Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, spinal muscular atrophy (SMA), and synaptic diseases like autism.

SUMMARY

[0004] Disclosed herein is a compound comprising a splice-switching oligonucleotide, and wherein the splice-switching oligonucleotide comprises a spacer. Additionally disclosed herein is a splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

[0005] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

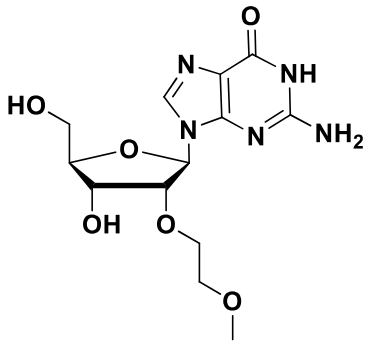
[0006] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0006a] In one aspect, the present disclosure provides a compound comprising a splice-switching oligonucleotide, wherein the splice- switching oligonucleotide comprises a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In another aspect, the present disclosure provides an oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, or SEQ ID NO: 9698-9707, 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 non-sugar substitute that is incapable of linking to a nucleotide base.

[0006b] In another aspect, the present disclosure provides a use of an oligonucleotide as disclosed herein in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof. In yet another aspect, the present disclosure provides a pharmaceutical composition comprising the oligonucleotide as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006c] In another aspect, the present disclosure provides a method for synthesizing an AON with a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base, the method comprising: obtaining compound A represented by the

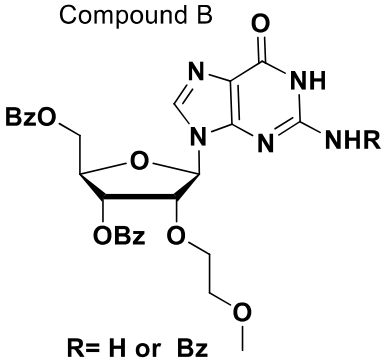
Compound A



formula of ;

performing a benzoyl protection reaction of compound A to generate compound B

Compound B

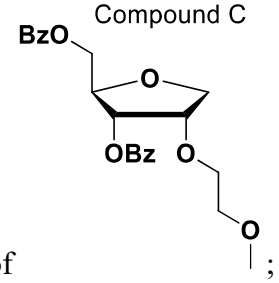


R= H or Bz
Used as mixture

represented by the formula of ;

performing reductive nucleobase cleavage of compound B to generate compound C

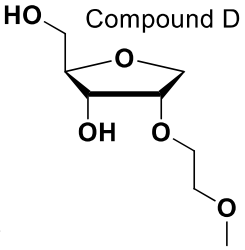
Compound C



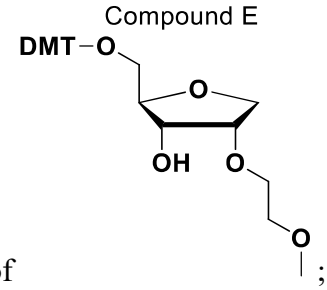
represented by the formula of ;

performing a saponification reaction of compound C to generate compound D represented

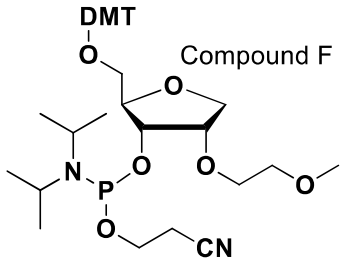
Compound D

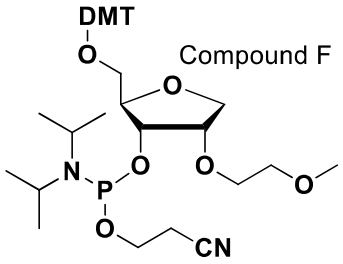


by the formula of ;

performing a protection reaction of compound D to generate compound E represented by the formula of 

; and

performing a phosphoramidite installation reaction of compound E to generate compound F represented by the formula of 

[0006d] In another aspect, the present disclosure provides a composition comprising: compound F having formula 

.

[0007] In various examples, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0008] In various examples, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0009] Additionally disclosed herein is a compound comprising a modified splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0010] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

[0011] Additionally disclosed herein is a compound comprising a splice-switching oligonucleotide, wherein the splice-switching oligonucleotide comprises a spacer.

[0012] In various examples, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

[0013] In various examples, the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, 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.

[0014] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2. In various examples, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0015] Additionally disclosed herein is a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, 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.

[0016] In various examples, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof.

[0017] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a

transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0018] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0019] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2. In various examples, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0020] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one of STMN2, KCNQ2, UNC13A, or SMN2, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

[0021] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0022] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage. In various examples, the oligonucleotide further comprises a spacer.

[0023] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease.

[0024] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript regulated by TDP-43,

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.

[0025] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2. In various examples, the modified oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0026] Additionally disclosed herein is a splice-switching oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, 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.

[0027] In various examples, the oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707.

[0028] Additionally disclosed herein is an oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707, 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.

[0029] In various examples, the oligonucleotide comprises a segment with at most 11 linked nucleosides. In various examples, the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides. In various examples, the oligonucleotide comprises a segment with at most 7 linked nucleosides. In various examples, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides. In various examples, every segment of the oligonucleotide comprises at most 7 linked nucleosides.

[0030] In various examples, the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-

3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

[0031] In various examples, the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

[0032] In various examples, the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

[0033] In various examples, the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

[0034] In various examples, the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24. In various examples, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24. In various examples, the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

[0035] In various examples, the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various examples, the oligonucleotide is at least 19 oligonucleotide units in length.

[0036] In various examples, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various examples, the spacer is located between positions 10 and 15 of the oligonucleotide. In various examples, the spacer is located between positions 7 and 11 of the oligonucleotide.

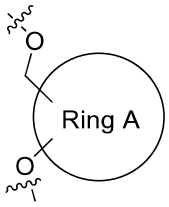
[0037] In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various examples, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various examples, the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various examples, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

[0038] In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various examples, the spacer is located between positions 2 and 5 of the oligonucleotide.

[0039] In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

[0040] In various examples, at least two of the three spacers are adjacent to a guanine nucleobase. In various examples, each of the at least two of the three spacers immediately precede a guanine nucleobase. In various examples, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

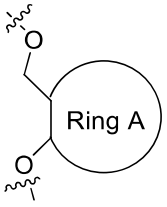
[0041] In various examples, each of the first, second or third spacers is independently represented by Formula (X), wherein:



Formula (X)

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

[0042] In various examples, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:

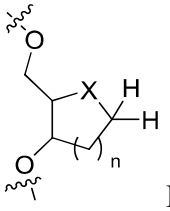


Formula (Xa).

[0043] In various examples, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

[0044] In various examples, ring A is tetrahydrofuranyl. In various examples, ring A is tetrahydropyranyl.

[0045] In various examples, each of the first, second or third spacers is independently represented by Formula I, wherein:

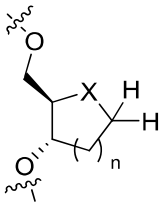


Formula (I)

X is selected from $-CH_2-$ and -O-; and

n is 0, 1, 2 or 3.

[0046] In various examples, each of the first, second or third spacers is independently represented by Formula I', wherein:

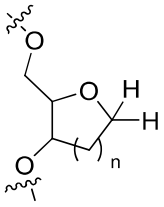


Formula (I')

X is selected from $-CH_2-$ and -O-; and

n is 0, 1, 2 or 3.

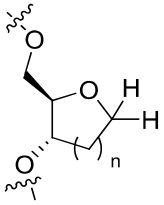
[0047] In various examples, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

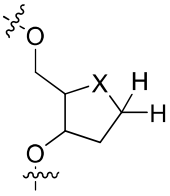
[0048] In various examples, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

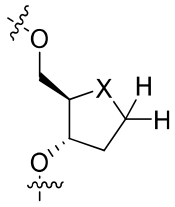
[0049] In various examples, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

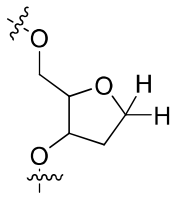
[0050] In various examples, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

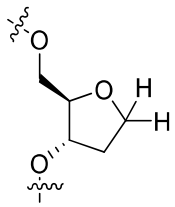
X is selected from -CH_2- and -O-.

[0051] In various examples, each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



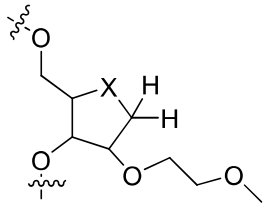
Formula (Iia).

[0052] In various examples, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

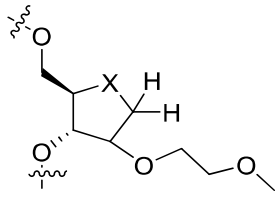
[0053] In some examples, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH_2- and -O-.

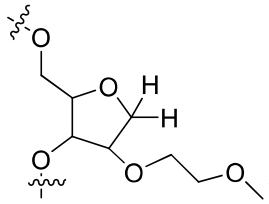
[0054] In some examples, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

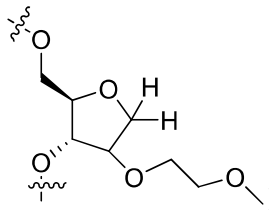
X is selected from -CH_2-and -O.

[0055] In some examples, the spacer is represented by Formula (IIib), wherein:



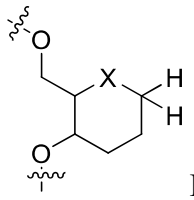
Formula (IIib).

[0056] In some examples, the spacer is represented by Formula (Iiib'), wherein:



Formula (IIib').

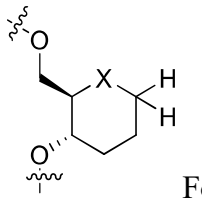
[0057] In various examples, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH_2- and -O-.

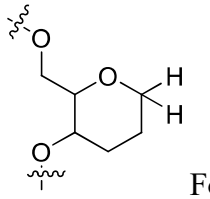
[0058] In various examples, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

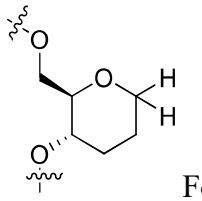
X is selected from -CH_2- and -O-.

[0059] In various examples, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

[0060] In various examples, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

[0061] In various examples, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 50%. In various examples, the oligonucleotide is between 12 and 40 oligonucleotide units in length.

[0062] In various examples, at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[0063] In various examples, one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various examples, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various examples, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

[0064] In various examples, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond. In various examples, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

[0065] In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

[0066] In various examples, the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

[0067] In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various examples,

the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

[0068] In various examples, one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various examples, the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various examples, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various examples, the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration.

[0069] In various examples, the oligonucleotide comprises at least one modified sugar moiety. In various examples, the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (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).

[0070] In various examples, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length STMN2, KCNQ2, UNC13A, or SMN2 protein. In various examples, the oligonucleotide exhibits at least a 100% increase of full length protein. In various examples, the oligonucleotide exhibits at least a 200% increase of full length protein. In various examples, the oligonucleotide exhibits at least a 300% increase of full length protein. In various examples, the oligonucleotide exhibits at least a 400% increase of full length protein.

[0071] In various examples, increase of the full length protein is measured in comparison to a reduced level of full length protein achieved using a TDP43 antisense oligonucleotide. In various examples, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length protein. In various examples, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced transcript.

[0072] 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 the patient a compound or an oligonucleotide as disclosed herein.

[0073] In various examples, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia,

dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, 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 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), Mucolipidosis 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 examples, the neurological disease is ALS. In various examples, the neurological disease is FTD. In various examples, the neurological disease is ALS with FTD. In various examples, the neurological disease is AD. In various examples, the neurological disease is PD. In various examples, the neurological disease is spinal muscular atrophy (SMA). In various examples, the neuropathy is chemotherapy induced neuropathy.

[0074] Additionally disclosed herein is a method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide as disclosed herein.

[0075] Additionally disclosed herein is a method of increasing, promoting, stabilizing, or maintaining any one of STMN2, KCNQ2, UNC13A, or SMN2 expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide as disclosed herein. In various examples, the neuron is a motor neuron. In various examples, the neuron is a spinal cord neuron. In various examples, the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy. In various examples, the neuropathy is chemotherapy induced neuropathy. In various examples, the exposing is performed *in vivo* or *ex vivo*. In various examples, the exposing comprises administering the oligonucleotide to a patient in need thereof.

[0076] In various examples, the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly. In various examples, the oligonucleotide is administered orally. In various examples, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically, intracerebroventricularly, or intracisternally. In various examples, the patient is a human.

[0077] Additionally disclosed herein is a pharmaceutical composition comprising the oligonucleotide disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0078] In various examples, the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

[0079] 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 herein.

[0080] In various examples, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, 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 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), Mucolipidosis 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.

[0081] In various examples, the neurological disease is ALS. In various examples, the neurological disease is FTD. In various examples, the neurological disease is ALS with FTD. In various examples, the neurological disease is AD. In various examples, the neurological disease is PD. In various examples, the neurological disease is spinal muscular atrophy (SMA). In various examples, the neuropathy is chemotherapy induced neuropathy.

[0082] In various examples, the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly. In various examples, the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally. In various examples, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various examples, the patient is human.

[0083] 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 the oligonucleotide is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, 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'-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.

[0084] 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 is at least 85% complementary to a sequence from a transcript of any one STMN2, KCNQ2, UNC13A, or SMN2, 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'-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.

[0085] Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs:

1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10670-10779, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10814-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24, 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'-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.

[0086] Additionally 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: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, or SEQ ID NOs: 4531-5794, or SEQ ID NOs: 7059-8322, 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'-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.

[0087] Additionally disclosed herein is 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: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, or SEQ ID NOs: 4531-5794, or SEQ ID NOs: 7059-8322, 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'-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

[0088] Additionally 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 oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, or SEQ ID NOs: 4531-5794, or SEQ ID NOs: 7059-8322, 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'-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.

[0089] Additionally 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: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, or SEQ ID NOs: 4531-5794, SEQ ID NOs: 7059-8322, 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'-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.

[0090] In various examples, nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages. In various examples, only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage. In various examples, nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond. In various examples, the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond. In various examples, one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond. In various examples, two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds. In various examples, the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds. In various examples, one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

[0091] In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases. In various examples, the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases. In various examples,

the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

[0092] In various examples, the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

[0093] In various examples, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various examples, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

[0094] 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: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, SEQ ID NO: 9587-9595, or SEQ ID NO: 9698-9707., 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 one or more of STMN2, KCNQ2, or UNC13A mRNA capable of translation of a functional 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.

[0095] In various examples, the pharmaceutical composition disclosed herein, or the oligonucleotide disclosed herein, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

[0096] In various examples, the pharmaceutical composition disclosed herein, or the oligonucleotide disclosed herein, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

[0097] 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, in combination with a second therapeutic agent.

[0098] In various examples, 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),

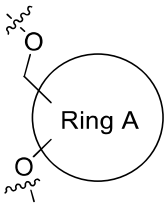
pridopidine, dual AON intrathecal administration (*e.g.,* BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), medroxyprogesetrone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants 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, aducanamab (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), medroxyprogestrone, 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.

[0099] 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, 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.

[00100] In various examples, the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base. In various examples, the

spacer is located between positions 10 and 15 of the oligonucleotide. In various examples, the spacer is located between positions 7 and 11 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide. In various examples, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various examples, the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various examples, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide. In various examples, the spacer is located between positions 2 and 5 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide. In various examples, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide. In various examples, the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides. In various examples, at least two of the three spacers are adjacent to a guanine nucleobase. In various examples, each of the at least two of the three spacers immediately precede a guanine nucleobase. In various examples, each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

[00101] In various examples, each of the first, second or third spacers is independently represented by Formula (X), wherein:



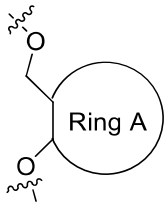
Formula (X)

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

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

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

[00102] In various examples, each of the first, second or third spacers is independently represented by Formula (Xa), wherein:

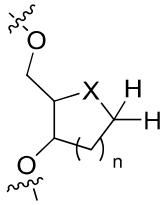


Formula (Xa).

[00103] In various examples, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

[00104] In various examples, ring A is tetrahydrofuranyl. In various examples, ring A is tetrahydropyranyl.

[00105] In various examples, each of the first, second or third spacers is independently represented by Formula (I), wherein:

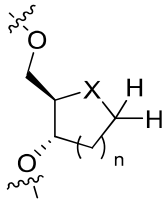


Formula (I)

X is selected from $-CH_2-$ and -O-; and

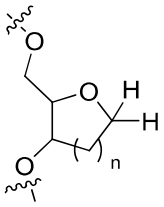
n is 0, 1, 2 or 3.

[00106] In various examples, each of the first, second or third spacers is independently represented by Formula (I'), wherein:



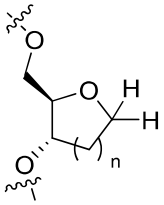
Formula (I').

[00107] In various examples, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



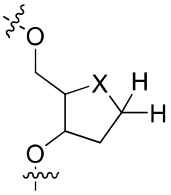
Formula (Ia).

[00108] In various examples, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

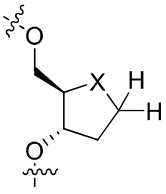
[00109] In various examples, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

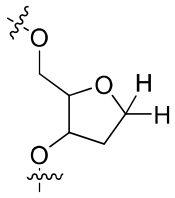
[00110] In various examples, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

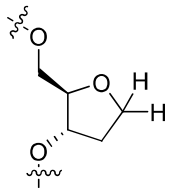
X is selected from -CH_2- and -O-.

[00111] In various examples, each of the first, second or third spacers is independently represented by Formula (IIa), wherein:



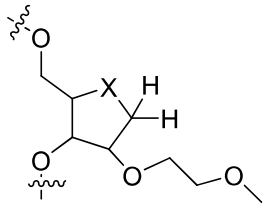
Formula (IIa).

[00112] In various examples, each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



Formula (Iia').

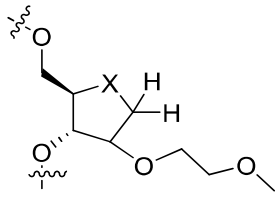
[00113] In some examples, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH_2- and -O-.

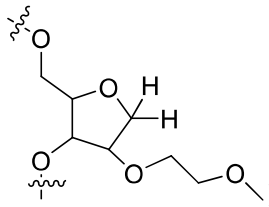
[00114] In some examples, the spacer is represented by Formula (IIi'), wherein:



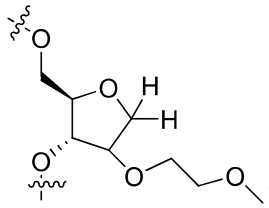
Formula (IIi')

X is selected from -CH_2-and -O.

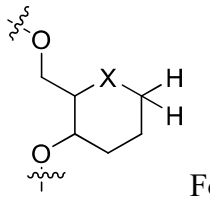
[00115] In some examples, the spacer is represented by Formula (IIib), wherein:


Formula (IIib).

[00116] In some examples, the spacer is represented by Formula (IIib'), wherein:

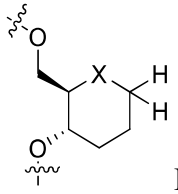

Formula (IIib').

[00117] In various examples, each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

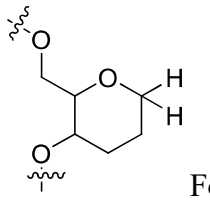
X is selected from -CH_2- and -O-.

[00118] T In various examples, each of the first, second or third spacers is independently represented by Formula III', wherein:


Formula (III'); and

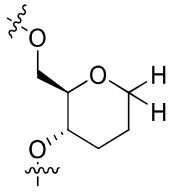
X is selected from -CH_2- and -O-.

[00119] In various examples, each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

[00120] In various examples, each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

[00121] In various examples, the oligonucleotide comprising the spacer has a GC content of at least 10%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 20%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 25%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 30%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 40%. In various examples, the oligonucleotide comprising the spacer has a GC content of at least 50%.

BRIEF DESCRIPTION OF THE DRAWINGS

[00122] FIG. 1 is a schematic depiction of portions of the STMN2 transcript and STMN2 antisense oligonucleotides that are designed to target certain portions of the STMN2 transcript.

[00123] FIG. 2 is a bar graph showing the results of RT-qPCR analysis of TDP43 and STMN2 full-length mRNA levels in the presence of TDP43 antisense, and restoration of the full-length STMN2 transcript in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 36, SEQ ID NO: 55, SEQ ID NO: 177, SEQ ID NO: 203, SEQ ID NO: 244, and SEQ ID NO: 395).

[00124] FIG. 3 is a bar graph showing the results of RT-qPCR analysis of STMN2 transcript with cryptic exon mRNA levels in the presence of TDP43 antisense, and reduction of the STMN2 transcript with cryptic exon mRNA levels in the presence of 6 different STMN2 parent oligonucleotides (SEQ ID NO: 173, SEQ ID NO: 181, SEQ ID NO: 197, SEQ ID NO: 215, SEQ ID NO: 385, and SEQ ID NO: 400).

WHAT IS CLAIMED IS:

1. A compound comprising a splice-switching oligonucleotide, wherein the splice- switching oligonucleotide comprises a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

2. The compound of claim 1, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript whose mis-splicing leads to a neurological disease or a transcript whose splicing is capable of being modulated to treat a neurological disease, optionally wherein the equal length portion of the sequence is from a transcript regulated by TDP-43.

3. The compound of claim 1 or 2, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of a sequence from a transcript of any one STMN2, KCNQ2, or SMN2.

4. The compound of any one of claims 1-3, wherein the splice-switching oligonucleotide comprises a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, or SEQ ID NO: 9698-9707.

5. An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 1339 or SEQ ID NO: 1341, SEQ ID NO: 3032-3043, or SEQ ID NO: 9698-9707, 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 non-sugar substitute that is incapable of linking to a nucleotide base.

6. The oligonucleotide of any one of claims 1-5, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

7. The oligonucleotide of any one of claims 1-6, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

8. The oligonucleotide of any one of claims 1-7, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

9. The oligonucleotide of any one of claims 1-8, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

10. The oligonucleotide of any one of claims 1-9, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

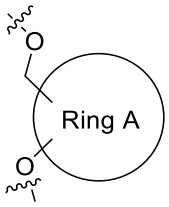
11. The oligonucleotide of any one of claims 1-10, wherein the oligonucleotide comprises a sequence that shares at least 85%, at least 90%, at least 95%, or 100% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10815-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

12. The oligonucleotide of any one of claims 1-11, wherein the oligonucleotide comprises a segment with at most 11, 6, 5, 4, 3, or 2 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% or at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-466, SEQ ID NOs: 893-1338, SEQ ID NOs: 1342-1366, SEQ ID NOs: 1392-1521, SEQ ID NOs: 1589-1664, or SEQ ID NOs: 10655-10669, SEQ ID NOs: 1676-1851, SEQ ID NOs: 2028-2529, SEQ ID NOs: 3046-3221, SEQ ID NOs: 3398-3899, and SEQ ID NOs: 4469-4530, SEQ ID NOs: 9710-10141, SEQ ID NOs: 10641-10651, SEQ ID NOs: 10783-10808, SEQ ID NOs: 10815-10820, and SEQ ID NOs: 10824-10828 or any sequence in Table 12A, 12B, 13, 14, 15A, 15B, 16, 17, 18A, 18B, 19, 20, 21, 22, 23, or 24.

13. The oligonucleotide of any one of claims 1-12, wherein the nucleoside-replacement group is located between positions 7 and 9 of the oligonucleotide, and wherein a second nucleoside-replacement group is located between positions 15 and 18 of the oligonucleotide.

14. The oligonucleotide of any one of claims 1-13, wherein the nucleoside-replacement group is located at position 8 of the oligonucleotide, and wherein a second nucleoside-replacement group is located at position 16 of the oligonucleotide.

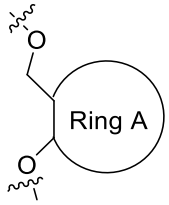
15. The oligonucleotide of any one of claims 1-14, wherein the nucleoside-replacement group is represented by Formula (X), wherein:



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.

16. The oligonucleotide of claim 15, wherein the nucleoside-replacement group is represented by Formula (Xa), wherein:



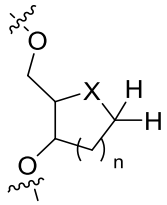
Formula (Xa).

17. The oligonucleotide of claim 15 or 16, 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.

18. The oligonucleotide of any one of claims 1-17, wherein the nucleoside-replacement group is represented by any of Formula I, Formula I', Formula Ia, Formula (Ia'), Formula II,

Formula (II'), Formula (Iia), Formula (Iia'), Formula (Iii), Formula (IIi'), Formula (IIib), Formula (IIib'), Formula (III), Formula (III'),

wherein Formula (I) is represented by:

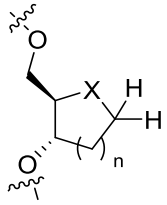


Formula (I)

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3',

wherein Formula (I') is represented by:

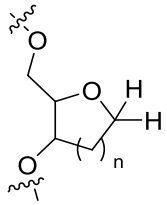


Formula (I')

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3,

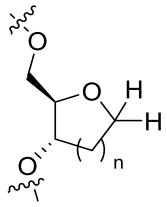
wherein Formula (Ia) is represented by:



Formula (Ia); and

n is 0, 1, 2 or 3,

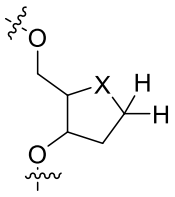
wherein Formula (Ia') is represented by:



Formula (Ia'); and

n is 0, 1, 2 or 3,

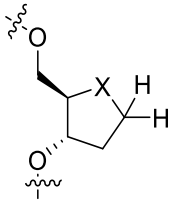
wherein Formula II is represented by:



Formula (II); and

X is selected from -CH_2- and -O-,

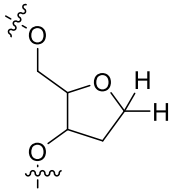
wherein Formula (II') is represented by:



Formula (II'); and

X is selected from -CH_2- and -O-,

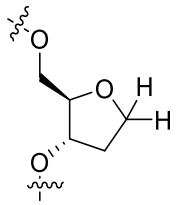
wherein Formula Iia is represented by:



Formula (Iia),

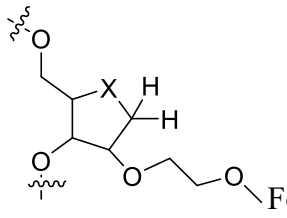
wherein Formula (Iia') is represented by,

wherein Formula (Iia') is represented by:



Formula (Iia'),

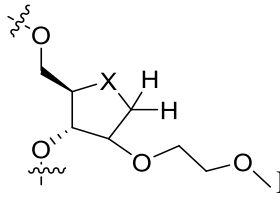
wherein Formula (IIi) is represented by:



Formula (IIi)

X is selected from -CH_2- and -O-,

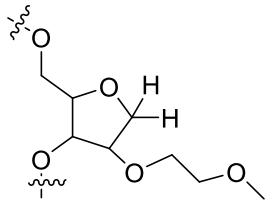
wherein Formula (IIi') is represented by



Formula (IIi')

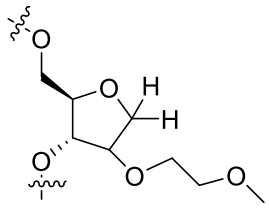
X is selected from -CH_2- and -O-,

wherein Formula (IIib) is represented by:

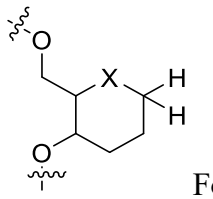


Formula (IIib),

wherein Formula (IIib') is represented by:

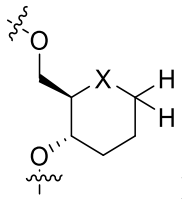

Formula (IIib'),

wherein Formula III is represented by:


Formula (III); and

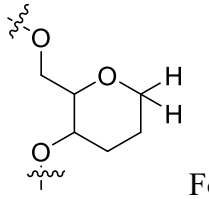
X is selected from -CH_2- and -O-,

wherein Formula III' is represented by:

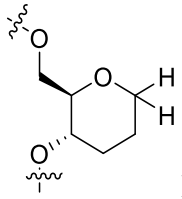

Formula (III'); and

X is selected from -CH_2- and -O-,

and wherein Formula (IIIa) is represented by:


Formula (IIIa),

wherein Formula (IIIa') is represented by:



Formula (IIIa').

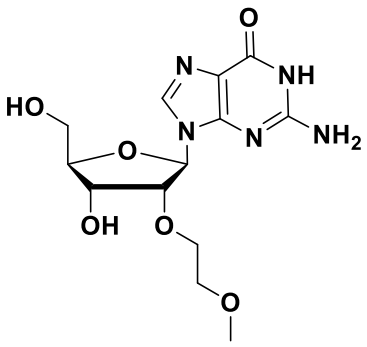
19. Use of an oligonucleotide of any one of claims 1-18 in the manufacture of a medicament for treating a neurological disease and/or a neuropathy in a patient in need thereof.

20. The use of claim 19, 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 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), Mucolipidosis 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.

21. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

22. A method for synthesizing an AON with a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base, the method comprising:

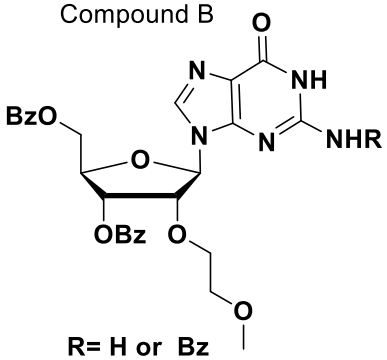
Compound A



obtaining compound A represented by the formula of ;

performing a benzoyl protection reaction of compound A to generate compound B

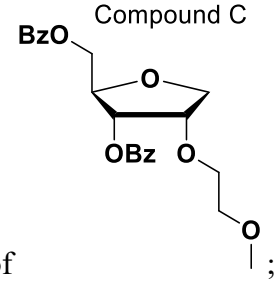
Compound B



represented by the formula of ;

performing reductive nucleobase cleavage of compound B to generate compound C

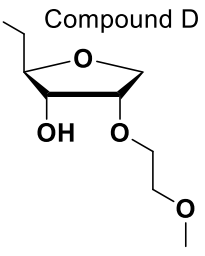
Compound C



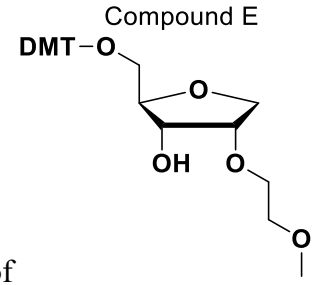
represented by the formula of ;

performing a saponification reaction of compound C to generate compound D represented by

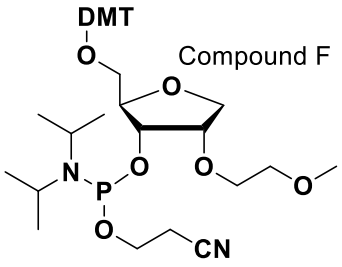
HO Compound D



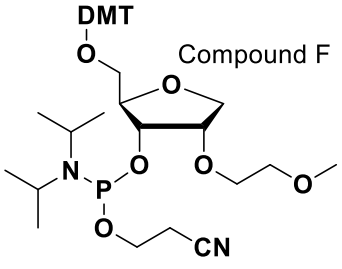
the formula of ;

performing a protection reaction of compound D to generate compound E represented by the formula of 

; and

performing a phosphoramidite installation reaction of compound E to generate compound F represented by the formula of 

23. A composition comprising:

compound F having formula 

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