doses, the performance of an AON with SEQ ID NO: 5352 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5351).

[00422] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5359

(CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to 47.94%. A 500 nM dose of SEQ ID NO: 5359 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to 83.19%. Comparatively, a 200 nM dose of SEQ ID NO: 5358 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 47.68%. A 500 nM dose of SEQ ID NO: 5358 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 41.16%. This indicates that at a 200 nM dose, the performance of SEQ ID NO: 5359 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5358). However, at a 500 nM dose, the addition of spacers of SEQ ID NO: 5359 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5358).

[00423] Additionally shown in Table 7, a 500 nM dose of SEQ ID NO: 5361

(CCCACCCSTCTAACTSCCCCAA with two spacers) rescued full length UNC13A mRNA to

43.10%. Comparatively, a 500 nM dose of SEQ ID NO: 5360 (CCCACCCATCTAACTACCCCAA with no spacers) rescued full length UNC13A mRNA to 23.37%. This indicates that at a 500 nM dose, the addition of spacers improves the performance of an AON with SEQ ID NO: 5361 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5360).

[00424] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5368 (AAGTGTCTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 35.39%. A 500 nM dose of SEQ ID NO: 5368 (AAGTGTCTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 6.60%. Comparatively, a 200 nM dose of SEQ ID NO: 5367 (AAGTGTCTGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 19.04%. A 500 nM dose of SEQ ID NO: 5367 (AAGTGTCTGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to -34.58%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 5164 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5367).

[00425] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5370 (GAAAGTGTCTGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 67.77%. A 500 nM dose of SEQ ID NO: 5370 (GAAAGTGTCTGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 84.79%. Comparatively, a 200 nM dose of SEQ ID NO: 5362 (GAAAGTGTCTGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 22.48%. A 500 nM dose of SEQ ID NO: 5362 (GAAAGTGTCTGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 24.84%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 5142 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 1248).

[00426] Altogether, these results demonstrate that different UNC13A AONs including two spacers are capable of increasing UNC13A-FL mRNA to levels that are comparable to or improved beyond their non-spacer counterparts.

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Table 7: Performance of UNC13A AONs in UNC13A full length assay (UNC13A oligonucleotides without spacers, or with one or two spacers).

SEQ ID NO:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	QPCR potency		
		200 nM	200 nM	500 nM
		Normalized CS	Normalized CS SD	Normalized CS SD
5293	GAAGAGCTGGGCAGGCAGGAATGGT	3.79367	0.480565	-63.053
5294	TGTGGATGTTGTGGCCAGAAAGAGG	60.6986	0.724229	-23.435
5295	GGCCAGGAGAGTGTGGATGGTGTGG	154.828	1.127288	434.631
5296	ATGTCATGGCGGCAGTCTCAGAGG	37.1601	0.448286	12.6634
5297	AAAGGGAATGGCATGGCGGGCAGTC	-26.139	0.13718	22.9464
5298	AGGTAAAGGGAATGGCATGGCGGGC	-5.3242	0.383369	-37.199
5299	GGTAAAGGGGAATGGCATGGCGGGG	-29.228	0.227001	-33.566
5300	GGTAAAGSGAATGGCSTGGCGGG	-16.331	0.304608	-29.739
5301	AGGTAAAGGGAATGGCATGGCGG	-13.385	0.322337	-40.436
5302	AGGTAAASGGAAATGGSATGGCGG	-13.664	0.320657	-24.027
5303	GTAAAGGGAATGGCATGGCGGGC	-29.989	0.222419	-26.677
5304	GTAAAGCSAATGGCASGGCGGGC	25.771	0.557959	-18.428
5305	TCCAGGTAAAGGGAATGGCATGGCG	-7.8349	0.268854	40.2877
5306	AGGGAGGAGTTTTCCAGGTAAAGGG	-32.255	0.392785	-25.109
5307	AGGGAGSAGTTTTCCAGGSAAAGGG	6.97605	0.572906	-3.6889
5308	AGGGAGGASTTTTCCAGGSAAAGGG	-70.51	0.217148	-78.696
5309	AGAGGAGGTGACCCCTGAATCTGGAC	129.033	0.93262	110.34
5310	GAGGAGGTGACCCCTGAATCTGGA	169.855	1.024819	164.814

5311	GAGGAGGSGACCCCTGSAATCTGGA	-72.457	0.658323	138.629	1.28191
5312	AGAGGAGGTGACCCCTGAATCTGG	171.498	1.135638	3.26987	0.54512
5313	AGAGGAGSTGACCCCTSAATCTGG	7.49253	0.565048	-57.946	0.25617
5314	AGGAGGTGACCCCTGAATCTGGAC	44.7095	0.740715	125.001	1.1197
5315	AGGAGGTSACCCCTGASTCTGGAC	-44.26	0.320771	12.8179	0.59018
5316	GAGAGTCAACCTGTGGAGGCCAAGGTG	32.5688	0.559505	57.0338	0.7355
5317	GTAGTGAGAGTCAACCTGGAGGCCA	70.681	0.905428	67.6819	0.88671
5318	TGAGTAGTGAGAGTCAACCTGGAGG	91.2119	1.033573	59.7857	0.83742
5319	CCTGAGTGGTTAGGGCTGGAATAGA	46.7792	0.756244	-24.332	0.3124
5320	CAATCCTGAGTGGTTAGGGCTGGAA	-8.5	0.411217	73.8646	0.9253
5321	ACGGCCCCAATCCTGAGTGGTTAGGG	66.8521	0.88153	45.3726	0.74746
5322	ACACAAAACGGCCCCAATCCTGAGTGG	-11.42	0.462541	75.8487	0.8839
5323	CACAAAACGGCCCCAATCCTGAGTG	-11.128	0.463949	-41.939	0.31518
5324	CACAAAACSGCCCCAATCCTGAGTG	50.7872	0.762897	-14.314	0.44857
5325	ACACAAAACGGCCCCAATCCTGAGT	-27.43	0.385239	41.8694	0.71984
5326	ACACAAAASGGCCCCAASCCTGAGT	-14.732	0.44655	55.6902	0.78657
5327	ACAAAACGGCCCCAATCCTGAGTGG	-49.751	0.277462	-20.306	0.41964
5328	ACAAAACSGCCCCAATCCTGAGTGG	105.349	1.026341	47.8744	0.74883
5329	CAGACACAAAACGGCCCCAATCCTGAG	-40.7843	0.3272	-5.4793	0.5486
5330	CATACCCAGACACAAAACGGCCCCAAT	-21.2475	0.3317	14.4015	0.5542
5331	GAGACATACCCAGACACAAAACGGCC	47.2141	0.7590	116.3656	1.1906
5332	GCAGCTGGAAGAGACATACCCAGAC	4.7146	0.5625	-66.6389	0.2349
5333	GCAGCTSGAAGAGACATASCCAGAC	33.7840	0.6960	-6.4957	0.5111

5334	GCAGCTGGSAGAGACATATSCCAGAC	3.7461	0.5581	35.3538	0.7032
5335	TCTTTCCAGGAAACCCAGGCAGCTG	17.5514	0.5395	30.5680	0.5952
5336	GTTCTTTCCAGGAAACCCAGGCAGC	41.1141	0.5932	-27.3254	0.2666
5337	TTCTTTCCAGGAAACCCAGGCAG	-31.8396	0.2450	-7.7732	0.3599
5338	TTCTTTCSAGGAAACSCAGGCAG	-72.0800	0.0530	-37.1813	0.2196
5339	GTTCTTTCCAGGAAACCCAGGCA	-14.5643	0.3275	44.7209	0.6104
5340	GTTCTTTSCAGGAAASCCAGGCA	-38.7597	0.2120	-22.4863	0.2897
5341	TCTTTCCAGGAAACCCAGGCAGC	2.0002	0.4065	-15.1244	0.3248
5342	TCTTTCCSGGAAACCSAGGCAGC	-59.9899	0.1107	-64.5153	0.0891
5343	CACGAATCTACCCACCAACTCATCC	-39.5824	0.2948	-56.2924	0.2233
5344	TCTAGCCACGAAATCTACCCACCAAC	75.4170	0.7873	-12.0685	0.4126
5345	GTCTGTCCACGAGCCACTCACAACC	121.2337	0.9834	-62.7895	0.1955
5346	TTCGTCTGTCCACCAGCCACTCACA	-18.2285	0.3863	-45.7096	0.2686
5347	TCCATTTTTCGTCTGTCTCCACCAGCC	-63.8195	0.2479	-54.2647	0.2917
5348	GATCCGCAACTTAAATCCACCTACCC	88.0305	0.9091	44.9905	0.5436
5349	ATCCGCAAACTTAATCCACCTACC	30.7027	0.4223	45.1113	0.5446
5350	ATCCGCASCTTAATCSACCTACC	38.8278	0.4913	50.8796	0.5936
5351	GATCCGCAACTTAATCCACCTAC	43.8789	0.5342	66.9823	0.7303
5352	GATCCGCSACTTAATSCACCTAC	55.8768	0.6360	66.6162	0.7272
5353	TCCGCAAACTTAATCCACCTACCC	64.3790	0.7082	67.3066	0.7331
5354	TCCGCAAASTTAATCCSCTACCC	53.4236	0.6152	51.3988	0.5980
5355	CACCCACCCATCTAACTACCCCAAA	64.1844	0.6729	44.6783	0.4941
5356	ACCCACCCATCTAACTACCCCAA	41.2908	0.4631	64.1844	0.6729

5357	ACCCACCSATCTAACSAACCCCAA	46.9810	0.4070	58.8250	0.6238
5358	CACCCACCCCATCTAACTACCCCA	47.6810	0.5217	41.0564	0.4609
5359	CACCCACSCATCTA^STACCCCA	47.9432	0.5241	83.1895	0.8471
5360	CCCACCCCATCTAACTACCCCAAA	72.0651	0.5775	23.3677	0.2988
5361	CCCACCCSTCTAACTSCCCCAAA	41.8445	0.4682	43.0965	0.4796
5362	GAAAGTGTTCATGGAGAGTGCAAGGG	22.4754	0.5041	24.8358	0.5167
5363	AAAGTGTTCATGGAGAGTGCAAGG	82.5919	0.8245	7.0300	0.4218
5364	AAAGTGTSATGGAGASTGCAAGG	61.0070	0.7095	-4.8799	0.3583
5365	GAAAGTGTTCATGGAGAGTGCAAG	55.7844	0.6816	-19.7864	0.2789
5366	GAAAGTGSCATGGAGSGTGCAAG	40.0402	0.5977	3.6974	0.4040
5367	AAGTGTTCATGGAGAGTGCAAGGG	19.0435	0.4858	-34.5807	0.2001
5368	AAGTGTCTSTGGAGAGSGCAAGGG	35.3880	0.5729	6.6020	0.4195
5369	GAAAGTSTCATGGAGAGTSCAAGGG	-10.6183	0.3278	50.6900	0.6545
5370	GAAAGTGTSATGGAGAGTSCAAGGG	67.7691	0.7455	84.7852	0.8362
5371	CACCATGGGAGAGAAAGTGTCATGG	17.7544	0.4529	64.3335	0.7880

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (Iia') as disclosed herein.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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Claims

1. 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.
2. The compound of claim 0, wherein the modified oligonucleotide comprises a spacer.
3. 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.
4. 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, 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.
5. The oligonucleotide of claim 4, further comprising a spacer.
6. An oligonucleotide comprising a sequence that is at least 85 98% 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.
7. The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.
8. The compound of claims 1-3 or 7, or oligonucleotides of claims 5-7, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

9. The compound of any one of claims 1-3 or 7-8 or oligonucleotide of any one of claims 44-8, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.
10. The compound of any one of claims 1-3 or 7-9 or oligonucleotide of any one of claims 5-9, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.
11. The compound of any one of claims 1-3 or 7-10 or oligonucleotide of any one of claims 5-10, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.
12. The compound or oligonucleotide of any one of claims 7-11, wherein 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.
13. The compound or oligonucleotide of any one of claims 7-12, wherein 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 sequences in Tables 3A, 3B, 4 and 5.
14. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares at least 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.
15. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares 100% 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.

16. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 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 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.

17. The compound or oligonucleotide of claim 16, wherein 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 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.

18. The compound or oligonucleotide of claim 16 or 17, wherein 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 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, 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.

19. The compound or oligonucleotide of any one of claims 1-18, wherein 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.

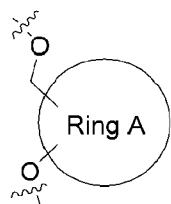
20. The compound or oligonucleotide of claim 19, wherein the oligonucleotide is at least 19 oligonucleotide units in length.

21. The compound or oligonucleotide of any one of claims 1-3 and 5-20, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

22. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

23. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.
24. The compound or oligonucleotide of claim 21 or 23, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.
25. The compound or oligonucleotide of claim 24, wherein 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.
26. The compound or oligonucleotide of claim 24 or 25, wherein 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.
27. The compound or oligonucleotide of any one of claims 24-26, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.
28. The compound or oligonucleotide of any one of claims 24-27, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.
29. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.
30. The compound or oligonucleotide of claim 29, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.
31. The compound or oligonucleotide of claim 30, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

32. The compound or oligonucleotide of claim 21, wherein 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.
33. The compound or oligonucleotide of claim 32, wherein at least two of the three spacers are adjacent to a guanine nucleobase.
34. The compound or oligonucleotide of claim 33, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.
35. The compound or oligonucleotide of any one of claims 21-34, wherein 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.
36. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

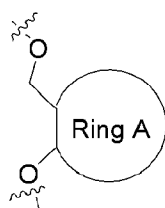


Formula (X)

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

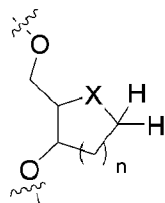
the  symbol represents the point of connection to an internucleoside linkage.

37. The compound or oligonucleotide of claim 36, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



Formula (Xa).

38. The compound or nucleotide of claim 36 or 37, wherein 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.
39. The compound or nucleotide of claim 38 wherein ring A is tetrahydrofuranyl.
40. The compound or nucleotide of claim 38 wherein ring A is tetrahydropyranyl.
41. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I, wherein:

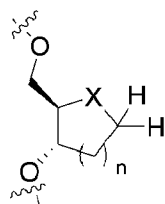


Formula (I)

X is selected from $\text{-CH}_2\text{-}$ and -O- ; and

n is 0, 1, 2 or 3.

42. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I', wherein:

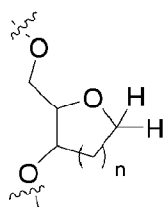


Formula (I')

X is selected from -CH₂- and -O-; and

n is 0, 1, 2 or 3.

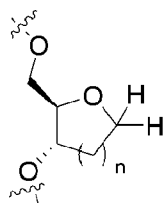
43. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

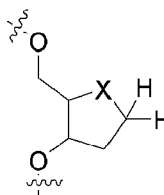
44. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

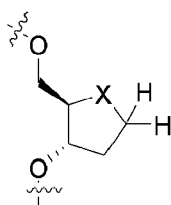
45. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH₂- and -O-.

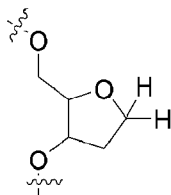
46. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

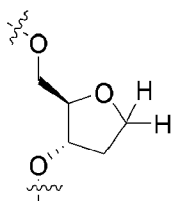
X is selected from -CH₂- and -O-.

47. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



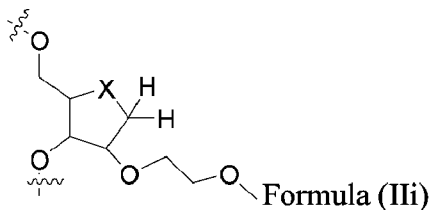
Formula (Iia).

48. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

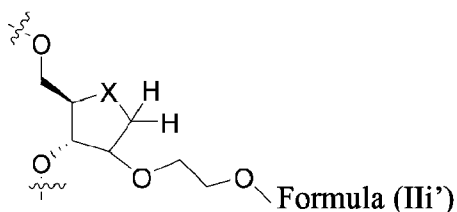
49. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ili), wherein:



Formula (Ili)

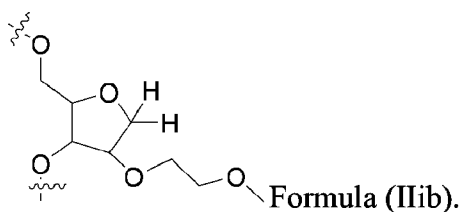
X is selected from -CH₂- and -O-.

50. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ili'), wherein:

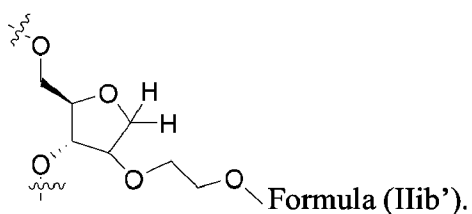


X is selected from -CH₂- and -O-.

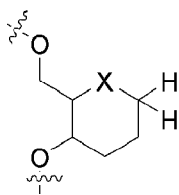
51. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:



52. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:



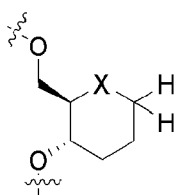
53. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH₂- and -O-.

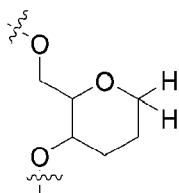
54. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

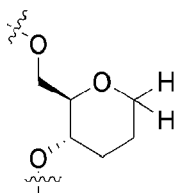
X is selected from -CH₂- and -O-.

55. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

56. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

57. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide further comprises a locked nucleic acid (LNA).

58. The compound or oligonucleotide of claim 57, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.
59. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.
60. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.
61. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.
62. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.
63. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.
64. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.
65. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.
66. The compound or oligonucleotide of any one of the above claims, 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 linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

67. The compound or oligonucleotide of any one of claims 0-66, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.
68. The compound or oligonucleotide of claim 67, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.
69. The compound or oligonucleotide of any one of claims 0-66, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.
70. The compound or oligonucleotide of any one of claims 0-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.
71. The compound or oligonucleotide of claim 70, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.
72. The compound or oligonucleotide of claim 71, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.
73. The compound or oligonucleotide of claim 71, wherein 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.
74. The compound or oligonucleotide of any one of claims 0-66, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.
75. The compound or oligonucleotide of claim 74, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.
76. The compound or oligonucleotide of claim 70, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

77. The compound or oligonucleotide of any one of claims 0-66, wherein 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.
78. The compound or oligonucleotide of claim 77, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.
79. The compound or oligonucleotide of claim 77 or 78, wherein 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.
80. The compound or oligonucleotide of claim 79, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.
81. The compound or oligonucleotide of any one of claims 0-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.
82. The compound or oligonucleotide of any one of claims 0-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.
83. The compound or oligonucleotide of claim 81 or 82, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.
84. 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.

85. 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, or SEQ ID NOs: 5168-5202.

86. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein 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.

87. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein 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.

88. The compound or oligonucleotide of any of claims 67-87, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

89. The compound or oligonucleotide of any one of the above claims, wherein one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage.

90. The compound or oligonucleotide of claim 89, wherein the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

91. The compound or oligonucleotide of claim 89 or 90, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

92. The compound or oligonucleotide of claim 90, wherein the phosphorothioate linkage is in one of a *Rp* configuration or a *Sp* configuration.

93. The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.
94. The compound or oligonucleotide of claim 93, 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 (*e.g.*, tcDNA).
95. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein.
96. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein.
97. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein.
98. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.
99. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein.
100. The compound or oligonucleotide of any one of claims 95-99, wherein 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.
101. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein.

102. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

103. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient a compound or an oligonucleotide of any one of claims 1-102.

104. The method of claim 103, wherein 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, 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.

105. The method of claim 104, wherein the neurological disease is ALS.

106. The method of claim 104, wherein the neurological disease is FTD.

107. The method of claim 104, wherein the neurological disease is ALS with FTD.

108. The method of claim 104, wherein the neurological disease is AD.

109. The method of claim 104, wherein the neurological disease is PD.

110. The method of claim 103, wherein the neuropathy is chemotherapy induced neuropathy.

111. A method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide of any one of claims 1-102.

112. A method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-102.
113. The method of claim 111 or 112, wherein the neuron is a motor neuron.
114. The method of claim 111 or 112, wherein the neuron is a spinal cord neuron.
115. The method of any one of claims 111-114, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.
116. The method of claim 115, wherein the neuropathy is chemotherapy induced neuropathy.
117. The method of any one of claims 111-116, wherein the exposing is performed *in vivo* or *ex vivo*.
118. The method of any one of claims 111-116, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.
119. The method of any one of claims 111-118, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.
120. The method of claim 119, wherein the oligonucleotide is administered orally.
121. The method of any one of claims 111-119, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.
122. The method of any one of claims 111-121, wherein the patient is a human.
123. A pharmaceutical composition comprising the oligonucleotide of any one of claims 0-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
124. The pharmaceutical composition of claim 123, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular,

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

125. 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 thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124.

126. The method of claim 125, wherein 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, 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 as 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, and facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, Perry disease, and synaptic diseases like autism.

127. The method of claim 126, wherein the neurological disease is ALS.

128. The method of claim 126, wherein the neurological disease is FTD.

129. The method of claim 126, wherein the neurological disease is ALS with FTD.

130. The method of claim 126, wherein the neurological disease is AD.

131. The method of claim 126, wherein the neurological disease is PD.

132. The method of claim 125, wherein the neuropathy is chemotherapy induced neuropathy.
133. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.
134. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.
135. The method of any one of claims 125-134, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.
136. The method of any one of claims 125-135, wherein the patient is human.
137. 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 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- β -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.

138. A method for treating amyotrophic lateral sclerosis (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 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- β -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.

139. A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (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 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- β -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

140. A method for treating frontotemporal dementia (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 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- β -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.

141. A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (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 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- β -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.

142. The method of any one of claims 137-141, wherein nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

143. The method of claim 142, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

144. The method of any one of claims 137-141, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

145. The method of any one of claims 137-141, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

146. The method of claim 145, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

147. The method of claim 146, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

148. The method of claim 146, wherein 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.

149. The method of any one of claims 137-141, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.
150. The method of claim 149, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.
151. The method of any one of claims 137-141, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.
152. The method of any one of claims 137-141, wherein 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.
153. The method of claim 152, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.
154. The method of claim 152 or 153, wherein 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.
155. The method of claim 154, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.
156. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.
157. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.
158. The method of claim 156 or 157, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

159. The method of any of claims 142-158, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

160. The method of any one of claims 137-141, wherein at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

161. The method of any one of claims 137-141, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

162. 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 NOs: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally 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.

163. The method of any one of claims 103-122 or 125-161, the pharmaceutical composition of claim 123 or 124, or the oligonucleotide of any one of claims 1-102 or 162, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

164. The method of any one of claims 103-122, 125-161, or 163, the pharmaceutical composition of claim 123, 124, or 163, or the oligonucleotide of any one of claims 1-102 or 162-163, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

165. 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 of claim 123 or 124, in combination with a second therapeutic agent.

166. The method of claim 165, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, 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, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents, a therapy (*e.g.*, selected from breathing care, physical therapy, occupational therapy, speech therapy, nutritional support), 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 (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), lecanemab, olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), 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), and/or zonisamide (zonegran), for treating said neurologic disease.

167. 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 of claim 123 or 124, wherein at least one

nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally 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.

168. The method of any one of claims 103-122, 125-161, or 163-167, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

169. The method of claim 168, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

170. The method of claim 168, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

171. The method of claim 168 or 170, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

172. The method of claim 171, wherein 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.

173. The method of claim 171 or 172, wherein 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.

174. The method of any one of claims 171-173, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

175. The method of any one of claims 171 -174, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

176. The method of claim 168, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

177. The method of claim 176, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

178. The method of claim 177, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

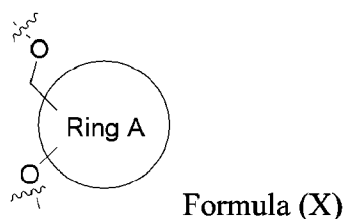
179. The method of claim 168, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

180. The method of claim 179, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

181. The method of claim 180, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

182. The method of any one of claims 168-181, wherein 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.

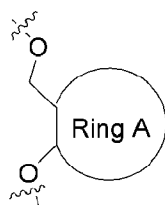
183. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:



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  symbol represents the point of connection to an internucleoside linkage.

184. The method of claim 183, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



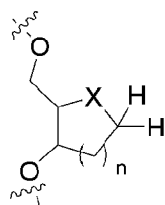
Formula (Xa).

185. The method of claim 183 or 184, wherein 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.

186. The method of claim 185, wherein ring A is tetrahydrofuranyl.

187. The method of claim 185, wherein ring A is tetrahydropyranyl.

188. The method of any one of claims 168-181 wherein each of the first, second or third spacers is independently represented by Formula (I), wherein:

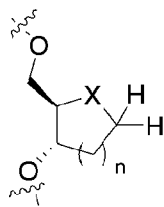


Formula (I)

X is selected from $-\text{CH}_2-$ and $-\text{O}-$; and

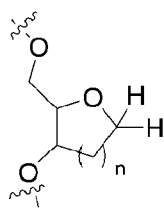
n is 0, 1, 2 or 3.

189. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (I'), wherein:



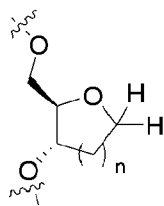
Formula (I').

190. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



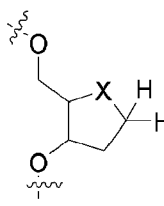
Formula (Ia).

191. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

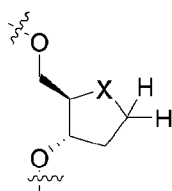
192. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH₂- and -O-.

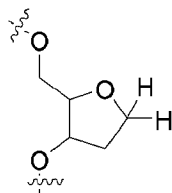
193. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

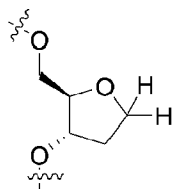
X is selected from -CH₂- and -O-.

194. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



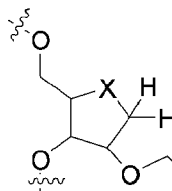
Formula (Iia).

195. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

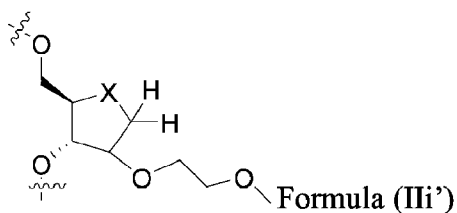
196. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iii), wherein:



Formula (Iii)

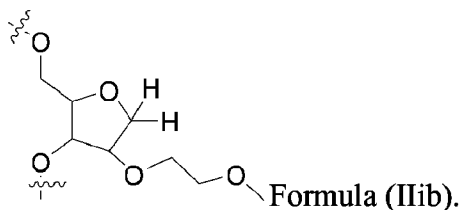
X is selected from -CH₂- and -O-.

197. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (III'), wherein:

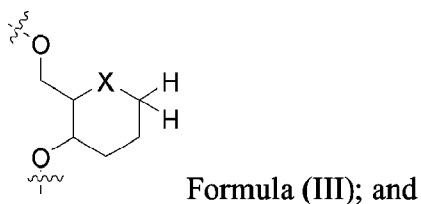
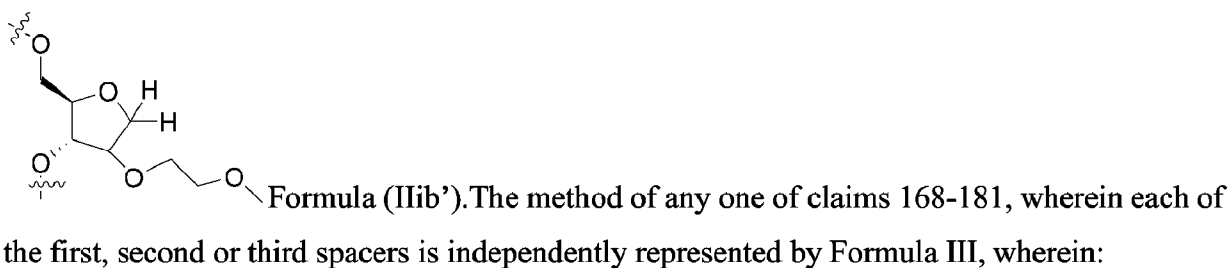


X is selected from -CH₂- and -O-.

198. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:

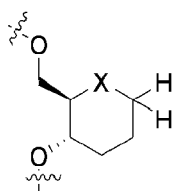


199. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:



X is selected from -CH₂- and -O-.

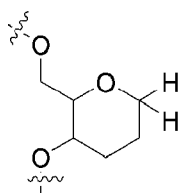
200. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

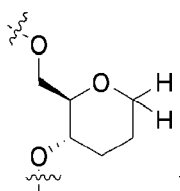
X is selected from -CH₂- and -O-.

201. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

202. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

203. The method of any one of claims 168-202, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

204. The method of any one of claims 168-203, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

205. The method of any one of claims 168-204, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

206. The method of any one of claims 168-205, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.
207. The method of any one of claims 168-206, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.
208. The method of any one of claims 168-207, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.
209. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon.
210. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% reduction of an UNC13A transcript with a cryptic exon.
211. The compound or oligonucleotide of any one of claims 200-201, wherein reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide.
212. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

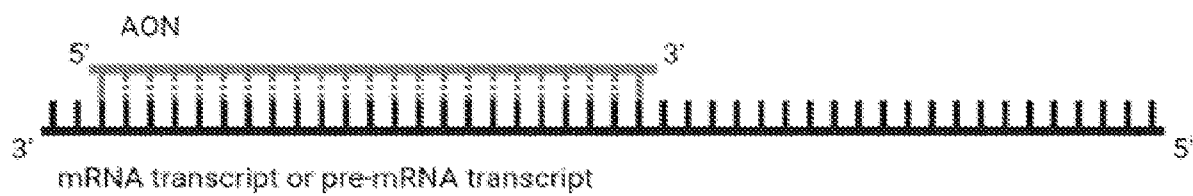


FIGURE 1

