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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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Title of Invention

TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

Application Information

APPLICATION TYPE	International Application (PCT) for filing in the US receiving office	PATENT #	-
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Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
QRL_014WO_Response to Invitation to submit amendments.pdf	3	Miscellaneous incoming letter from Applicant - International Application	94 KB
QRL_014WO_Amended_Claims_Marked_Up.pdf	34	Claims	250 KB
QRL_014WO_Amended_Claims_Clean.pdf	34	Claims	249 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

AMENDMENTS TO THE CLAIMS

1. A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

2. The compound of claim 1, wherein the modified oligonucleotide comprises a spacer.

3. A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

5. The oligonucleotide of claim 4, further comprising a spacer.

6. An oligonucleotide comprising a sequence that is at least 85 98% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

8. The compound of claims 1-3 or 7, or oligonucleotides of claims 5-7, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

9. The compound of any one of claims 1-3 or 7-8 or oligonucleotide of any one of claims 44-8, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

10. The compound of any one of claims 1-3 or 7-9 or oligonucleotide of any one of claims 5-9, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

11. The compound of any one of claims 1-3 or 7-10 or oligonucleotide of any one of claims 5-10, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

12. The compound or oligonucleotide of any one of claims 7-11, wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

13. The compound or oligonucleotide of any one of claims 7-12, wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

14. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 51335166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

15. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

16. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

17. The compound or oligonucleotide of claim 16, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

18. The compound or oligonucleotide of claim 16 or 17, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

19. The compound or oligonucleotide of any one of claims 1-18, wherein the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length.

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

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

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

23. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

24. The compound or oligonucleotide of claim 21 or 23, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

25. The compound or oligonucleotide of claim 24, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

26. The compound or oligonucleotide of claim 24 or 25, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

27. The compound or oligonucleotide of any one of claims 24-26, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

28. The compound or oligonucleotide of any one of claims 24-27, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

29. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

30. The compound or oligonucleotide of claim 29, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

31. The compound or oligonucleotide of claim 30, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

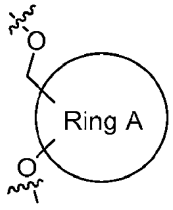
32. The compound or oligonucleotide of claim 21, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

33. The compound or oligonucleotide of claim 32, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

34. The compound or oligonucleotide of claim 33, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

35. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

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

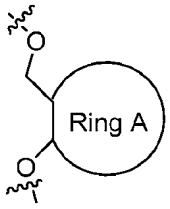


Formula (X)

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

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

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



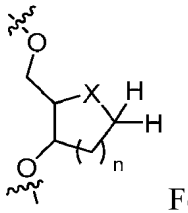
Formula (Xa).

38. The compound or nucleotide of claim 36 or 37, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, 6yrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

39. The compound or nucleotide of claim 38 wherein ring A is tetrahydrofuranyl.

40. The compound or nucleotide of claim 38 wherein ring A is tetrahydropyranyl.

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

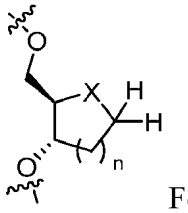


Formula (I)

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

n is 0, 1, 2 or 3.

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

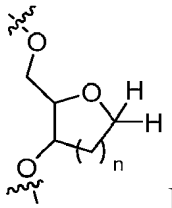


Formula (I')

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

n is 0, 1, 2 or 3.

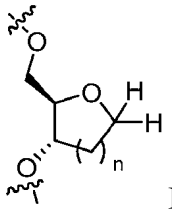
43. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

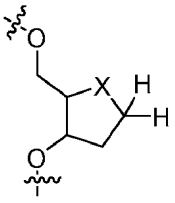
44. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

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

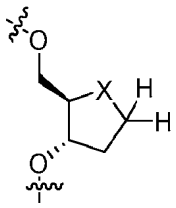


Formula (II); and

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

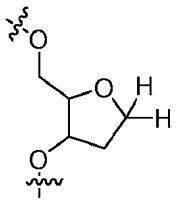
46. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

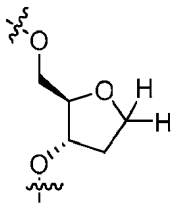
X is selected from $-CH_2-$ and -O-.

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



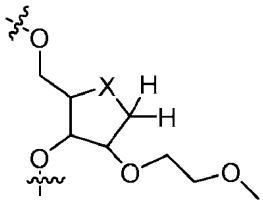
Formula (Iia).

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



Formula (Iia').

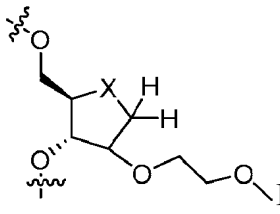
49. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:



Formula (IIi)

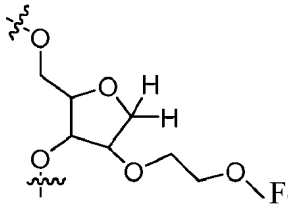
X is selected from -CH_2- and -O-.

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

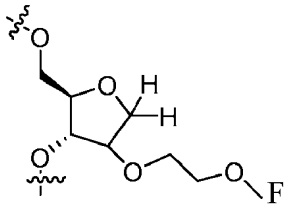

Formula (IIi')

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

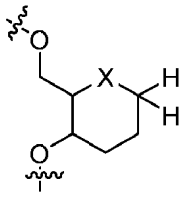
51. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

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


Formula (IIib').

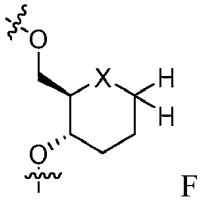
53. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

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

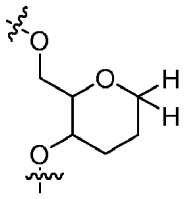
54. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

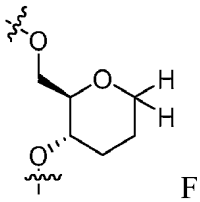
X is selected from -CH_2- and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

58. The compound or oligonucleotide of claim 57, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

59. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

60. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

61. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

62. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

63. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

64. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

65. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

67. The compound or oligonucleotide of any one of claims 1-66, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

68. The compound or oligonucleotide of claim 67, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

69. The compound or oligonucleotide of any one of claims 1-66, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

70. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

71. The compound or oligonucleotide of claim 70, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

72. The compound or oligonucleotide of claim 71, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

73. The compound or oligonucleotide of claim 71, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

74. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

75. The compound or oligonucleotide of claim 74, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

76. The compound or oligonucleotide of claim 70, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

77. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

78. The compound or oligonucleotide of claim 77, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

79. The compound or oligonucleotide of claim 77 or 78, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

80. The compound or oligonucleotide of claim 79, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

81. The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

82. The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

83. The compound or oligonucleotide of claim 81 or 82, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

84. A compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ

ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

85. An oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, or SEQ ID NOs: 5168-5202.

86. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

87. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

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

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

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

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93. The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

94. The compound or oligonucleotide of claim 93, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

95. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein.

96. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein.

97. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein.

98. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.

99. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein.

100. The compound or oligonucleotide of any one of claims 95-99, wherein increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide.

101. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein.

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

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

104. The method of claim 103, wherein the neurological disease selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

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

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

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

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

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

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

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

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112. A method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-102.

113. The method of claim 111 or 112, wherein the neuron is a motor neuron.

114. The method of claim 111 or 112, wherein the neuron is a spinal cord neuron.

115. The method of any one of claims 111-114, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

116. The method of claim 115, wherein the neuropathy is chemotherapy induced neuropathy.

117. The method of any one of claims 111-116, wherein the exposing is performed *in vivo* or *ex vivo*.

118. The method of any one of claims 111-116, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.

119. The method of any one of claims 111-118, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.

120. The method of claim 119, wherein the oligonucleotide is administered orally.

121. The method of any one of claims 111-119, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

122. The method of any one of claims 111-121, wherein the patient is a human.

123. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

124. The pharmaceutical composition of claim 123, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular,

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

125. A method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124.

126. The method of claim 125, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such 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.

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

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

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

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

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

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132. The method of claim 125, wherein the neuropathy is chemotherapy induced neuropathy.

133. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.

134. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.

135. The method of any one of claims 125-134, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

136. The method of any one of claims 125-135, wherein the patient is human.

137. A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

138. A method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

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139. A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

140. A method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

141. A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a

thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

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

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

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

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

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

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

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

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

150. The method of claim 149, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

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

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

153. The method of claim 152, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

154. The method of claim 152 or 153, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

155. The method of claim 154, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

156. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

157. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

158. The method of claim 156 or 157, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

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

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

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

162. An oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

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

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

165. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, in combination with a second therapeutic agent.

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166. The method of claim 165, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), 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.

167. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, wherein at least one

nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

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

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

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

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

172. The method of claim 171, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

173. The method of claim 171 or 172, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

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

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

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

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

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

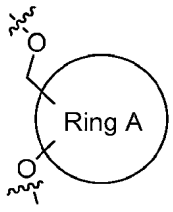
179. The method of claim 168, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

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

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

182. The method of any one of claims 168-181, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

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



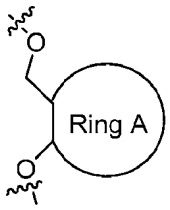
Formula (X)

Ring A is 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.

AMENDMENTS TO THE CLAIMS – CLEAN COPY

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



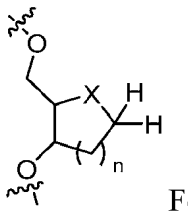
Formula (Xa).

185. The method of claim 183 or 184, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

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

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

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



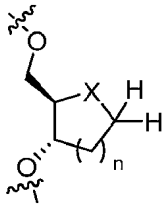
Formula (I)

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

n is 0, 1, 2 or 3.

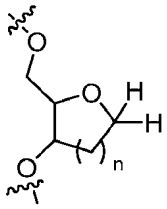
189. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (I'), wherein:

AMENDMENTS TO THE CLAIMS – CLEAN COPY



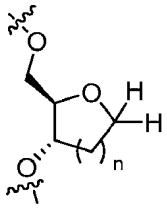
Formula (I').

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



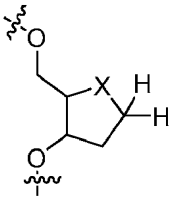
Formula (Ia).

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



Formula (Ia').

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

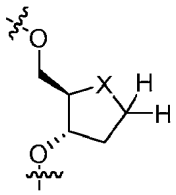


Formula (II); and

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

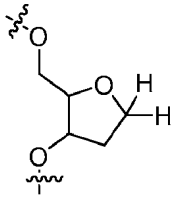
193. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

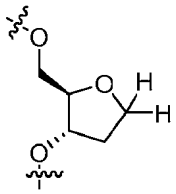
X is selected from $-CH_2-$ and -O-.

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



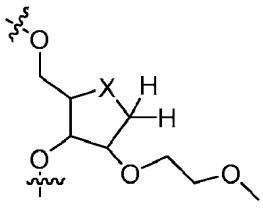
Formula (Iia).

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



Formula (Iia').

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

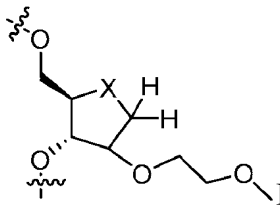


Formula (IIi)

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

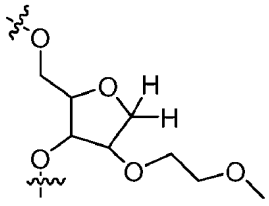
AMENDMENTS TO THE CLAIMS – CLEAN COPY

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

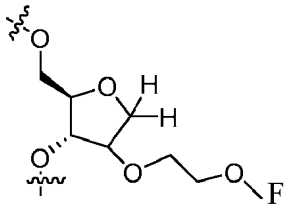

Formula (IIi')

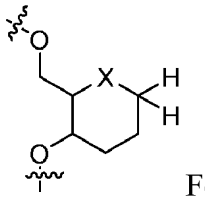
X is selected from -CH_2- and -O-.

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


Formula (IIib).

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

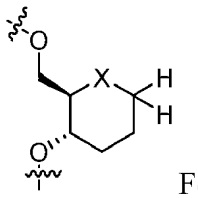

Formula (IIib').The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:


Formula (III); and

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

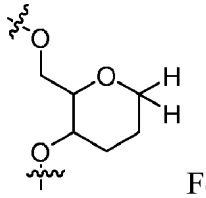
200. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

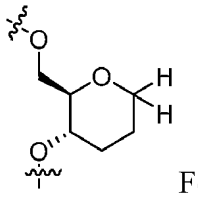
X is selected from $-CH_2-$ and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

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

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

AMENDMENTS TO THE CLAIMS – CLEAN COPY

206. The method of any one of claims 168-205, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

207. The method of any one of claims 168-206, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

208. The method of any one of claims 168-207, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

209. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon.

210. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% reduction of an UNC13A transcript with a cryptic exon.

211. The compound or oligonucleotide of any one of claims 200-201, wherein reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide.

212. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

IN THE U.S. PATENT AND TRADEMARK OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
FOR THE PATENT COOPERATION TREATY

International Application No.:	PCT/US2022/051713
International Filing Date:	December 2, 2022
Applicant:	QurAlis Corporation
Title:	TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS
Attorney Reference No.:	QRL-014WO

RESPONSE TO INVITATION TO SUBMIT AMENDMENTS (PCT RULE 60.1(G))

Dear Sir or Madam:

In response to the Invitation to Submit Amendments ("Invitation") mailed from the International Preliminary Examining Authority (IPEA/US) on October 5, 2023, Applicant submits amended claims (marked-up and clean version) that do not include claim statuses (as requested in the Invitation). Apart from the removal of the claim statuses, the enclosed claims align with the claim amendments made under Article 34 filed on October 2, 2023. No new matter has been added.

Amendments to the Claims begin on page 2.

Remarks begin on page 3.

AMENDMENTS TO THE CLAIMS

Please replace the claims as filed with the amended claims enclosed herewith. No new matter has been added.

Attachments:

Amended claims (Clean)

Amended claims (Marked up)

REMARKS

Applicant believes that this Response corrects the defects noted in the Invitation to Submit Amendments (PCT Rule 60.1(g)). No new matter has been added. In the event any fee variance exists, please charge the fee to our Deposit Account No. 07-1700, Order No. QRL-014WO. If there are any questions, please contact the undersigned.

Dated: October 13, 2023

Respectfully submitted,

By /Clark Zhang/
ZHANG, CLARK
GOODWIN PROCTER LLP
Patent Administrator
100 Northern Avenue
Boston, Massachusetts 02210
(617) 570-1000
Agent for the Applicant

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

AMENDMENTS TO THE CLAIMS

1. A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

2. The compound of claim 1, wherein the modified oligonucleotide comprises a spacer.

3. A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

5. The oligonucleotide of claim 4, further comprising a spacer.

6. An oligonucleotide comprising a sequence that is at least 85 98% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

8. The compound of claims 1-3 or 7, or oligonucleotides of claims 5-7, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

9. The compound of any one of claims 1-3 or 7-8 or oligonucleotide of any one of claims 44-8, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

10. The compound of any one of claims 1-3 or 7-9 or oligonucleotide of any one of claims 5-9, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

11. The compound of any one of claims 1-3 or 7-10 or oligonucleotide of any one of claims 5-10, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

12. The compound or oligonucleotide of any one of claims 7-11, wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; ~~5066~~5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-~~5292~~5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

13. The compound or oligonucleotide of any one of claims 7-12, wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

14. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

15. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

16. The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

17. The compound or oligonucleotide of claim 16, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

18. The compound or oligonucleotide of claim 16 or 17, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

19. The compound or oligonucleotide of any one of claims 1-18, wherein the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length.

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

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

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

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

23. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

24. The compound or oligonucleotide of claim 21 or 23, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

25. The compound or oligonucleotide of claim 24, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

26. The compound or oligonucleotide of claim 24 or 25, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

27. The compound or oligonucleotide of any one of claims 24-26, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

28. The compound or oligonucleotide of any one of claims 24-27, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

29. The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

30. The compound or oligonucleotide of claim 29, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

31. The compound or oligonucleotide of claim 30, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

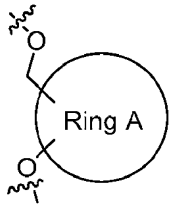
32. The compound or oligonucleotide of claim 21, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

33. The compound or oligonucleotide of claim 32, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

34. The compound or oligonucleotide of claim 33, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

35. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

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

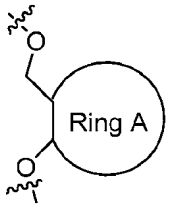


Formula (X)

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

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

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



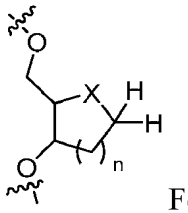
Formula (Xa).

38. The compound or nucleotide of claim 36 or 37, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, 6yrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

39. The compound or nucleotide of claim 38 wherein ring A is tetrahydrofuranyl.

40. The compound or nucleotide of claim 38 wherein ring A is tetrahydropyranyl.

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

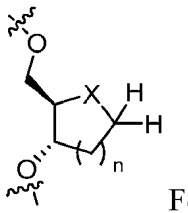


Formula (I)

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

n is 0, 1, 2 or 3.

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

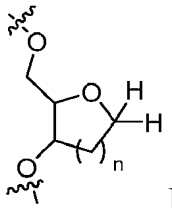


Formula (I')

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

n is 0, 1, 2 or 3.

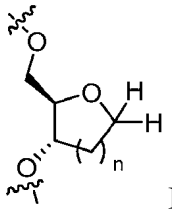
43. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

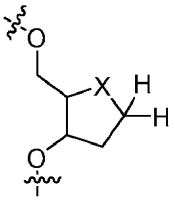
44. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

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

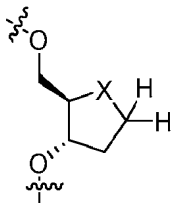


Formula (II); and

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

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

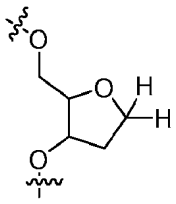
46. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

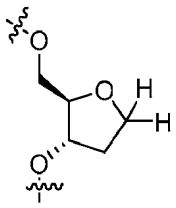
X is selected from $-CH_2-$ and -O-.

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



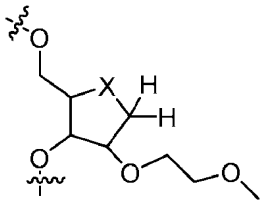
Formula (Iia).

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



Formula (Iia').

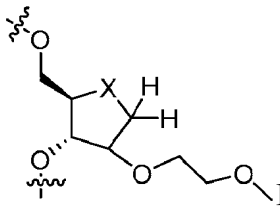
49. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:



Formula (IIi)

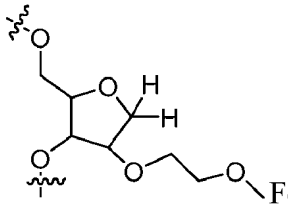
X is selected from -CH_2- and -O-.

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

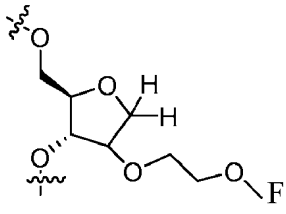

Formula (IIi')

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

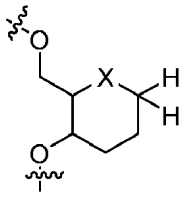
51. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

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


Formula (IIib').

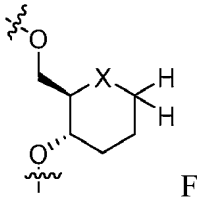
53. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

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

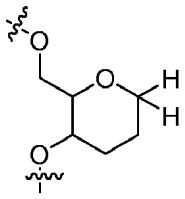
54. The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

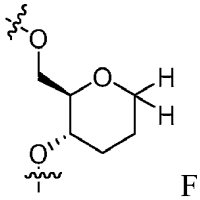
X is selected from -CH_2- and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

58. The compound or oligonucleotide of claim 57, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

59. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

60. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

61. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

62. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

63. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

64. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

65. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.

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

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

67. The compound or oligonucleotide of any one of claims 1-66, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

68. The compound or oligonucleotide of claim 67, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

69. The compound or oligonucleotide of any one of claims 1-66, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

70. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

71. The compound or oligonucleotide of claim 70, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

72. The compound or oligonucleotide of claim 71, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

73. The compound or oligonucleotide of claim 71, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

74. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

75. The compound or oligonucleotide of claim 74, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

76. The compound or oligonucleotide of claim 70, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

77. The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

78. The compound or oligonucleotide of claim 77, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

79. The compound or oligonucleotide of claim 77 or 78, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

80. The compound or oligonucleotide of claim 79, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

81. The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

82. The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

83. The compound or oligonucleotide of claim 81 or 82, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

84. A compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ

ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

85. An oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, or SEQ ID NOs: 5168-5202.

86. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

87. The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

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

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

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

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

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

93. The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

94. The compound or oligonucleotide of claim 93, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

95. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein.

96. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein.

97. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein.

98. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.

99. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein.

100. The compound or oligonucleotide of any one of claims 95-99, wherein increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide.

101. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein.

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

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

104. The method of claim 103, wherein the neurological disease selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

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

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

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

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

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

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

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

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

112. A method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-102.

113. The method of claim 111 or 112, wherein the neuron is a motor neuron.

114. The method of claim 111 or 112, wherein the neuron is a spinal cord neuron.

115. The method of any one of claims 111-114, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

116. The method of claim 115, wherein the neuropathy is chemotherapy induced neuropathy.

117. The method of any one of claims 111-116, wherein the exposing is performed *in vivo* or *ex vivo*.

118. The method of any one of claims 111-116, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.

119. The method of any one of claims 111-118, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.

120. The method of claim 119, wherein the oligonucleotide is administered orally.

121. The method of any one of claims 111-119, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

122. The method of any one of claims 111-121, wherein the patient is a human.

123. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

124. The pharmaceutical composition of claim 123, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular,

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

125. A method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124.

126. The method of claim 125, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such 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.

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

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

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

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

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

132. The method of claim 125, wherein the neuropathy is chemotherapy induced neuropathy.

133. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.

134. The method of any one of claims 125-132, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.

135. The method of any one of claims 125-134, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

136. The method of any one of claims 125-135, wherein the patient is human.

137. A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

138. A method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

139. A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

140. A method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

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

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

141. A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a

thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

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

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

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

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

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

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

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

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

150. The method of claim 149, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

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

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

153. The method of claim 152, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

154. The method of claim 152 or 153, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

155. The method of claim 154, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

156. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

157. The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

158. The method of claim 156 or 157, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

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

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

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

162. An oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

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

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

165. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, in combination with a second therapeutic agent.

166. The method of claim 165, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), 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.

167. A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, wherein at least one

nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

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

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

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

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

172. The method of claim 171, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

173. The method of claim 171 or 172, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

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

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

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

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

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

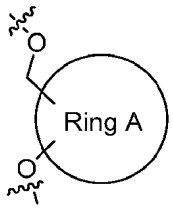
179. The method of claim 168, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

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

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

182. The method of any one of claims 168-181, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

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

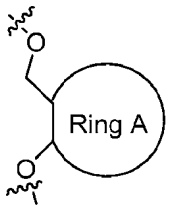


Formula (X)

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

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

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



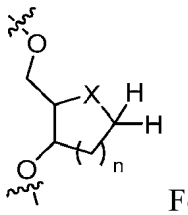
Formula (Xa).

185. The method of claim 183 or 184, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

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

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

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

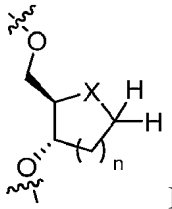


Formula (I)

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

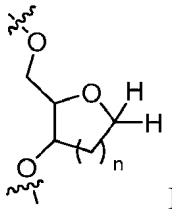
n is 0, 1, 2 or 3.

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



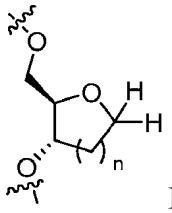
Formula (I').

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



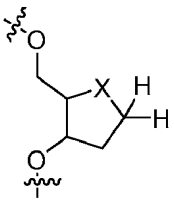
Formula (Ia).

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



Formula (Ia').

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

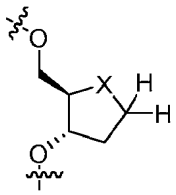


Formula (II); and

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

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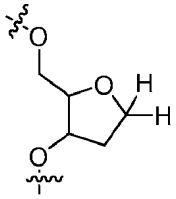
193. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

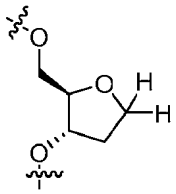
X is selected from $-CH_2-$ and -O-.

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



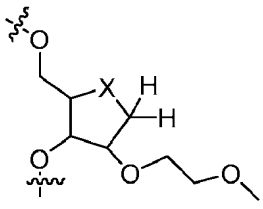
Formula (Iia).

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



Formula (Iia').

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

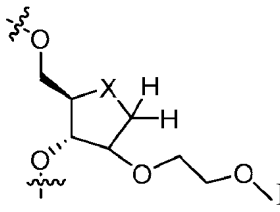


Formula (IIi)

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

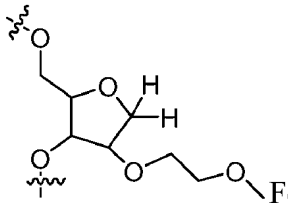
AMENDMENTS TO THE CLAIMS – MARKED-UP COPY

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

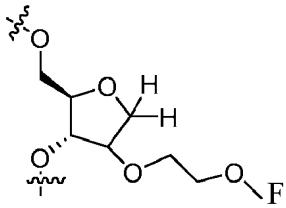

Formula (IIi')

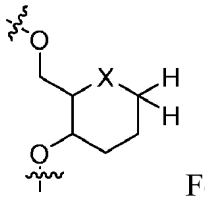
X is selected from -CH_2- and -O-.

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


Formula (IIib).

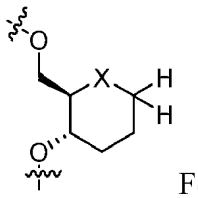
199. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:


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


Formula (III); and

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

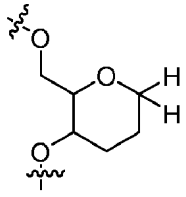
200. The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

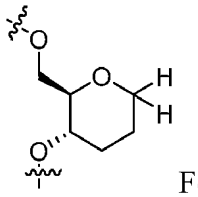
X is selected from $-CH_2-$ and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

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

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

206. The method of any one of claims 168-205, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

207. The method of any one of claims 168-206, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

208. The method of any one of claims 168-207, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

209. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon.

210. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% reduction of an UNC13A transcript with a cryptic exon.

211. The compound or oligonucleotide of any one of claims 200-201, wherein reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide.

212. The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
PCT/US22/51713	**10/02/2023 07:14:55 PM ET**	**QRL-014WO**

Title of Invention

TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

Application Information

APPLICATION TYPE	International Application (PCT) for filing in the US receiving office	PATENT #	-
CONFIRMATION #	5980	FILED BY	Ema Hysesani
PATENT CENTER #	62914090	FILING DATE	12/02/2022
CUSTOMER #	51414	APPLICANT NAME	SANDRA HINCKLEY
CORRESPONDENCE ADDRESS	CLARK ZHANG, GOODWIN PROCTER LLP 100 NORTHERN AVENUE/IP DOCKETING 7TH FL BOSTON, MA 02210 US	AUTHORIZED BY	Clark Zhang

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
QRL_014WO_Amendments_to_Claims_Marked_Up.pdf	34	Chapter II - Amendment to the claims - PCT Article 34	226 KB
QRL_014WO_Chapter_II_Demand_and_Article_34_Amendment.pdf	5	Chapter II - Amendments to description/drawings - PCT Article 34	104 KB
QRL_014WO_Substitue_Specification_Marked_Up.pdf	260	Substitute Sheets - International Application	1474 KB
QRL_014WO_Substitue_Spe	260	Substitute Sheets -	1456 KB

cification_Clean.pdf		International Application	
QRL_014WO_CHAPTER_II_Demand_Form.pdf	4	Chapter II - Form PCT/IPEA/401 - Demand	239 KB
QRL_014WO_Amendments_to_Claims_Clean.pdf	34	Chapter II - Amendment to the claims - PCT Article 34	310 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
PCT/US22/51713	**10/02/2023 07:14:55 PM ET**	**QRL-014WO**

Title of Invention

TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

Application Information

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CONFIRMATION #	5980	FILED BY	Ema Hysesani
PATENT CENTER #	62914090	AUTHORIZED BY	Clark Zhang
CUSTOMER #	51414	FILING DATE	12/02/2022
CORRESPONDENCE ADDRESS	CLARK ZHANG, GOODWIN PROCTER LLP 100 NORTHERN AVENUE/IP DOCKETING 7TH FL BOSTON, MA 02210 US	APPLICANT NAME	SANDRA HINCKLEY

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1146	**E202302J 15299811**	**Ema Hysesani**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
071700	**37 CFR 1.445(a)(1), (a)(2), (a)(4) and (b) (International application filing, processing and search fees); 37 CFR 1.17(m) (Acceptance of an unintentionally delayed claim for priority); PCT Rule 14; PCT Rule 15; PCT Rule 16**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2605	PRELIMINARY EXAMINATION FEE - US. WAS THE ISA	256.00	1	256.00
1705	HANDLING FEE (PCT - WIPO)	216.00	1	216.00
			TOTAL AMOUNT:	**$472.00**

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TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

CROSS-REFERENCE TO RELATED APPLICATIONS

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

REFERENCE TO A SEQUENCE LISTING XML

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

FIELD OF THE DISCLOSURE

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

BACKGROUND

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

[0004] Amyotrophic lateral sclerosis (ALS) is a group of motor neuron diseases affecting about 15,000 individuals in the United States of America. ALS is characterized by degeneration and death of upper and lower motor neurons, resulting in loss of voluntary muscle control. Motor neuron death is accompanied by muscle fasciculation and atrophy. Early symptoms of ALS include muscle cramps, muscle spasticity, muscle weakness (for example, affecting an arm, a leg,

neck, or diaphragm), slurred and nasal speech, and difficulty chewing or swallowing. Loss of strength and control over movements, including those necessary for speech, eating, and breathing, eventually occur. Disease progression may be accompanied by weight loss, malnourishment, anxiety, depression, increased risk of pneumonia, muscle cramps, neuropathy, and possibly dementia. Most individuals diagnosed with ALS die of respiratory failure within five years of the first appearance of symptoms. Currently, there is no effective treatment for ALS.

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

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

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

[0008] Thus, there is a pressing need to identify compounds and/or compositions capable of preventing, ameliorating, and treating neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant

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

SUMMARY

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

[0010] In one aspect the present disclosure provides a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage. In various embodiments, the oligonucleotide comprises a spacer.

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

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

SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.. In various embodiments, the oligonucleotide comprises a sequence that shares 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.. In various embodiments, the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

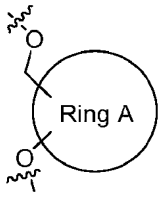
[0015] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer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

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

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

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

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

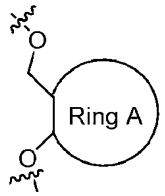


Formula (X)

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

the $-\!\!\lesssim$ symbol represents the point of connection to an internucleoside linkage.

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



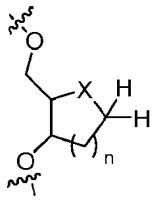
Formula (Xa).

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

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

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

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

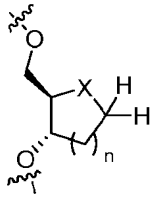


Formula (I)

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

n is 0, 1, 2 or 3.

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

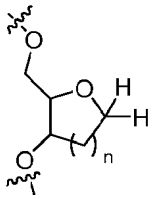


Formula (I')

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

n is 0, 1, 2 or 3.

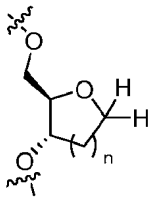
[0025] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

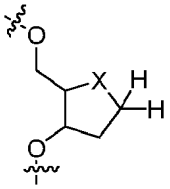
[0026] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

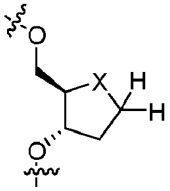
[0027] In certain embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

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

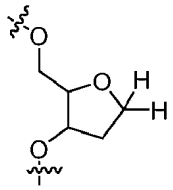
[0028] In further embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

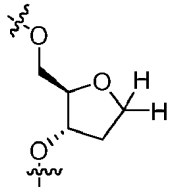
X is selected from -CH_2- and -O-.

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



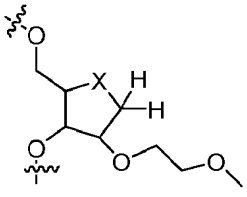
Formula (Iia).

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



Formula (Iia').

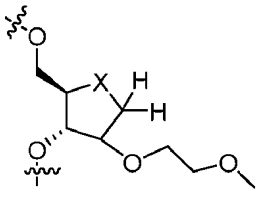
[0031] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

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

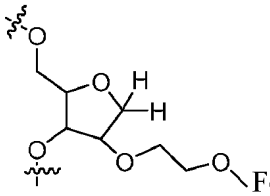
[0032] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

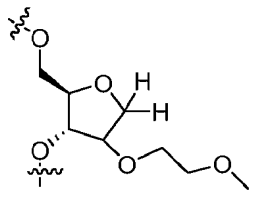
X is selected from -CH_2-and -O.

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

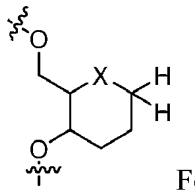


Formula (IIib).

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

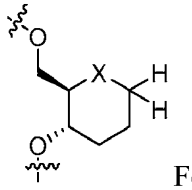

Formula (IIib').

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


Formula (III); and

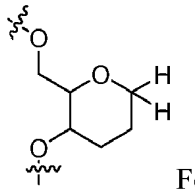
X is selected from -CH_2- and -O-.

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

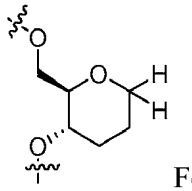

Formula (III'); and

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

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


Formula (IIIa).

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


Formula (IIIa').

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

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

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

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

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

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

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

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

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

[0045] In various embodiments, an internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various embodiments, the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various embodiments, the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration. In various embodiments, the oligonucleotide comprises at least one modified sugar moiety. In various embodiments, the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid (tcDNA) (e.g., tricyclic nucleic acid with ethyl (2'O-CH_2-CH_2-4'C) as the bridge or tricyclic nucleic acid with methyl substituted methyl (2'O-CH(CH_2)-4'C) bridge), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), tricyclic analog (*e.g.*, tcDNA), and unlocked nucleic acids.

[0046] In various embodiments, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein. In various embodiments, increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. In various embodiments, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

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

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

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

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

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

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

[0051] Additionally disclosed herein is a method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition disclosed above. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, 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 embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various embodiments, the neuropathy is chemotherapy induced neuropathy. In various embodiments, the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, intravenously, intramuscularly, transdermally, or intraduodenally. In various embodiments, wherein the pharmaceutical composition is administered intrathecally, intrathalamically intracerebroventricularly, or intracisternally. In various embodiments, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various embodiments, the patient is human.

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

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

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

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

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

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

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

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

[0058] In various embodiments, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

[0059] Additionally disclosed herein is an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a

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

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

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

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

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

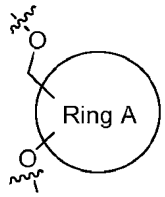
between positions 14 and 22 of the oligonucleotide. In various embodiments, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 9 of the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

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

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

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

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



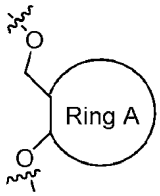
Formula (X)

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

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

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

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



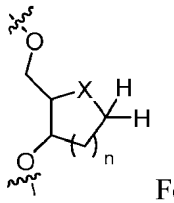
Formula (Xa).

[0069] In some embodiments, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

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

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

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

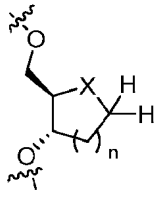


Formula (I)

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

n is 0, 1, 2 or 3.

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

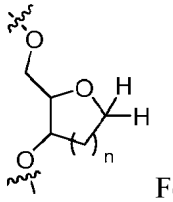


Formula (I')

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

n is 0, 1, 2 or 3.

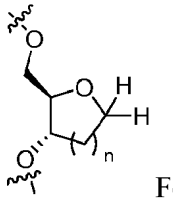
[0074] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

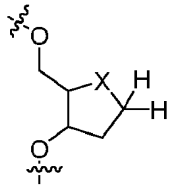
[0075] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

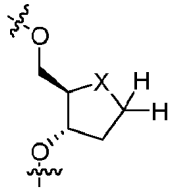
[0076] In certain embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

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

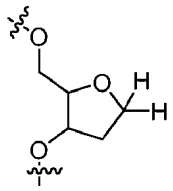
[0077] In further embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

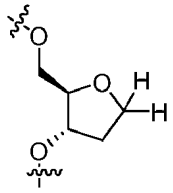
X is selected from -CH_2- and -O-.

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



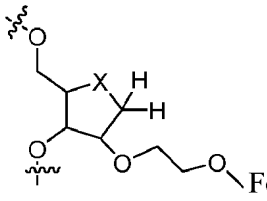
Formula (Iia).

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



Formula (Iia').

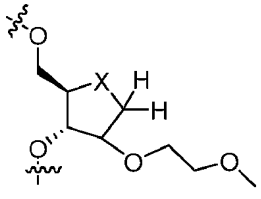
[0080] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

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

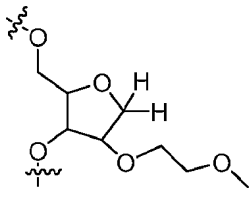
[0081] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

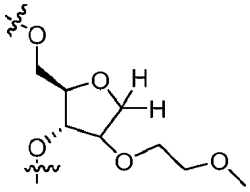
X is selected from -CH_2-and -O.

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



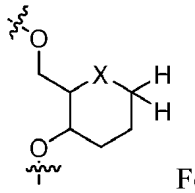
Formula (IIib).

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



Formula (IIib').

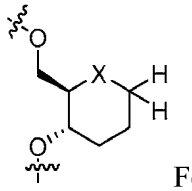
[0084] In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

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

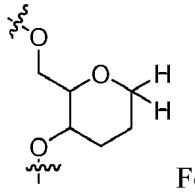
[0085] In further embodiments, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

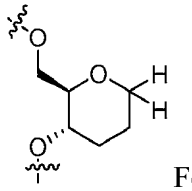
X is selected from -CH_2- and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

DETAILED DESCRIPTION

[0090] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

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

Definitions

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

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

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

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

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

[0096] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or non-human primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, non-human primates, and the like). In some embodiments, the mammal treated in

the methods of the invention is desirably a mammal in whom modulation of UNC13A expression and/or activity is desired.

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

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

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

[00100] In various embodiments, UNC13A oligonucleotides are characterized by having one or more spacers, where each spacer divides up the UNC13A oligonucleotide into segments of linked nucleosides. In various embodiments, UNC13A oligonucleotides have two spacers. In one embodiment, UNC13A oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, UNC13A oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, UNC13A oligonucleotides have one segment with at most 7 linked nucleosides. For example, a UNC13A oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various

embodiments, UNC13A oligonucleotides have three spacers that divide the UNC13A oligonucleotide into four segments. In various embodiments, each of the four segments of the UNC13A oligonucleotide have at most 7 linked nucleosides.

[00101] As used herein, the term "UNC13A oligonucleotide" encompasses a "UNC13A parent oligonucleotide," a "UNC13A oligonucleotide with one or more spacers" (e.g., UNC13A oligonucleotide with two spacers or a UNC13A oligonucleotide with three spacers), a "UNC13A oligonucleotide variant with one or more spacers." Examples of UNC13A oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

[00102] The term "UNC13A parent oligonucleotide" refers to an oligonucleotide that targets a UNC13A transcript and is capable of increasing, restoring, or stabilizing full-length UNC13A activity e.g., full length UNC13A expression, for example, full length UNC13A mRNA and/or full length UNC13A protein expression. UNC13A parent oligonucleotides do not include a spacer. Examples of UNC13A parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NO: 1-1264. As described hereafter, UNC13A oligonucleotide with spacers and UNC13A oligonucleotide variants are described in relation to a corresponding UNC13A parent oligonucleotide.

[00103] The term "UNC13A oligonucleotide variant" refers to a UNC13A oligonucleotide that represents a modified version of a corresponding UNC13A parent oligonucleotide. For example, a UNC13A oligonucleotide variant represents a shortened version of a UNC13A parent oligonucleotide. In various embodiments, a UNC13A oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of UNC13A oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NO: 2529-3792. In various embodiments, UNC13A oligonucleotide variants comprise one or more spacers. Such UNC13A oligonucleotide variants comprise a sequence of any one of SEQ ID NO: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

[00105] Generally, UNC13A oligonucleotides comprising one or more spacers are described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A oligonucleotide variant. Example UNC13A oligonucleotides comprising one or more spacers include any of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

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

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

[00109] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in a UNC13A oligonucleotide used in the present compositions. A UNC13A oligonucleotide included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A UNC13A oligonucleotide included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, and lithium salts. Pharmaceutically acceptable salts of the disclosure include, for example, pharmaceutically acceptable salts of UNC13A oligonucleotides that include a sequence of any of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

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

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

[00113] The disclosure also embraces fluorescently labeled compounds of the invention. The disclosure also embraces isotopically labeled compounds of the invention (*i.e.*, isotopically

labeled UNC13A oligonucleotide) which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number abundantly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{33}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

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

[00115] As used herein, "2'-*O*-(2-methoxyethyl)" (also 2'-MOE and 2'-$O(CH_2)_2OCH_3$ and MOE) refers to an *O*-methoxyethyl modification of the 2' position of a furanose ring. A 2'-O-(2-methoxyethyl) is used interchangeably as "2'-*O*-methoxyethyl" in the present disclosure. A sugar moiety in a nucleoside modified with 2'-MOE is a modified sugar.

[00116] As used herein, "2'-MOE nucleoside" (also 2'-*O*-(2-methoxyethyl) nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

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

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

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

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

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

[00122] As used herein, "cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-$CH(CH_3)$—*O*-2'.

[00123] As used herein, "constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$—*O*-2' bridge. In some embodiments, cEt can be modified. In some embodiments, the cEt can be *S*-cEt (in an *S*-constrained ethyl 2'-4'-bridged nucleic acid). In some other embodiments, the cEt can be *R*-cEt.

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

[00125] As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence. As an example to the contrary, two nucleosides separated by a spacer are not contiguous.

[00126] As used herein, "locked nucleic acid" or "LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to (A) α-L-Methyleneoxy (4'-CH_2—O-2') LNA, (B) β-D-Methyleneoxy (4'-CH_2—O-2') LNA, (C) Ethyleneoxy (4'-$(CH_2)_2$—O-2') LNA, (D) Aminooxy (4'-CH_2—O—N(R)-2') LNA and (E) Oxyamino (4'-CH_2—N(R)—O-2') LNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00127] As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_1)(R_2)]_n$ —, —$C(R_1)$=$C(R_2)$—, —$C(R_1)$=N—, —C(=NR_1)—, —C(=O)—, —C(=S)—, —O—, —$Si(R_1)_2$—, —$S(=O)_x$— and —$N(R_1)$ —; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O) —H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl

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

[00128] Examples of 4'-2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: —$[C(R_1)(R_2)]_n$ —, — $[C(R_1)(R_2)]_n$—O—, — $C(R_1R_2)$—$N(R_1)$—O— or —$C(R_1R_2)$—O—$N(R_1)$—. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'- CH_2—O—$N(R_1)$-2' and 4'- CH_2—$N(R_1)$—O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

[00129] Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a bridge to form the bicyclic sugar moiety. The bridge can be a methylene (—CH_2—) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2—O-2') LNA is used. Furthermore, in the case of the bicyclic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2—O-2') LNA is used.

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

the nucleoside (A, C, G, or U) at the same corresponding position of the target UNC13A transcript)).

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

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

[00133] As used herein, "modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymine, or uracil. Examples of a modified nucleobase include 5-methyl cytosine, pseudouridine, or 5-methoxyuridine. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[00134] As used herein, a "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. Modified nucleosides include abasic nucleosides, which lack a nucleobase. However, modified nucleosides do not include spacers or other groups that are incapable of linking a nucleobase.

[00135] As used herein, "linked nucleosides" are nucleosides that are connected in a contiguous sequence (*i.e.*, no additional nucleosides are presented between those that are linked). In various embodiments, an oligonucleotide may have different segments of linked nucleosides connected through a spacer. Here, the spacer (*i.e.*, nucleoside replacement) is not considered a nucleoside and therefore, divides up the oligonucleotide into two segments of linked nucleosides. The oligonucleotide may have a first segment of Y linked nucleosides (*e.g.*, Y nucleosides that are connected in a contiguous sequence), followed by a spacer, and then a second segment of Z linked nucleosides. Here, the Y and Z linked nucleosides is described in either the 5' to 3' direction or the 3' to 5' direction. In various embodiments, the first segment consists of 7 or fewer linked nucleosides (e.g., Y = 7 or fewer) whereas the second segment comprises 8 or more linked nucleosides (*e.g.*, Z = 8 or more).

[00136] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one (*i.e.*, one or more) modified internucleoside linkage, modified sugar, and/or modified nucleobase.

[00137] As used herein, "modified sugar" or "modified sugar moiety" means a modified furanosyl sugar moiety or a modified sugar moiety having other than a furanosyl moiety that can

link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide.

[00138] As used herein, "monomer" means a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.

[00139] As used herein, "motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

[00140] As used herein, "natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

[00141] As used herein, "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

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

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

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

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

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

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

[00148] As used herein, "nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo, or tricyclo sugar mimetics, *e.g.*, non-furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by a phosphorodiamidate or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

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

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

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

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

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

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

Antisense Therapeutics

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

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

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

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

various embodiments, the oligonucleotide is at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 26 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 27 oligonucleotide units in length.

[00159] In certain embodiments, AONs may include chemically modified nucleosides (for example, 2'-O-methylated nucleosides or 2'-O-(2-methoxyethyl) nucleosides) as well as modified internucleoside linkages (for example, phosphorothioate linkages). In certain embodiments, AONs described herein include oligonucleotide sequences that are complementary to RNA sequences, such as UNC13A mRNA sequences. In certain embodiments, AONs described herein can include chemically modified nucleosides and modified internucleoside linkages (for example, phosphorothioate linkages). In particular embodiments, AONs described herein include one or more spacers.

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

[00161] In some embodiments, an antisense oligonucleotide can be, but is not limited to, inhibitors of a gene transcript (for example, shRNAs, siRNAs, PNAs, LNAs, 2'-*O*-methyl (2'OMe) antisense oligonucleotide (AON), 2'-*O*-(2-methoxyethyl) (MOE) AON, or morpholino oligomers (*e.g.*, phosphorodiamidate morpholino (PMO))), or compositions that include such compounds. In some embodiments an oligonucleotide is an antisense oligonucleotide (AON) comprising 2'OMe (*e.g.*, a AON comprising one or more 2'OMe modified sugar), MOE (*e.g.*, a AON comprising one or more MOE modified sugar), peptide nucleic acids (*e.g.*, a AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl

methylene linkage as repeating units in place of a sugar-phosphate backbone), locked nucleic acids (*e.g.*, a AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a AON comprising one or more cET sugar), constrained methoxyethyl (cMOE) (*e.g.*, a AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tricyclo-DNAs (tcDNA) (*e.g.*, a AON comprising one or more tcDNA modified sugar), 2'-O,4'-C-Ethylene-bridged nucleic acid (ENA) (*e.g.*, a AON comprising one or more ENA modified sugar), or hexitol nucleic acids (HNA) (*e.g.*, a AON comprising one or more HNA modified sugar). In some embodiments, a AON comprises one or more internucleoside linkage independently selected from a phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

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

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

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

UNC13A Oligonucleotides Complementary to UNC13A Transcript

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

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

[00166] In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

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

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

[00169] In some embodiments, a UNC13A AON can include a non-duplexed oligonucleotide. In some embodiments, a UNC13A AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a UNC13A pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

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

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

Table 1. Example UNC13A AON Sequences.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
1	GGAGGGGCCGAGCAATGACCCTCAC	1265	GTGAGGGTCATTGCTCGGCCCCTCC
2	GGGAGGGGCCGAGCAATGACCCTCA	1266	TGAGGGTCATTGCTCGGCCCCTCCC
3	TGGGAGGGGCCGAGCAATGACCCTC	1267	GAGGGTCATTGCTCGGCCCCTCCCA
4	ATGGGAGGGGCCGAGCAATGACCCT	1268	AGGGTCATTGCTCGGCCCCTCCCAT
5	CATGGGAGGGGCCGAGCAATGACCC	1269	GGGTCATTGCTCGGCCCCTCCCATG
6	GCATGGGAGGGGCCGAGCAATGACC	1270	GGTCATTGCTCGGCCCCTCCCATGC
7	GGCATGGGAGGGGCCGAGCAATGAC	1271	GTCATTGCTCGGCCCCTCCCATGCC
8	TGGCATGGGAGGGGCCGAGCAATGA	1272	TCATTGCTCGGCCCCTCCCATGCCA
9	GTGGCATGGGAGGGGCCGAGCAATG	1273	CATTGCTCGGCCCCTCCCATGCCAC
10	AGTGGCATGGGAGGGGCCGAGCAAT	1274	ATTGCTCGGCCCCTCCCATGCCACT
11	AAGTGGCATGGGAGGGGCCGAGCAA	1275	TTGCTCGGCCCCTCCCATGCCACTT
12	GAAGTGGCATGGGAGGGGCCGAGCA	1276	TGCTCGGCCCCTCCCATGCCACTTC
13	GGAAGTGGCATGGGAGGGGCCGAGC	1277	GCTCGGCCCCTCCCATGCCACTTCC
14	TGGAAGTGGCATGGGAGGGGCCGAG	1278	CTCGGCCCCTCCCATGCCACTTCCA
15	GTGGAAGTGGCATGGGAGGGGCCGA	1279	TCGGCCCCTCCCATGCCACTTCCAC
16	AGTGGAAGTGGCATGGGAGGGGCCG	1280	CGGCCCCTCCCATGCCACTTCCACT
17	GAGTGGAAGTGGCATGGGAGGGGCC	1281	GGCCCCTCCCATGCCACTTCCACTC
18	TGAGTGGAAGTGGCATGGGAGGGGC	1282	GCCCCTCCCATGCCACTTCCACTCA
19	GTGAGTGGAAGTGGCATGGGAGGGG	1283	CCCCTCCCATGCCACTTCCACTCAC
20	GGTGAGTGGAAGTGGCATGGGAGGG	1284	CCCTCCCATGCCACTTCCACTCACC
21	TGGTGAGTGGAAGTGGCATGGGAGG	1285	CCTCCCATGCCACTTCCACTCACCA
22	ATGGTGAGTGGAAGTGGCATGGGAG	1286	CTCCCATGCCACTTCCACTCACCAT
23	AATGGTGAGTGGAAGTGGCATGGGA	1287	TCCCATGCCACTTCCACTCACCATT
24	GAATGGTGAGTGGAAGTGGCATGGG	1288	CCCATGCCACTTCCACTCACCATTC
25	GGAATGGTGAGTGGAAGTGGCATGG	1289	CCATGCCACTTCCACTCACCATTCC
26	AGGAATGGTGAGTGGAAGTGGCATG	1290	CATGCCACTTCCACTCACCATTCCT
27	CAGGAATGGTGAGTGGAAGTGGCAT	1291	ATGCCACTTCCACTCACCATTCCTG
28	GCAGGAATGGTGAGTGGAAGTGGCA	1292	TGCCACTTCCACTCACCATTCCTGC
29	GGCAGGAATGGTGAGTGGAAGTGGC	1293	GCCACTTCCACTCACCATTCCTGCC
30	AGGCAGGAATGGTGAGTGGAAGTGG	1294	CCACTTCCACTCACCATTCCTGCCT
31	CAGGCAGGAATGGTGAGTGGAAGTG	1295	CACTTCCACTCACCATTCCTGCCTG
32	GCAGGCAGGAATGGTGAGTGGAAGT	1296	ACTTCCACTCACCATTCCTGCCTGC
33	GGCAGGCAGGAATGGTGAGTGGAAG	1297	CTTCCACTCACCATTCCTGCCTGCC
34	GGGCAGGCAGGAATGGTGAGTGGAA	1298	TTCCACTCACCATTCCTGCCTGCCC
35	TGGGCAGGCAGGAATGGTGAGTGGA	1299	TCCACTCACCATTCCTGCCTGCCCA

36	CTGGGCAGGCAGGAATGGTGAGTGG	1300	CCACTCACCATTCCTGCCTGCCCAG
37	GCTGGGCAGGCAGGAATGGTGAGTG	1301	CACTCACCATTCCTGCCTGCCCAGC
38	AGCTGGGCAGGCAGGAATGGTGAGT	1302	ACTCACCATTCCTGCCTGCCCAGCT
39	GAGCTGGGCAGGCAGGAATGGTGAG	1303	CTCACCATTCCTGCCTGCCCAGCTC
40	AGAGCTGGGCAGGCAGGAATGGTGA	1304	TCACCATTCCTGCCTGCCCAGCTCT
41	AAGAGCTGGGCAGGCAGGAATGGTG	1305	CACCATTCCTGCCTGCCCAGCTCTT
42	GAAGAGCTGGGCAGGCAGGAATGGT	1306	ACCATTCCTGCCTGCCCAGCTCTTC
43	GGAAGAGCTGGGCAGGCAGGAATGG	1307	CCATTCCTGCCTGCCCAGCTCTTCC
44	AGGAAGAGCTGGGCAGGCAGGAATG	1308	CATTCCTGCCTGCCCAGCTCTTCCT
45	GAGGAAGAGCTGGGCAGGCAGGAAT	1309	ATTCCTGCCTGCCCAGCTCTTCCTC
46	AGAGGAAGAGCTGGGCAGGCAGGAA	1310	TTCCTGCCTGCCCAGCTCTTCCTCT
47	AAGAGGAAGAGCTGGGCAGGCAGGA	1311	TCCTGCCTGCCCAGCTCTTCCTCTT
48	AAAGAGGAAGAGCTGGGCAGGCAGG	1312	CCTGCCTGCCCAGCTCTTCCTCTTT
49	GAAAGAGGAAGAGCTGGGCAGGCAG	1313	CTGCCTGCCCAGCTCTTCCTCTTTC
50	AGAAAGAGGAAGAGCTGGGCAGGCA	1314	TGCCTGCCCAGCTCTTCCTCTTTCT
51	CAGAAAGAGGAAGAGCTGGGCAGGC	1315	GCCTGCCCAGCTCTTCCTCTTTCTG
52	CCAGAAAGAGGAAGAGCTGGGCAGG	1316	CCTGCCCAGCTCTTCCTCTTTCTGG
53	GCCAGAAAGAGGAAGAGCTGGGCAG	1317	CTGCCCAGCTCTTCCTCTTTCTGGC
54	GGCCAGAAAGAGGAAGAGCTGGGCA	1318	TGCCCAGCTCTTCCTCTTTCTGGCC
55	TGGCCAGAAAGAGGAAGAGCTGGGC	1319	GCCCAGCTCTTCCTCTTTCTGGCCA
56	GTGGCCAGAAAGAGGAAGAGCTGGG	1320	CCCAGCTCTTCCTCTTTCTGGCCAC
57	TGTGGCCAGAAAGAGGAAGAGCTGG	1321	CCAGCTCTTCCTCTTTCTGGCCACA
58	GTGTGGCCAGAAAGAGGAAGAGCTG	1322	CAGCTCTTCCTCTTTCTGGCCACAC
59	GGTGTGGCCAGAAAGAGGAAGAGCT	1323	AGCTCTTCCTCTTTCTGGCCACACC
60	TGGTGTGGCCAGAAAGAGGAAGAGC	1324	GCTCTTCCTCTTTCTGGCCACACCA
61	ATGGTGTGGCCAGAAAGAGGAAGAG	1325	CTCTTCCTCTTTCTGGCCACACCAT
62	GATGGTGTGGCCAGAAAGAGGAAGA	1326	TCTTCCTCTTTCTGGCCACACCATC
63	GGATGGTGTGGCCAGAAAGAGGAAG	1327	CTTCCTCTTTCTGGCCACACCATCC
64	TGGATGGTGTGGCCAGAAAGAGGAA	1328	TTCCTCTTTCTGGCCACACCATCCA
65	GTGGATGGTGTGGCCAGAAAGAGGA	1329	TCCTCTTTCTGGCCACACCATCCAC
66	TGTGGATGGTGTGGCCAGAAAGAGG	1330	CCTCTTTCTGGCCACACCATCCACA
67	GTGTGGATGGTGTGGCCAGAAAGAG	1331	CTCTTTCTGGCCACACCATCCACAC
68	AGTGTGGATGGTGTGGCCAGAAAGA	1332	TCTTTCTGGCCACACCATCCACACT
69	GAGTGTGGATGGTGTGGCCAGAAAG	1333	CTTTCTGGCCACACCATCCACACTC
70	AGAGTGTGGATGGTGTGGCCAGAAA	1334	TTTCTGGCCACACCATCCACACTCT
71	GAGAGTGTGGATGGTGTGGCCAGAA	1335	TTCTGGCCACACCATCCACACTCTC
72	GGAGAGTGTGGATGGTGTGGCCAGA	1336	TCTGGCCACACCATCCACACTCTCC
73	AGGAGAGTGTGGATGGTGTGGCCAG	1337	CTGGCCACACCATCCACACTCTCCT
74	CAGGAGAGTGTGGATGGTGTGGCCA	1338	TGGCCACACCATCCACACTCTCCTG
75	CCAGGAGAGTGTGGATGGTGTGGCC	1339	GGCCACACCATCCACACTCTCCTGG
76	GCCAGGAGAGTGTGGATGGTGTGGC	1340	GCCACACCATCCACACTCTCCTGGC
77	GGCCAGGAGAGTGTGGATGGTGTGG	1341	CCACACCATCCACACTCTCCTGGCC

78	GGGCCAGGAGAGTGTGGATGGTGTG	1342	CACACCATCCACACTCTCCTGGCCC
79	AGGGCCAGGAGAGTGTGGATGGTGT	1343	ACACCATCCACACTCTCCTGGCCCT
80	GAGGGCCAGGAGAGTGTGGATGGTG	1344	CACCATCCACACTCTCCTGGCCCTC
81	AGAGGGCCAGGAGAGTGTGGATGGT	1345	ACCATCCACACTCTCCTGGCCCTCT
82	CAGAGGGCCAGGAGAGTGTGGATGG	1346	CCATCCACACTCTCCTGGCCCTCTG
83	TCAGAGGGCCAGGAGAGTGTGGATG	1347	CATCCACACTCTCCTGGCCCTCTGA
84	CTCAGAGGGCCAGGAGAGTGTGGAT	1348	ATCCACACTCTCCTGGCCCTCTGAG
85	TCTCAGAGGGCCAGGAGAGTGTGGA	1349	TCCACACTCTCCTGGCCCTCTGAGA
86	GTCTCAGAGGGCCAGGAGAGTGTGG	1350	CCACACTCTCCTGGCCCTCTGAGAC
87	AGTCTCAGAGGGCCAGGAGAGTGTG	1351	CACACTCTCCTGGCCCTCTGAGACT
88	CAGTCTCAGAGGGCCAGGAGAGTGT	1352	ACACTCTCCTGGCCCTCTGAGACTG
89	GCAGTCTCAGAGGGCCAGGAGAGTG	1353	CACTCTCCTGGCCCTCTGAGACTGC
90	GGCAGTCTCAGAGGGCCAGGAGAGT	1354	ACTCTCCTGGCCCTCTGAGACTGCC
91	GGGCAGTCTCAGAGGGCCAGGAGAG	1355	CTCTCCTGGCCCTCTGAGACTGCCC
92	CGGGCAGTCTCAGAGGGCCAGGAGA	1356	TCTCCTGGCCCTCTGAGACTGCCCG
93	GCGGGCAGTCTCAGAGGGCCAGGAG	1357	CTCCTGGCCCTCTGAGACTGCCCGC
94	GGCGGGCAGTCTCAGAGGGCCAGGA	1358	TCCTGGCCCTCTGAGACTGCCCGCC
95	TGGCGGGCAGTCTCAGAGGGCCAGG	1359	CCTGGCCCTCTGAGACTGCCCGCCA
96	ATGGCGGGCAGTCTCAGAGGGCCAG	1360	CTGGCCCTCTGAGACTGCCCGCCAT
97	CATGGCGGGCAGTCTCAGAGGGCCA	1361	TGGCCCTCTGAGACTGCCCGCCATG
98	GCATGGCGGGCAGTCTCAGAGGGCC	1362	GGCCCTCTGAGACTGCCCGCCATGC
99	GGCATGGCGGGCAGTCTCAGAGGGC	1363	GCCCTCTGAGACTGCCCGCCATGCC
100	TGGCATGGCGGGCAGTCTCAGAGGG	1364	CCCTCTGAGACTGCCCGCCATGCCA
101	ATGGCATGGCGGGCAGTCTCAGAGG	1365	CCTCTGAGACTGCCCGCCATGCCAT
102	AATGGCATGGCGGGCAGTCTCAGAG	1366	CTCTGAGACTGCCCGCCATGCCATT
103	GAATGGCATGGCGGGCAGTCTCAGA	1367	TCTGAGACTGCCCGCCATGCCATTC
104	GGAATGGCATGGCGGGCAGTCTCAG	1368	CTGAGACTGCCCGCCATGCCATTCC
105	GGGAATGGCATGGCGGGCAGTCTCA	1369	TGAGACTGCCCGCCATGCCATTCCC
106	AGGGAATGGCATGGCGGGCAGTCTC	1370	GAGACTGCCCGCCATGCCATTCCCT
107	AAGGGAATGGCATGGCGGGCAGTCT	1371	AGACTGCCCGCCATGCCATTCCCTT
108	AAAGGGAATGGCATGGCGGGCAGTC	1372	GACTGCCCGCCATGCCATTCCCTTT
109	TAAAGGGAATGGCATGGCGGGCAGT	1373	ACTGCCCGCCATGCCATTCCCTTTA
110	GTAAAGGGAATGGCATGGCGGGCAG	1374	CTGCCCGCCATGCCATTCCCTTTAC
111	GGTAAAGGGAATGGCATGGCGGGCA	1375	TGCCCGCCATGCCATTCCCTTTACC
112	AGGTAAAGGGAATGGCATGGCGGGC	1376	GCCCGCCATGCCATTCCCTTTACCT
113	CAGGTAAAGGGAATGGCATGGCGGG	1377	CCCGCCATGCCATTCCCTTTACCTG
114	CCAGGTAAAGGGAATGGCATGGCGG	1378	CCGCCATGCCATTCCCTTTACCTGG
115	TCCAGGTAAAGGGAATGGCATGGCG	1379	CGCCATGCCATTCCCTTTACCTGGA
116	TTCCAGGTAAAGGGAATGGCATGGC	1380	GCCATGCCATTCCCTTTACCTGGAA
117	TTTCCAGGTAAAGGGAATGGCATGG	1381	CCATGCCATTCCCTTTACCTGGAAA
118	TTTTCCAGGTAAAGGGAATGGCATG	1382	CATGCCATTCCCTTTACCTGGAAAA
119	GTTTTCCAGGTAAAGGGAATGGCAT	1383	ATGCCATTCCCTTTACCTGGAAAAC

120	AGTTTTCCAGGTAAAGGGAATGGCA	1384	TGCCATTCCCTTTACCTGGAAAACT
121	GAGTTTTCCAGGTAAAGGGAATGGC	1385	GCCATTCCCTTTACCTGGAAAACTC
122	GGAGTTTTCCAGGTAAAGGGAATGG	1386	CCATTCCCTTTACCTGGAAAACTCC
123	AGGAGTTTTCCAGGTAAAGGGAATG	1387	CATTCCCTTTACCTGGAAAACTCCT
124	GAGGAGTTTTCCAGGTAAAGGGAAT	1388	ATTCCCTTTACCTGGAAAACTCCTC
125	GGAGGAGTTTTCCAGGTAAAGGGAA	1389	TTCCCTTTACCTGGAAAACTCCTCC
126	GGGAGGAGTTTTCCAGGTAAAGGGA	1390	TCCCTTTACCTGGAAAACTCCTCCC
127	AGGGAGGAGTTTTCCAGGTAAAGGG	1391	CCCTTTACCTGGAAAACTCCTCCCT
128	TAGGGAGGAGTTTTCCAGGTAAAGG	1392	CCTTTACCTGGAAAACTCCTCCCTA
129	ATAGGGAGGAGTTTTCCAGGTAAAG	1393	CTTTACCTGGAAAACTCCTCCCTAT
130	GATAGGGAGGAGTTTTCCAGGTAAA	1394	TTTACCTGGAAAACTCCTCCCTATC
131	GGATAGGGAGGAGTTTTCCAGGTAA	1395	TTACCTGGAAAACTCCTCCCTATCC
132	TGGATAGGGAGGAGTTTTCCAGGTA	1396	TACCTGGAAAACTCCTCCCTATCCA
133	ATGGATAGGGAGGAGTTTTCCAGGT	1397	ACCTGGAAAACTCCTCCCTATCCAT
134	GATGGATAGGGAGGAGTTTTCCAGG	1398	CCTGGAAAACTCCTCCCTATCCATC
135	TGATGGATAGGGAGGAGTTTTCCAG	1399	CTGGAAAACTCCTCCCTATCCATCA
136	TTGATGGATAGGGAGGAGTTTTCCA	1400	TGGAAAACTCCTCCCTATCCATCAA
137	TTTGATGGATAGGGAGGAGTTTTCC	1401	GGAAAACTCCTCCCTATCCATCAAA
138	CTTTGATGGATAGGGAGGAGTTTTC	1402	GAAAACTCCTCCCTATCCATCAAAG
139	ACTTTGATGGATAGGGAGGAGTTTT	1403	AAAACTCCTCCCTATCCATCAAAGT
140	GACTTTGATGGATAGGGAGGAGTTT	1404	AAACTCCTCCCTATCCATCAAAGTC
141	GGACTTTGATGGATAGGGAGGAGTT	1405	AACTCCTCCCTATCCATCAAAGTCC
142	TGGACTTTGATGGATAGGGAGGAGT	1406	ACTCCTCCCTATCCATCAAAGTCCA
143	CTGGACTTTGATGGATAGGGAGGAG	1407	CTCCTCCCTATCCATCAAAGTCCAG
144	TCTGGACTTTGATGGATAGGGAGGA	1408	TCCTCCCTATCCATCAAAGTCCAGA
145	ATCTGGACTTTGATGGATAGGGAGG	1409	CCTCCCTATCCATCAAAGTCCAGAT
146	AATCTGGACTTTGATGGATAGGGAG	1410	CTCCCTATCCATCAAAGTCCAGATT
147	GAATCTGGACTTTGATGGATAGGGA	1411	TCCCTATCCATCAAAGTCCAGATTC
148	TGAATCTGGACTTTGATGGATAGGG	1412	CCCTATCCATCAAAGTCCAGATTCA
149	CTGAATCTGGACTTTGATGGATAGG	1413	CCTATCCATCAAAGTCCAGATTCAG
150	CCTGAATCTGGACTTTGATGGATAG	1414	CTATCCATCAAAGTCCAGATTCAGG
151	CCCTGAATCTGGACTTTGATGGATA	1415	TATCCATCAAAGTCCAGATTCAGGG
152	ACCCTGAATCTGGACTTTGATGGAT	1416	ATCCATCAAAGTCCAGATTCAGGGT
153	GACCCTGAATCTGGACTTTGATGGA	1417	TCCATCAAAGTCCAGATTCAGGGTC
154	TGACCCTGAATCTGGACTTTGATGG	1418	CCATCAAAGTCCAGATTCAGGGTCA
155	GTGACCCTGAATCTGGACTTTGATG	1419	CATCAAAGTCCAGATTCAGGGTCAC
156	GGTGACCCTGAATCTGGACTTTGAT	1420	ATCAAAGTCCAGATTCAGGGTCACC
157	AGGTGACCCTGAATCTGGACTTTGA	1421	TCAAAGTCCAGATTCAGGGTCACCT
158	GAGGTGACCCTGAATCTGGACTTTG	1422	CAAAGTCCAGATTCAGGGTCACCTC
159	GGAGGTGACCCTGAATCTGGACTTT	1423	AAAGTCCAGATTCAGGGTCACCTCC
160	AGGAGGTGACCCTGAATCTGGACTT	1424	AAGTCCAGATTCAGGGTCACCTCCT
161	GAGGAGGTGACCCTGAATCTGGACT	1425	AGTCCAGATTCAGGGTCACCTCCTC

162	AGAGGAGGTGACCCTGAATCTGGAC	1426	GTCCAGATTCAGGGTCACCTCCTCT
163	CAGAGGAGGTGACCCTGAATCTGGA	1427	TCCAGATTCAGGGTCACCTCCTCTG
164	CCAGAGGAGGTGACCCTGAATCTGG	1428	CCAGATTCAGGGTCACCTCCTCTGG
165	CCCAGAGGAGGTGACCCTGAATCTG	1429	CAGATTCAGGGTCACCTCCTCTGGG
166	TCCCAGAGGAGGTGACCCTGAATCT	1430	AGATTCAGGGTCACCTCCTCTGGGA
167	TTCCCAGAGGAGGTGACCCTGAATC	1431	GATTCAGGGTCACCTCCTCTGGGAA
168	CTTCCCAGAGGAGGTGACCCTGAAT	1432	ATTCAGGGTCACCTCCTCTGGGAAG
169	GCTTCCCAGAGGAGGTGACCCTGAA	1433	TTCAGGGTCACCTCCTCTGGGAAGC
170	GGCTTCCCAGAGGAGGTGACCCTGA	1434	TCAGGGTCACCTCCTCTGGGAAGCC
171	GGGCTTCCCAGAGGAGGTGACCCTG	1435	CAGGGTCACCTCCTCTGGGAAGCCC
172	TGGGCTTCCCAGAGGAGGTGACCCT	1436	AGGGTCACCTCCTCTGGGAAGCCCA
173	GTGGGCTTCCCAGAGGAGGTGACCC	1437	GGGTCACCTCCTCTGGGAAGCCCAC
174	GGTGGGCTTCCCAGAGGAGGTGACC	1438	GGTCACCTCCTCTGGGAAGCCCACC
175	AGGTGGGCTTCCCAGAGGAGGTGAC	1439	GTCACCTCCTCTGGGAAGCCCACCT
176	AAGGTGGGCTTCCCAGAGGAGGTGA	1440	TCACCTCCTCTGGGAAGCCCACCTT
177	CAAGGTGGGCTTCCCAGAGGAGGTG	1441	CACCTCCTCTGGGAAGCCCACCTTG
178	CCAAGGTGGGCTTCCCAGAGGAGGT	1442	ACCTCCTCTGGGAAGCCCACCTTGG
179	GCCAAGGTGGGCTTCCCAGAGGAGG	1443	CCTCCTCTGGGAAGCCCACCTTGGC
180	GGCCAAGGTGGGCTTCCCAGAGGAG	1444	CTCCTCTGGGAAGCCCACCTTGGCC
181	AGGCCAAGGTGGGCTTCCCAGAGGA	1445	TCCTCTGGGAAGCCCACCTTGGCCT
182	GAGGCCAAGGTGGGCTTCCCAGAGG	1446	CCTCTGGGAAGCCCACCTTGGCCTC
183	GGAGGCCAAGGTGGGCTTCCCAGAG	1447	CTCTGGGAAGCCCACCTTGGCCTCC
184	TGGAGGCCAAGGTGGGCTTCCCAGA	1448	TCTGGGAAGCCCACCTTGGCCTCCA
185	CTGGAGGCCAAGGTGGGCTTCCCAG	1449	CTGGGAAGCCCACCTTGGCCTCCAG
186	CCTGGAGGCCAAGGTGGGCTTCCCA	1450	TGGGAAGCCCACCTTGGCCTCCAGG
187	ACCTGGAGGCCAAGGTGGGCTTCCC	1451	GGGAAGCCCACCTTGGCCTCCAGGT
188	AACCTGGAGGCCAAGGTGGGCTTCC	1452	GGAAGCCCACCTTGGCCTCCAGGTT
189	CAACCTGGAGGCCAAGGTGGGCTTC	1453	GAAGCCCACCTTGGCCTCCAGGTTG
190	TCAACCTGGAGGCCAAGGTGGGCTT	1454	AAGCCCACCTTGGCCTCCAGGTTGA
191	GTCAACCTGGAGGCCAAGGTGGGCT	1455	AGCCCACCTTGGCCTCCAGGTTGAC
192	AGTCAACCTGGAGGCCAAGGTGGGC	1456	GCCCACCTTGGCCTCCAGGTTGACT
193	GAGTCAACCTGGAGGCCAAGGTGGG	1457	CCCACCTTGGCCTCCAGGTTGACTC
194	AGAGTCAACCTGGAGGCCAAGGTGG	1458	CCACCTTGGCCTCCAGGTTGACTCT
195	GAGAGTCAACCTGGAGGCCAAGGTG	1459	CACCTTGGCCTCCAGGTTGACTCTC
196	TGAGAGTCAACCTGGAGGCCAAGGT	1460	ACCTTGGCCTCCAGGTTGACTCTCA
197	GTGAGAGTCAACCTGGAGGCCAAGG	1461	CCTTGGCCTCCAGGTTGACTCTCAC
198	AGTGAGAGTCAACCTGGAGGCCAAG	1462	CTTGGCCTCCAGGTTGACTCTCACT
199	TAGTGAGAGTCAACCTGGAGGCCAA	1463	TTGGCCTCCAGGTTGACTCTCACTA
200	GTAGTGAGAGTCAACCTGGAGGCCA	1464	TGGCCTCCAGGTTGACTCTCACTAC
201	AGTAGTGAGAGTCAACCTGGAGGCC	1465	GGCCTCCAGGTTGACTCTCACTACT
202	GAGTAGTGAGAGTCAACCTGGAGGC	1466	GCCTCCAGGTTGACTCTCACTACTC
203	TGAGTAGTGAGAGTCAACCTGGAGG	1467	CCTCCAGGTTGACTCTCACTACTCA

204	ATGAGTAGTGAGAGTCAACCTGGAG	1468	CTCCAGGTTGACTCTCACTACTCAT
205	GATGAGTAGTGAGAGTCAACCTGGA	1469	TCCAGGTTGACTCTCACTACTCATC
206	TGATGAGTAGTGAGAGTCAACCTGG	1470	CCAGGTTGACTCTCACTACTCATCA
207	ATGATGAGTAGTGAGAGTCAACCTG	1471	CAGGTTGACTCTCACTACTCATCAT
208	GATGATGAGTAGTGAGAGTCAACCT	1472	AGGTTGACTCTCACTACTCATCATC
209	TGATGATGAGTAGTGAGAGTCAACC	1473	GGTTGACTCTCACTACTCATCATCA
210	CTGATGATGAGTAGTGAGAGTCAAC	1474	GTTGACTCTCACTACTCATCATCAG
211	CCTGATGATGAGTAGTGAGAGTCAA	1475	TTGACTCTCACTACTCATCATCAGG
212	ACCTGATGATGAGTAGTGAGAGTCA	1476	TGACTCTCACTACTCATCATCAGGT
213	AACCTGATGATGAGTAGTGAGAGTC	1477	GACTCTCACTACTCATCATCAGGTT
214	GAACCTGATGATGAGTAGTGAGAGT	1478	ACTCTCACTACTCATCATCAGGTTC
215	AGAACCTGATGATGAGTAGTGAGAG	1479	CTCTCACTACTCATCATCAGGTTCT
216	AAGAACCTGATGATGAGTAGTGAGA	1480	TCTCACTACTCATCATCAGGTTCTT
217	GAAGAACCTGATGATGAGTAGTGAG	1481	CTCACTACTCATCATCAGGTTCTTC
218	GGAAGAACCTGATGATGAGTAGTGA	1482	TCACTACTCATCATCAGGTTCTTCC
219	AGGAAGAACCTGATGATGAGTAGTG	1483	CACTACTCATCATCAGGTTCTTCCT
220	AAGGAAGAACCTGATGATGAGTAGT	1484	ACTACTCATCATCAGGTTCTTCCTT
221	GAAGGAAGAACCTGATGATGAGTAG	1485	CTACTCATCATCAGGTTCTTCCTTC
222	AGAAGGAAGAACCTGATGATGAGTA	1486	TACTCATCATCAGGTTCTTCCTTCT
223	TAGAAGGAAGAACCTGATGATGAGT	1487	ACTCATCATCAGGTTCTTCCTTCTA
224	ATAGAAGGAAGAACCTGATGATGAG	1488	CTCATCATCAGGTTCTTCCTTCTAT
225	AATAGAAGGAAGAACCTGATGATGA	1489	TCATCATCAGGTTCTTCCTTCTATT
226	GAATAGAAGGAAGAACCTGATGATG	1490	CATCATCAGGTTCTTCCTTCTATTC
227	GGAATAGAAGGAAGAACCTGATGAT	1491	ATCATCAGGTTCTTCCTTCTATTCC
228	TGGAATAGAAGGAAGAACCTGATGA	1492	TCATCAGGTTCTTCCTTCTATTCCA
229	CTGGAATAGAAGGAAGAACCTGATG	1493	CATCAGGTTCTTCCTTCTATTCCAG
230	GCTGGAATAGAAGGAAGAACCTGAT	1494	ATCAGGTTCTTCCTTCTATTCCAGC
231	GGCTGGAATAGAAGGAAGAACCTGA	1495	TCAGGTTCTTCCTTCTATTCCAGCC
232	GGGCTGGAATAGAAGGAAGAACCTG	1496	CAGGTTCTTCCTTCTATTCCAGCCC
233	AGGGCTGGAATAGAAGGAAGAACCT	1497	AGGTTCTTCCTTCTATTCCAGCCCT
234	TAGGGCTGGAATAGAAGGAAGAACC	1498	GGTTCTTCCTTCTATTCCAGCCCTA
235	TTAGGGCTGGAATAGAAGGAAGAAC	1499	GTTCTTCCTTCTATTCCAGCCCTAA
236	GTTAGGGCTGGAATAGAAGGAAGAA	1500	TTCTTCCTTCTATTCCAGCCCTAAC
237	GGTTAGGGCTGGAATAGAAGGAAGA	1501	TCTTCCTTCTATTCCAGCCCTAACC
238	TGGTTAGGGCTGGAATAGAAGGAAG	1502	CTTCCTTCTATTCCAGCCCTAACCA
239	GTGGTTAGGGCTGGAATAGAAGGAA	1503	TTCCTTCTATTCCAGCCCTAACCAC
240	AGTGGTTAGGGCTGGAATAGAAGGA	1504	TCCTTCTATTCCAGCCCTAACCACT
241	GAGTGGTTAGGGCTGGAATAGAAGG	1505	CCTTCTATTCCAGCCCTAACCACTC
242	TGAGTGGTTAGGGCTGGAATAGAAG	1506	CTTCTATTCCAGCCCTAACCACTCA
243	CTGAGTGGTTAGGGCTGGAATAGAA	1507	TTCTATTCCAGCCCTAACCACTCAG
244	CCTGAGTGGTTAGGGCTGGAATAGA	1508	TCTATTCCAGCCCTAACCACTCAGG
245	TCCTGAGTGGTTAGGGCTGGAATAG	1509	CTATTCCAGCCCTAACCACTCAGGA

246	ATCCTGAGTGGTTAGGGCTGGAATA	1510	TATTCCAGCCCTAACCACTCAGGAT
247	AATCCTGAGTGGTTAGGGCTGGAAT	1511	ATTCCAGCCCTAACCACTCAGGATT
248	CAATCCTGAGTGGTTAGGGCTGGAA	1512	TTCCAGCCCTAACCACTCAGGATTG
249	CCAATCCTGAGTGGTTAGGGCTGGA	1513	TCCAGCCCTAACCACTCAGGATTGG
250	CCCAATCCTGAGTGGTTAGGGCTGG	1514	CCAGCCCTAACCACTCAGGATTGGG
251	GCCCAATCCTGAGTGGTTAGGGCTG	1515	CAGCCCTAACCACTCAGGATTGGGC
252	GGCCCAATCCTGAGTGGTTAGGGCT	1516	AGCCCTAACCACTCAGGATTGGGCC
253	CGGCCCAATCCTGAGTGGTTAGGGC	1517	GCCCTAACCACTCAGGATTGGGCCG
254	ACGGCCCAATCCTGAGTGGTTAGGG	1518	CCCTAACCACTCAGGATTGGGCCGT
255	AACGGCCCAATCCTGAGTGGTTAGG	1519	CCTAACCACTCAGGATTGGGCCGTT
256	AAACGGCCCAATCCTGAGTGGTTAG	1520	CTAACCACTCAGGATTGGGCCGTTT
257	CAAACGGCCCAATCCTGAGTGGTTA	1521	TAACCACTCAGGATTGGGCCGTTTG
258	ACAAACGGCCCAATCCTGAGTGGTT	1522	AACCACTCAGGATTGGGCCGTTTGT
259	CACAAACGGCCCAATCCTGAGTGGT	1523	ACCACTCAGGATTGGGCCGTTTGTG
260	ACACAAACGGCCCAATCCTGAGTGG	1524	CCACTCAGGATTGGGCCGTTTGTGT
261	GACACAAACGGCCCAATCCTGAGTG	1525	CACTCAGGATTGGGCCGTTTGTGTC
262	AGACACAAACGGCCCAATCCTGAGT	1526	ACTCAGGATTGGGCCGTTTGTGTCT
263	CAGACACAAACGGCCCAATCCTGAG	1527	CTCAGGATTGGGCCGTTTGTGTCTG
264	CCAGACACAAACGGCCCAATCCTGA	1528	TCAGGATTGGGCCGTTTGTGTCTGG
265	CCCAGACACAAACGGCCCAATCCTG	1529	CAGGATTGGGCCGTTTGTGTCTGGG
266	ACCCAGACACAAACGGCCCAATCCT	1530	AGGATTGGGCCGTTTGTGTCTGGGT
267	TACCCAGACACAAACGGCCCAATCC	1531	GGATTGGGCCGTTTGTGTCTGGGTA
268	ATACCCAGACACAAACGGCCCAATC	1532	GATTGGGCCGTTTGTGTCTGGGTAT
269	CATACCCAGACACAAACGGCCCAAT	1533	ATTGGGCCGTTTGTGTCTGGGTATG
270	ACATACCCAGACACAAACGGCCCAA	1534	TTGGGCCGTTTGTGTCTGGGTATGT
271	GACATACCCAGACACAAACGGCCCA	1535	TGGGCCGTTTGTGTCTGGGTATGTC
272	AGACATACCCAGACACAAACGGCCC	1536	GGGCCGTTTGTGTCTGGGTATGTCT
273	GAGACATACCCAGACACAAACGGCC	1537	GGCCGTTTGTGTCTGGGTATGTCTC
274	AGAGACATACCCAGACACAAACGGC	1538	GCCGTTTGTGTCTGGGTATGTCTCT
275	AAGAGACATACCCAGACACAAACGG	1539	CCGTTTGTGTCTGGGTATGTCTCTT
276	GAAGAGACATACCCAGACACAAACG	1540	CGTTTGTGTCTGGGTATGTCTCTTC
277	GGAAGAGACATACCCAGACACAAAC	1541	GTTTGTGTCTGGGTATGTCTCTTCC
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279	CTGGAAGAGACATACCCAGACACAA	1543	TTGTGTCTGGGTATGTCTCTTCCAG
280	GCTGGAAGAGACATACCCAGACACA	1544	TGTGTCTGGGTATGTCTCTTCCAGC
281	AGCTGGAAGAGACATACCCAGACAC	1545	GTGTCTGGGTATGTCTCTTCCAGCT
282	CAGCTGGAAGAGACATACCCAGACA	1546	TGTCTGGGTATGTCTCTTCCAGCTG
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284	GGCAGCTGGAAGAGACATACCCAGA	1548	TCTGGGTATGTCTCTTCCAGCTGCC
285	AGGCAGCTGGAAGAGACATACCCAG	1549	CTGGGTATGTCTCTTCCAGCTGCCT
286	CAGGCAGCTGGAAGAGACATACCCA	1550	TGGGTATGTCTCTTCCAGCTGCCTG
287	CCAGGCAGCTGGAAGAGACATACCC	1551	GGGTATGTCTCTTCCAGCTGCCTGG

288	CCCAGGCAGCTGGAAGAGACATACC	1552	GGTATGTCTCTTCCAGCTGCCTGGG
289	ACCCAGGCAGCTGGAAGAGACATAC	1553	GTATGTCTCTTCCAGCTGCCTGGGT
290	AACCCAGGCAGCTGGAAGAGACATA	1554	TATGTCTCTTCCAGCTGCCTGGGTT
291	AAACCCAGGCAGCTGGAAGAGACAT	1555	ATGTCTCTTCCAGCTGCCTGGGTTT
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293	GGAAACCCAGGCAGCTGGAAGAGAC	1557	GTCTCTTCCAGCTGCCTGGGTTTCC
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295	CAGGAAACCCAGGCAGCTGGAAGAG	1559	CTCTTCCAGCTGCCTGGGTTTCCTG
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301	TCTTTCCAGGAAACCCAGGCAGCTG	1565	CAGCTGCCTGGGTTTCCTGGAAAGA
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303	GTTCTTTCCAGGAAACCCAGGCAGC	1567	GCTGCCTGGGTTTCCTGGAAAGAAC
304	AGTTCTTTCCAGGAAACCCAGGCAG	1568	CTGCCTGGGTTTCCTGGAAAGAACT
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306	AGAGTTCTTTCCAGGAAACCCAGGC	1570	GCCTGGGTTTCCTGGAAAGAACTCT
307	AAGAGTTCTTTCCAGGAAACCCAGG	1571	CCTGGGTTTCCTGGAAAGAACTCTT
308	TAAGAGTTCTTTCCAGGAAACCCAG	1572	CTGGGTTTCCTGGAAAGAACTCTTA
309	ATAAGAGTTCTTTCCAGGAAACCCA	1573	TGGGTTTCCTGGAAAGAACTCTTAT
310	GATAAGAGTTCTTTCCAGGAAACCC	1574	GGGTTTCCTGGAAAGAACTCTTATC
311	GGATAAGAGTTCTTTCCAGGAAACC	1575	GGTTTCCTGGAAAGAACTCTTATCC
312	GGGATAAGAGTTCTTTCCAGGAAAC	1576	GTTTCCTGGAAAGAACTCTTATCCC
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314	TGGGGATAAGAGTTCTTTCCAGGAA	1578	TTCCTGGAAAGAACTCTTATCCCCA
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320	AGTTCCTGGGGATAAGAGTTCTTTC	1584	GAAAGAACTCTTATCCCCAGGAACT
321	TAGTTCCTGGGGATAAGAGTTCTTT	1585	AAAGAACTCTTATCCCCAGGAACTA
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323	ACTAGTTCCTGGGGATAAGAGTTCT	1587	AGAACTCTTATCCCCAGGAACTAGT
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326	CAAACTAGTTCCTGGGGATAAGAGT	1590	ACTCTTATCCCCAGGAACTAGTTTG
327	ACAAACTAGTTCCTGGGGATAAGAG	1591	CTCTTATCCCCAGGAACTAGTTTGT
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336	ATTTATTCAACAAACTAGTTCCTGG	1600	CCAGGAACTAGTTTGTTGAATAAAT
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483	TCTGTCCATCCATCCATCATCCATC	1747	GATGGATGATGGATGGATGGACAGA
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487	TCCATCTGTCCATCCATCCATCATC	1751	GATGATGGATGGATGGACAGATGGA
488	ATCCATCTGTCCATCCATCCATCAT	1752	ATGATGGATGGATGGACAGATGGAT
489	CATCCATCTGTCCATCCATCCATCA	1753	TGATGGATGGATGGACAGATGGATG
490	CCATCCATCTGTCCATCCATCCATC	1754	GATGGATGGATGGACAGATGGATGG
491	TCCATCCATCTGTCCATCCATCCAT	1755	ATGGATGGATGGACAGATGGATGGA
492	ATCCATCCATCTGTCCATCCATCCA	1756	TGGATGGATGGACAGATGGATGGAT
493	TATCCATCCATCTGTCCATCCATCC	1757	GGATGGATGGACAGATGGATGGATA
494	ATATCCATCCATCTGTCCATCCATC	1758	GATGGATGGACAGATGGATGGATAT
495	TATATCCATCCATCTGTCCATCCAT	1759	ATGGATGGACAGATGGATGGATATA
496	ATATATCCATCCATCTGTCCATCCA	1760	TGGATGGACAGATGGATGGATATAT
497	CATATATCCATCCATCTGTCCATCC	1761	GGATGGACAGATGGATGGATATATG

498	TCATATATCCATCCATCTGTCCATC	1762	GATGGACAGATGGATGGATATATGA
499	ATCATATATCCATCCATCTGTCCAT	1763	ATGGACAGATGGATGGATATATGAT
500	AATCATATATCCATCCATCTGTCCA	1764	TGGACAGATGGATGGATATATGATT
501	CAATCATATATCCATCCATCTGTCC	1765	GGACAGATGGATGGATATATGATTG
502	TCAATCATATATCCATCCATCTGTC	1766	GACAGATGGATGGATATATGATTGA
503	TTCAATCATATATCCATCCATCTGT	1767	ACAGATGGATGGATATATGATTGAA
504	GTTCAATCATATATCCATCCATCTG	1768	CAGATGGATGGATATATGATTGAAC
505	AGTTCAATCATATATCCATCCATCT	1769	AGATGGATGGATATATGATTGAACT
506	TAGTTCAATCATATATCCATCCATC	1770	GATGGATGGATATATGATTGAACTA
507	ATAGTTCAATCATATATCCATCCAT	1771	ATGGATGGATATATGATTGAACTAT
508	AATAGTTCAATCATATATCCATCCA	1772	TGGATGGATATATGATTGAACTATT
509	CAATAGTTCAATCATATATCCATCC	1773	GGATGGATATATGATTGAACTATTG
510	TCAATAGTTCAATCATATATCCATC	1774	GATGGATATATGATTGAACTATTGA
511	TTCAATAGTTCAATCATATATCCAT	1775	ATGGATATATGATTGAACTATTGAA
512	TTTCAATAGTTCAATCATATATCCA	1776	TGGATATATGATTGAACTATTGAAA
513	CTTTCAATAGTTCAATCATATATCC	1777	GGATATATGATTGAACTATTGAAAG
514	ACTTTCAATAGTTCAATCATATATC	1778	GATATATGATTGAACTATTGAAAGT
515	TACTTTCAATAGTTCAATCATATAT	1779	ATATATGATTGAACTATTGAAAGTA
516	ATACTTTCAATAGTTCAATCATATA	1780	TATATGATTGAACTATTGAAAGTAT
517	TATACTTTCAATAGTTCAATCATAT	1781	ATATGATTGAACTATTGAAAGTATA
518	CTATACTTTCAATAGTTCAATCATA	1782	TATGATTGAACTATTGAAAGTATAG
519	TCTATACTTTCAATAGTTCAATCAT	1783	ATGATTGAACTATTGAAAGTATAGA
520	ATCTATACTTTCAATAGTTCAATCA	1784	TGATTGAACTATTGAAAGTATAGAT
521	CATCTATACTTTCAATAGTTCAATC	1785	GATTGAACTATTGAAAGTATAGATG
522	ACATCTATACTTTCAATAGTTCAAT	1786	ATTGAACTATTGAAAGTATAGATGT
523	TACATCTATACTTTCAATAGTTCAA	1787	TTGAACTATTGAAAGTATAGATGTA
524	ATACATCTATACTTTCAATAGTTCA	1788	TGAACTATTGAAAGTATAGATGTAT
525	CATACATCTATACTTTCAATAGTTC	1789	GAACTATTGAAAGTATAGATGTATG
526	CCATACATCTATACTTTCAATAGTT	1790	AACTATTGAAAGTATAGATGTATGG
527	TCCATACATCTATACTTTCAATAGT	1791	ACTATTGAAAGTATAGATGTATGGA
528	ATCCATACATCTATACTTTCAATAG	1792	CTATTGAAAGTATAGATGTATGGAT
529	CATCCATACATCTATACTTTCAATA	1793	TATTGAAAGTATAGATGTATGGATG
530	CCATCCATACATCTATACTTTCAAT	1794	ATTGAAAGTATAGATGTATGGATGG
531	CCCATCCATACATCTATACTTTCAA	1795	TTGAAAGTATAGATGTATGGATGGG
532	ACCCATCCATACATCTATACTTTCA	1796	TGAAAGTATAGATGTATGGATGGGT
533	CACCCATCCATACATCTATACTTTC	1797	GAAAGTATAGATGTATGGATGGGTG
534	TCACCCATCCATACATCTATACTTT	1798	AAAGTATAGATGTATGGATGGGTGA
535	TTCACCCATCCATACATCTATACTT	1799	AAGTATAGATGTATGGATGGGTGAA
536	ATTCACCCATCCATACATCTATACT	1800	AGTATAGATGTATGGATGGGTGAAT
537	AATTCACCCATCCATACATCTATAC	1801	GTATAGATGTATGGATGGGTGAATT
538	AAATTCACCCATCCATACATCTATA	1802	TATAGATGTATGGATGGGTGAATTT
539	CAAATTCACCCATCCATACATCTAT	1803	ATAGATGTATGGATGGGTGAATTTG

540	CCAAATTCACCCATCCATACATCTA	1804	TAGATGTATGGATGGGTGAATTTGG
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542	CCCCAAATTCACCCATCCATACATC	1806	GATGTATGGATGGGTGAATTTGGGG
543	CCCCCAAATTCACCCATCCATACAT	1807	ATGTATGGATGGGTGAATTTGGGGG
544	ACCCCCAAATTCACCCATCCATACA	1808	TGTATGGATGGGTGAATTTGGGGGT
545	TACCCCCAAATTCACCCATCCATAC	1809	GTATGGATGGGTGAATTTGGGGGTA
546	TTACCCCCAAATTCACCCATCCATA	1810	TATGGATGGGTGAATTTGGGGGTAA
547	ATTACCCCCAAATTCACCCATCCAT	1811	ATGGATGGGTGAATTTGGGGGTAAT
548	AATTACCCCCAAATTCACCCATCCA	1812	TGGATGGGTGAATTTGGGGGTAATT
549	CAATTACCCCCAAATTCACCCATCC	1813	GGATGGGTGAATTTGGGGGTAATTG
550	ACAATTACCCCCAAATTCACCCATC	1814	GATGGGTGAATTTGGGGGTAATTGT
551	AACAATTACCCCCAAATTCACCCAT	1815	ATGGGTGAATTTGGGGGTAATTGTT
552	TAACAATTACCCCCAAATTCACCCA	1816	TGGGTGAATTTGGGGGTAATTGTTA
553	CTAACAATTACCCCCAAATTCACCC	1817	GGGTGAATTTGGGGGTAATTGTTAG
554	TCTAACAATTACCCCCAAATTCACC	1818	GGTGAATTTGGGGGTAATTGTTAGA
555	ATCTAACAATTACCCCCAAATTCAC	1819	GTGAATTTGGGGGTAATTGTTAGAT
556	CATCTAACAATTACCCCCAAATTCA	1820	TGAATTTGGGGGTAATTGTTAGATG
557	TCATCTAACAATTACCCCCAAATTC	1821	GAATTTGGGGGTAATTGTTAGATGA
558	ATCATCTAACAATTACCCCCAAATT	1822	AATTTGGGGGTAATTGTTAGATGAT
559	CATCATCTAACAATTACCCCCAAAT	1823	ATTTGGGGGTAATTGTTAGATGATG
560	CCATCATCTAACAATTACCCCCAAA	1824	TTTGGGGGTAATTGTTAGATGATGG
561	TCCATCATCTAACAATTACCCCCAA	1825	TTGGGGGTAATTGTTAGATGATGGA
562	ATCCATCATCTAACAATTACCCCCA	1826	TGGGGGTAATTGTTAGATGATGGAT
563	CATCCATCATCTAACAATTACCCCC	1827	GGGGGTAATTGTTAGATGATGGATG
564	TCATCCATCATCTAACAATTACCCC	1828	GGGGTAATTGTTAGATGATGGATGA
565	CTCATCCATCATCTAACAATTACCC	1829	GGGTAATTGTTAGATGATGGATGAG
566	ACTCATCCATCATCTAACAATTACC	1830	GGTAATTGTTAGATGATGGATGAGT
567	TACTCATCCATCATCTAACAATTAC	1831	GTAATTGTTAGATGATGGATGAGTA
568	ATACTCATCCATCATCTAACAATTA	1832	TAATTGTTAGATGATGGATGAGTAT
569	TATACTCATCCATCATCTAACAATT	1833	AATTGTTAGATGATGGATGAGTATA
570	CTATACTCATCCATCATCTAACAAT	1834	ATTGTTAGATGATGGATGAGTATAG
571	TCTATACTCATCCATCATCTAACAA	1835	TTGTTAGATGATGGATGAGTATAGA
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576	ATTCATCTATACTCATCCATCATCT	1840	AGATGATGGATGAGTATAGATGAAT
577	CATTCATCTATACTCATCCATCATC	1841	GATGATGGATGAGTATAGATGAATG
578	TCATTCATCTATACTCATCCATCAT	1842	ATGATGGATGAGTATAGATGAATGA
579	ATCATTCATCTATACTCATCCATCA	1843	TGATGGATGAGTATAGATGAATGAT
580	CATCATTCATCTATACTCATCCATC	1844	GATGGATGAGTATAGATGAATGATG
581	CCATCATTCATCTATACTCATCCAT	1845	ATGGATGAGTATAGATGAATGATGG

582	TCCATCATTCATCTATACTCATCCA	1846	TGGATGAGTATAGATGAATGATGGA
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585	CCATCCATCATTCATCTATACTCAT	1849	ATGAGTATAGATGAATGATGGATGG
586	TCCATCCATCATTCATCTATACTCA	1850	TGAGTATAGATGAATGATGGATGGA
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588	TATCCATCCATCATTCATCTATACT	1852	AGTATAGATGAATGATGGATGGATA
589	TTATCCATCCATCATTCATCTATAC	1853	GTATAGATGAATGATGGATGGATAA
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592	AAGTTATCCATCCATCATTCATCTA	1856	TAGATGAATGATGGATGGATAACTT
593	CAAGTTATCCATCCATCATTCATCT	1857	AGATGAATGATGGATGGATAACTTG
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596	CATCAAGTTATCCATCCATCATTCA	1860	TGAATGATGGATGGATAACTTGATG
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598	CTCATCAAGTTATCCATCCATCATT	1862	AATGATGGATGGATAACTTGATGAG
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603	ATCCACTCATCAAGTTATCCATCCA	1867	TGGATGGATAACTTGATGAGTGGAT
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613	CAATCTATCTATCCACTCATCAAGT	1877	ACTTGATGAGTGGATAGATAGATTG
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615	AGCAATCTATCTATCCACTCATCAA	1879	TTGATGAGTGGATAGATAGATTGCT
616	CAGCAATCTATCTATCCACTCATCA	1880	TGATGAGTGGATAGATAGATTGCTG
617	CCAGCAATCTATCTATCCACTCATC	1881	GATGAGTGGATAGATAGATTGCTGG
618	TCCAGCAATCTATCTATCCACTCAT	1882	ATGAGTGGATAGATAGATTGCTGGA
619	ATCCAGCAATCTATCTATCCACTCA	1883	TGAGTGGATAGATAGATTGCTGGAT
620	TATCCAGCAATCTATCTATCCACTC	1884	GAGTGGATAGATAGATTGCTGGATA
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622	TCTATCCAGCAATCTATCTATCCAC	1886	GTGGATAGATAGATTGCTGGATAGA
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624	CATCTATCCAGCAATCTATCTATCC	1888	GGATAGATAGATTGCTGGATAGATG
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636	CACCCAGTCAATCATCTATCCAGCA	1900	TGCTGGATAGATGATTGACTGGGTG
637	CCACCCAGTCAATCATCTATCCAGC	1901	GCTGGATAGATGATTGACTGGGTGG
638	TCCACCCAGTCAATCATCTATCCAG	1902	CTGGATAGATGATTGACTGGGTGGA
639	ATCCACCCAGTCAATCATCTATCCA	1903	TGGATAGATGATTGACTGGGTGGAT
640	TATCCACCCAGTCAATCATCTATCC	1904	GGATAGATGATTGACTGGGTGGATA
641	CTATCCACCCAGTCAATCATCTATC	1905	GATAGATGATTGACTGGGTGGATAG
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643	ATCTATCCACCCAGTCAATCATCTA	1907	TAGATGATTGACTGGGTGGATAGAT
644	CATCTATCCACCCAGTCAATCATCT	1908	AGATGATTGACTGGGTGGATAGATG
645	TCATCTATCCACCCAGTCAATCATC	1909	GATGATTGACTGGGTGGATAGATGA
646	TTCATCTATCCACCCAGTCAATCAT	1910	ATGATTGACTGGGTGGATAGATGAA
647	TTTCATCTATCCACCCAGTCAATCA	1911	TGATTGACTGGGTGGATAGATGAAA
648	ATTTCATCTATCCACCCAGTCAATC	1912	GATTGACTGGGTGGATAGATGAAAT
649	CATTTCATCTATCCACCCAGTCAAT	1913	ATTGACTGGGTGGATAGATGAAATG
650	ACATTTCATCTATCCACCCAGTCAA	1914	TTGACTGGGTGGATAGATGAAATGT
651	AACATTTCATCTATCCACCCAGTCA	1915	TGACTGGGTGGATAGATGAAATGTT
652	CAACATTTCATCTATCCACCCAGTC	1916	GACTGGGTGGATAGATGAAATGTTG
653	CCAACATTTCATCTATCCACCCAGT	1917	ACTGGGTGGATAGATGAAATGTTGG
654	TCCAACATTTCATCTATCCACCCAG	1918	CTGGGTGGATAGATGAAATGTTGGA
655	ATCCAACATTTCATCTATCCACCCA	1919	TGGGTGGATAGATGAAATGTTGGAT
656	CATCCAACATTTCATCTATCCACCC	1920	GGGTGGATAGATGAAATGTTGGATG
657	TCATCCAACATTTCATCTATCCACC	1921	GGTGGATAGATGAAATGTTGGATGA
658	CTCATCCAACATTTCATCTATCCAC	1922	GTGGATAGATGAAATGTTGGATGAG
659	GCTCATCCAACATTTCATCTATCCA	1923	TGGATAGATGAAATGTTGGATGAGC
660	TGCTCATCCAACATTTCATCTATCC	1924	GGATAGATGAAATGTTGGATGAGCA
661	CTGCTCATCCAACATTTCATCTATC	1925	GATAGATGAAATGTTGGATGAGCAG
662	TCTGCTCATCCAACATTTCATCTAT	1926	ATAGATGAAATGTTGGATGAGCAGA
663	ATCTGCTCATCCAACATTTCATCTA	1927	TAGATGAAATGTTGGATGAGCAGAT
664	AATCTGCTCATCCAACATTTCATCT	1928	AGATGAAATGTTGGATGAGCAGATT
665	TAATCTGCTCATCCAACATTTCATC	1929	GATGAAATGTTGGATGAGCAGATTA

666	TTAATCTGCTCATCCAACATTTCAT	1930	ATGAAATGTTGGATGAGCAGATTAA
667	CTTAATCTGCTCATCCAACATTTCA	1931	TGAAATGTTGGATGAGCAGATTAAG
668	ACTTAATCTGCTCATCCAACATTTC	1932	GAAATGTTGGATGAGCAGATTAAGT
669	AACTTAATCTGCTCATCCAACATTT	1933	AAATGTTGGATGAGCAGATTAAGTT
670	CAACTTAATCTGCTCATCCAACATT	1934	AATGTTGGATGAGCAGATTAAGTTG
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672	TACAACTTAATCTGCTCATCCAACA	1936	TGTTGGATGAGCAGATTAAGTTGTA
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675	CAATACAACTTAATCTGCTCATCCA	1939	TGGATGAGCAGATTAAGTTGTATTG
676	CCAATACAACTTAATCTGCTCATCC	1940	GGATGAGCAGATTAAGTTGTATTGG
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692	CTTCCATCCATCCCATCCAATACAA	1956	TTGTATTGGATGGGATGGATGGAAG
693	ACTTCCATCCATCCCATCCAATACA	1957	TGTATTGGATGGGATGGATGGAAGT
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695	ACACTTCCATCCATCCCATCCAATA	1959	TATTGGATGGGATGGATGGAAGTGT
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697	CCACACTTCCATCCATCCCATCCAA	1961	TTGGATGGGATGGATGGAAGTGTGG
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699	AACCACACTTCCATCCATCCCATCC	1963	GGATGGGATGGATGGAAGTGTGGTT
700	CAACCACACTTCCATCCATCCCATC	1964	GATGGGATGGATGGAAGTGTGGTTG
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703	ACTCAACCACACTTCCATCCATCCC	1967	GGGATGGATGGAAGTGTGGTTGAGT
704	AACTCAACCACACTTCCATCCATCC	1968	GGATGGATGGAAGTGTGGTTGAGTT
705	TAACTCAACCACACTTCCATCCATC	1969	GATGGATGGAAGTGTGGTTGAGTTA
706	ATAACTCAACCACACTTCCATCCAT	1970	ATGGATGGAAGTGTGGTTGAGTTAT
707	AATAACTCAACCACACTTCCATCCA	1971	TGGATGGAAGTGTGGTTGAGTTATT

708	TAATAACTCAACCACACTTCCATCC	1972	GGATGGAAGTGTGGTTGAGTTATTA
709	CTAATAACTCAACCACACTTCCATC	1973	GATGGAAGTGTGGTTGAGTTATTAG
710	TCTAATAACTCAACCACACTTCCAT	1974	ATGGAAGTGTGGTTGAGTTATTAGA
711	TTCTAATAACTCAACCACACTTCCA	1975	TGGAAGTGTGGTTGAGTTATTAGAA
712	CTTCTAATAACTCAACCACACTTCC	1976	GGAAGTGTGGTTGAGTTATTAGAAG
713	CCTTCTAATAACTCAACCACACTTC	1977	GAAGTGTGGTTGAGTTATTAGAAGG
714	TCCTTCTAATAACTCAACCACACTT	1978	AAGTGTGGTTGAGTTATTAGAAGGA
715	TTCCTTCTAATAACTCAACCACACT	1979	AGTGTGGTTGAGTTATTAGAAGGAA
716	CTTCCTTCTAATAACTCAACCACAC	1980	GTGTGGTTGAGTTATTAGAAGGAAG
717	TCTTCCTTCTAATAACTCAACCACA	1981	TGTGGTTGAGTTATTAGAAGGAAGA
718	ATCTTCCTTCTAATAACTCAACCAC	1982	GTGGTTGAGTTATTAGAAGGAAGAT
719	AATCTTCCTTCTAATAACTCAACCA	1983	TGGTTGAGTTATTAGAAGGAAGATT
720	CAATCTTCCTTCTAATAACTCAACC	1984	GGTTGAGTTATTAGAAGGAAGATTG
721	TCAATCTTCCTTCTAATAACTCAAC	1985	GTTGAGTTATTAGAAGGAAGATTGA
722	CTCAATCTTCCTTCTAATAACTCAA	1986	TTGAGTTATTAGAAGGAAGATTGAG
723	ACTCAATCTTCCTTCTAATAACTCA	1987	TGAGTTATTAGAAGGAAGATTGAGT
724	TACTCAATCTTCCTTCTAATAACTC	1988	GAGTTATTAGAAGGAAGATTGAGTA
725	CTACTCAATCTTCCTTCTAATAACT	1989	AGTTATTAGAAGGAAGATTGAGTAG
726	TCTACTCAATCTTCCTTCTAATAAC	1990	GTTATTAGAAGGAAGATTGAGTAGA
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728	TATCTACTCAATCTTCCTTCTAATA	1992	TATTAGAAGGAAGATTGAGTAGATA
729	CTATCTACTCAATCTTCCTTCTAAT	1993	ATTAGAAGGAAGATTGAGTAGATAG
730	CCTATCTACTCAATCTTCCTTCTAA	1994	TTAGAAGGAAGATTGAGTAGATAGG
731	ACCTATCTACTCAATCTTCCTTCTA	1995	TAGAAGGAAGATTGAGTAGATAGGT
732	CACCTATCTACTCAATCTTCCTTCT	1996	AGAAGGAAGATTGAGTAGATAGGTG
733	TCACCTATCTACTCAATCTTCCTTC	1997	GAAGGAAGATTGAGTAGATAGGTGA
734	TTCACCTATCTACTCAATCTTCCTT	1998	AAGGAAGATTGAGTAGATAGGTGAA
735	ATTCACCTATCTACTCAATCTTCCT	1999	AGGAAGATTGAGTAGATAGGTGAAT
736	AATTCACCTATCTACTCAATCTTCC	2000	GGAAGATTGAGTAGATAGGTGAATT
737	AAATTCACCTATCTACTCAATCTTC	2001	GAAGATTGAGTAGATAGGTGAATTT
738	CAAATTCACCTATCTACTCAATCTT	2002	AAGATTGAGTAGATAGGTGAATTTG
739	ACAAATTCACCTATCTACTCAATCT	2003	AGATTGAGTAGATAGGTGAATTTGT
740	AACAAATTCACCTATCTACTCAATC	2004	GATTGAGTAGATAGGTGAATTTGTT
741	CAACAAATTCACCTATCTACTCAAT	2005	ATTGAGTAGATAGGTGAATTTGTTG
742	TCAACAAATTCACCTATCTACTCAA	2006	TTGAGTAGATAGGTGAATTTGTTGA
743	ATCAACAAATTCACCTATCTACTCA	2007	TGAGTAGATAGGTGAATTTGTTGAT
744	TATCAACAAATTCACCTATCTACTC	2008	GAGTAGATAGGTGAATTTGTTGATA
745	CTATCAACAAATTCACCTATCTACT	2009	AGTAGATAGGTGAATTTGTTGATAG
746	ACTATCAACAAATTCACCTATCTAC	2010	GTAGATAGGTGAATTTGTTGATAGT
747	GACTATCAACAAATTCACCTATCTA	2011	TAGATAGGTGAATTTGTTGATAGTC
748	TGACTATCAACAAATTCACCTATCT	2012	AGATAGGTGAATTTGTTGATAGTCA
749	CTGACTATCAACAAATTCACCTATC	2013	GATAGGTGAATTTGTTGATAGTCAG

750	TCTGACTATCAACAAATTCACCTAT	2014	ATAGGTGAATTTGTTGATAGTCAGA
751	ATCTGACTATCAACAAATTCACCTA	2015	TAGGTGAATTTGTTGATAGTCAGAT
752	CATCTGACTATCAACAAATTCACCT	2016	AGGTGAATTTGTTGATAGTCAGATG
753	CCATCTGACTATCAACAAATTCACC	2017	GGTGAATTTGTTGATAGTCAGATGG
754	CCCATCTGACTATCAACAAATTCAC	2018	GTGAATTTGTTGATAGTCAGATGGG
755	ACCCATCTGACTATCAACAAATTCA	2019	TGAATTTGTTGATAGTCAGATGGGT
756	TACCCATCTGACTATCAACAAATTC	2020	GAATTTGTTGATAGTCAGATGGGTA
757	CTACCCATCTGACTATCAACAAATT	2021	AATTTGTTGATAGTCAGATGGGTAG
758	TCTACCCATCTGACTATCAACAAAT	2022	ATTTGTTGATAGTCAGATGGGTAGA
759	ATCTACCCATCTGACTATCAACAAA	2023	TTTGTTGATAGTCAGATGGGTAGAT
760	TATCTACCCATCTGACTATCAACAA	2024	TTGTTGATAGTCAGATGGGTAGATA
761	CTATCTACCCATCTGACTATCAACA	2025	TGTTGATAGTCAGATGGGTAGATAG
762	CCTATCTACCCATCTGACTATCAAC	2026	GTTGATAGTCAGATGGGTAGATAGG
763	ACCTATCTACCCATCTGACTATCAA	2027	TTGATAGTCAGATGGGTAGATAGGT
764	TACCTATCTACCCATCTGACTATCA	2028	TGATAGTCAGATGGGTAGATAGGTA
765	CTACCTATCTACCCATCTGACTATC	2029	GATAGTCAGATGGGTAGATAGGTAG
766	TCTACCTATCTACCCATCTGACTAT	2030	ATAGTCAGATGGGTAGATAGGTAGA
767	ATCTACCTATCTACCCATCTGACTA	2031	TAGTCAGATGGGTAGATAGGTAGAT
768	CATCTACCTATCTACCCATCTGACT	2032	AGTCAGATGGGTAGATAGGTAGATG
769	CCATCTACCTATCTACCCATCTGAC	2033	GTCAGATGGGTAGATAGGTAGATGG
770	TCCATCTACCTATCTACCCATCTGA	2034	TCAGATGGGTAGATAGGTAGATGGA
771	ATCCATCTACCTATCTACCCATCTG	2035	CAGATGGGTAGATAGGTAGATGGAT
772	CATCCATCTACCTATCTACCCATCT	2036	AGATGGGTAGATAGGTAGATGGATG
773	CCATCCATCTACCTATCTACCCATC	2037	GATGGGTAGATAGGTAGATGGATGG
774	TCCATCCATCTACCTATCTACCCAT	2038	ATGGGTAGATAGGTAGATGGATGGA
775	ATCCATCCATCTACCTATCTACCCA	2039	TGGGTAGATAGGTAGATGGATGGAT
776	CATCCATCCATCTACCTATCTACCC	2040	GGGTAGATAGGTAGATGGATGGATG
777	CCATCCATCCATCTACCTATCTACC	2041	GGTAGATAGGTAGATGGATGGATGG
778	TCCATCCATCCATCTACCTATCTAC	2042	GTAGATAGGTAGATGGATGGATGGA
779	ATCCATCCATCCATCTACCTATCTA	2043	TAGATAGGTAGATGGATGGATGGAT
780	CATCCATCCATCCATCTACCTATCT	2044	AGATAGGTAGATGGATGGATGGATG
781	CCATCCATCCATCCATCTACCTATC	2045	GATAGGTAGATGGATGGATGGATGG
782	TCCATCCATCCATCCATCTACCTAT	2046	ATAGGTAGATGGATGGATGGATGGA
783	ATCCATCCATCCATCCATCTACCTA	2047	TAGGTAGATGGATGGATGGATGGAT
784	CATCCATCCATCCATCCATCTACCT	2048	AGGTAGATGGATGGATGGATGGATG
785	CCATCCATCCATCCATCCATCTACC	2049	GGTAGATGGATGGATGGATGGATGG
786	TCCATCCATCCATCCATCCATCTAC	2050	GTAGATGGATGGATGGATGGATGGA
787	ATCCATCCATCCATCCATCCATCTA	2051	TAGATGGATGGATGGATGGATGGAT
788	CATCCATCCATCCATCCATCCATCT	2052	AGATGGATGGATGGATGGATGGATG
789	ACATCCATCCATCCATCCATCCATC	2053	GATGGATGGATGGATGGATGGATGT
790	TACATCCATCCATCCATCCATCCAT	2054	ATGGATGGATGGATGGATGGATGTA
791	ATACATCCATCCATCCATCCATCCA	2055	TGGATGGATGGATGGATGGATGTAT

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

834	TCCATTCATCCACCCACCCATTCAT	2098	ATGAATGGGTGGGTGGATGAATGGA
835	TTCCATTCATCCACCCACCCATTCA	2099	TGAATGGGTGGGTGGATGAATGGAA
836	CTTCCATTCATCCACCCACCCATTC	2100	GAATGGGTGGGTGGATGAATGGAAG
837	CCTTCCATTCATCCACCCACCCATT	2101	AATGGGTGGGTGGATGAATGGAAGG
838	TCCTTCCATTCATCCACCCACCCAT	2102	ATGGGTGGGTGGATGAATGGAAGGA
839	ATCCTTCCATTCATCCACCCACCCA	2103	TGGGTGGGTGGATGAATGGAAGGAT
840	CATCCTTCCATTCATCCACCCACCC	2104	GGGTGGGTGGATGAATGGAAGGATG
841	ACATCCTTCCATTCATCCACCCACC	2105	GGTGGGTGGATGAATGGAAGGATGT
842	CACATCCTTCCATTCATCCACCCAC	2106	GTGGGTGGATGAATGGAAGGATGTG
843	ACACATCCTTCCATTCATCCACCCA	2107	TGGGTGGATGAATGGAAGGATGTGT
844	CACACATCCTTCCATTCATCCACCC	2108	GGGTGGATGAATGGAAGGATGTGTG
845	CCACACATCCTTCCATTCATCCACC	2109	GGTGGATGAATGGAAGGATGTGTGG
846	ACCACACATCCTTCCATTCATCCAC	2110	GTGGATGAATGGAAGGATGTGTGGT
847	AACCACACATCCTTCCATTCATCCA	2111	TGGATGAATGGAAGGATGTGTGGTT
848	CAACCACACATCCTTCCATTCATCC	2112	GGATGAATGGAAGGATGTGTGGTTG
849	TCAACCACACATCCTTCCATTCATC	2113	GATGAATGGAAGGATGTGTGGTTGA
850	TTCAACCACACATCCTTCCATTCAT	2114	ATGAATGGAAGGATGTGTGGTTGAA
851	GTTCAACCACACATCCTTCCATTCA	2115	TGAATGGAAGGATGTGTGGTTGAAC
852	AGTTCAACCACACATCCTTCCATTC	2116	GAATGGAAGGATGTGTGGTTGAACT
853	TAGTTCAACCACACATCCTTCCATT	2117	AATGGAAGGATGTGTGGTTGAACTA
854	ATAGTTCAACCACACATCCTTCCAT	2118	ATGGAAGGATGTGTGGTTGAACTAT
855	AATAGTTCAACCACACATCCTTCCA	2119	TGGAAGGATGTGTGGTTGAACTATT
856	CAATAGTTCAACCACACATCCTTCC	2120	GGAAGGATGTGTGGTTGAACTATTG
857	GCAATAGTTCAACCACACATCCTTC	2121	GAAGGATGTGTGGTTGAACTATTGC
858	TGCAATAGTTCAACCACACATCCTT	2122	AAGGATGTGTGGTTGAACTATTGCA
859	TTGCAATAGTTCAACCACACATCCT	2123	AGGATGTGTGGTTGAACTATTGCAA
860	CTTGCAATAGTTCAACCACACATCC	2124	GGATGTGTGGTTGAACTATTGCAAG
861	ACTTGCAATAGTTCAACCACACATC	2125	GATGTGTGGTTGAACTATTGCAAGT
862	TACTTGCAATAGTTCAACCACACAT	2126	ATGTGTGGTTGAACTATTGCAAGTA
863	ATACTTGCAATAGTTCAACCACACA	2127	TGTGTGGTTGAACTATTGCAAGTAT
864	AATACTTGCAATAGTTCAACCACAC	2128	GTGTGGTTGAACTATTGCAAGTATT
865	CAATACTTGCAATAGTTCAACCACA	2129	TGTGGTTGAACTATTGCAAGTATTG
866	TCAATACTTGCAATAGTTCAACCAC	2130	GTGGTTGAACTATTGCAAGTATTGA
867	ATCAATACTTGCAATAGTTCAACCA	2131	TGGTTGAACTATTGCAAGTATTGAT
868	TATCAATACTTGCAATAGTTCAACC	2132	GGTTGAACTATTGCAAGTATTGATA
869	TTATCAATACTTGCAATAGTTCAAC	2133	GTTGAACTATTGCAAGTATTGATAA
870	ATTATCAATACTTGCAATAGTTCAA	2134	TTGAACTATTGCAAGTATTGATAAT
871	AATTATCAATACTTGCAATAGTTCA	2135	TGAACTATTGCAAGTATTGATAATT
872	CAATTATCAATACTTGCAATAGTTC	2136	GAACTATTGCAAGTATTGATAATTG
873	CCAATTATCAATACTTGCAATAGTT	2137	AACTATTGCAAGTATTGATAATTGG
874	CCCAATTATCAATACTTGCAATAGT	2138	ACTATTGCAAGTATTGATAATTGGG
875	ACCCAATTATCAATACTTGCAATAG	2139	CTATTGCAAGTATTGATAATTGGGT

876	AACCCAATTATCAATACTTGCAATA	2140	TATTGCAAGTATTGATAATTGGGTT
877	GAACCCAATTATCAATACTTGCAAT	2141	ATTGCAAGTATTGATAATTGGGTTC
878	TGAACCCAATTATCAATACTTGCAA	2142	TTGCAAGTATTGATAATTGGGTTCA
879	ATGAACCCAATTATCAATACTTGCA	2143	TGCAAGTATTGATAATTGGGTTCAT
880	TATGAACCCAATTATCAATACTTGC	2144	GCAAGTATTGATAATTGGGTTCATA
881	TTATGAACCCAATTATCAATACTTG	2145	CAAGTATTGATAATTGGGTTCATAA
882	ATTATGAACCCAATTATCAATACTT	2146	AAGTATTGATAATTGGGTTCATAAT
883	AATTATGAACCCAATTATCAATACT	2147	AGTATTGATAATTGGGTTCATAATT
884	AAATTATGAACCCAATTATCAATAC	2148	GTATTGATAATTGGGTTCATAATTT
885	GAAATTATGAACCCAATTATCAATA	2149	TATTGATAATTGGGTTCATAATTTC
886	AGAAATTATGAACCCAATTATCAAT	2150	ATTGATAATTGGGTTCATAATTTCT
887	CAGAAATTATGAACCCAATTATCAA	2151	TTGATAATTGGGTTCATAATTTCTG
888	TCAGAAATTATGAACCCAATTATCA	2152	TGATAATTGGGTTCATAATTTCTGA
889	TTCAGAAATTATGAACCCAATTATC	2153	GATAATTGGGTTCATAATTTCTGAA
890	ATTCAGAAATTATGAACCCAATTAT	2154	ATAATTGGGTTCATAATTTCTGAAT
891	TATTCAGAAATTATGAACCCAATTA	2155	TAATTGGGTTCATAATTTCTGAATA
892	ATATTCAGAAATTATGAACCCAATT	2156	AATTGGGTTCATAATTTCTGAATAT
893	AATATTCAGAAATTATGAACCCAAT	2157	ATTGGGTTCATAATTTCTGAATATT
894	AAATATTCAGAAATTATGAACCCAA	2158	TTGGGTTCATAATTTCTGAATATTT
895	TAAATATTCAGAAATTATGAACCCA	2159	TGGGTTCATAATTTCTGAATATTTA
896	CTAAATATTCAGAAATTATGAACCC	2160	GGGTTCATAATTTCTGAATATTTAG
897	TCTAAATATTCAGAAATTATGAACC	2161	GGTTCATAATTTCTGAATATTTAGA
898	ATCTAAATATTCAGAAATTATGAAC	2162	GTTCATAATTTCTGAATATTTAGAT
899	CATCTAAATATTCAGAAATTATGAA	2163	TTCATAATTTCTGAATATTTAGATG
900	CCATCTAAATATTCAGAAATTATGA	2164	TCATAATTTCTGAATATTTAGATGG
901	TCCATCTAAATATTCAGAAATTATG	2165	CATAATTTCTGAATATTTAGATGGA
902	ATCCATCTAAATATTCAGAAATTAT	2166	ATAATTTCTGAATATTTAGATGGAT
903	CATCCATCTAAATATTCAGAAATTA	2167	TAATTTCTGAATATTTAGATGGATG
904	CCATCCATCTAAATATTCAGAAATT	2168	AATTTCTGAATATTTAGATGGATGG
905	ACCATCCATCTAAATATTCAGAAAT	2169	ATTTCTGAATATTTAGATGGATGGT
906	AACCATCCATCTAAATATTCAGAAA	2170	TTTCTGAATATTTAGATGGATGGTT
907	CAACCATCCATCTAAATATTCAGAA	2171	TTCTGAATATTTAGATGGATGGTTG
908	ACAACCATCCATCTAAATATTCAGA	2172	TCTGAATATTTAGATGGATGGTTGT
909	CACAACCATCCATCTAAATATTCAG	2173	CTGAATATTTAGATGGATGGTTGTG
910	TCACAACCATCCATCTAAATATTCA	2174	TGAATATTTAGATGGATGGTTGTGA
911	CTCACAACCATCCATCTAAATATTC	2175	GAATATTTAGATGGATGGTTGTGAG
912	ACTCACAACCATCCATCTAAATATT	2176	AATATTTAGATGGATGGTTGTGAGT
913	CACTCACAACCATCCATCTAAATAT	2177	ATATTTAGATGGATGGTTGTGAGTG
914	CCACTCACAACCATCCATCTAAATA	2178	TATTTAGATGGATGGTTGTGAGTGG
915	GCCACTCACAACCATCCATCTAAAT	2179	ATTTAGATGGATGGTTGTGAGTGGC
916	AGCCACTCACAACCATCCATCTAAA	2180	TTTAGATGGATGGTTGTGAGTGGCT
917	CAGCCACTCACAACCATCCATCTAA	2181	TTAGATGGATGGTTGTGAGTGGCTG

918	CCAGCCACTCACAACCATCCATCTA	2182	TAGATGGATGGTTGTGAGTGGCTGG
919	ACCAGCCACTCACAACCATCCATCT	2183	AGATGGATGGTTGTGAGTGGCTGGT
920	CACCAGCCACTCACAACCATCCATC	2184	GATGGATGGTTGTGAGTGGCTGGTG
921	CCACCAGCCACTCACAACCATCCAT	2185	ATGGATGGTTGTGAGTGGCTGGTGG
922	TCCACCAGCCACTCACAACCATCCA	2186	TGGATGGTTGTGAGTGGCTGGTGGA
923	GTCCACCAGCCACTCACAACCATCC	2187	GGATGGTTGTGAGTGGCTGGTGGAC
924	TGTCCACCAGCCACTCACAACCATC	2188	GATGGTTGTGAGTGGCTGGTGGACA
925	CTGTCCACCAGCCACTCACAACCAT	2189	ATGGTTGTGAGTGGCTGGTGGACAG
926	TCTGTCCACCAGCCACTCACAACCA	2190	TGGTTGTGAGTGGCTGGTGGACAGA
927	GTCTGTCCACCAGCCACTCACAACC	2191	GGTTGTGAGTGGCTGGTGGACAGAC
928	CGTCTGTCCACCAGCCACTCACAAC	2192	GTTGTGAGTGGCTGGTGGACAGACG
929	TCGTCTGTCCACCAGCCACTCACAA	2193	TTGTGAGTGGCTGGTGGACAGACGA
930	TTCGTCTGTCCACCAGCCACTCACA	2194	TGTGAGTGGCTGGTGGACAGACGAA
931	TTTCGTCTGTCCACCAGCCACTCAC	2195	GTGAGTGGCTGGTGGACAGACGAAA
932	TTTTCGTCTGTCCACCAGCCACTCA	2196	TGAGTGGCTGGTGGACAGACGAAAA
933	TTTTTCGTCTGTCCACCAGCCACTC	2197	GAGTGGCTGGTGGACAGACGAAAAA
934	ATTTTTCGTCTGTCCACCAGCCACT	2198	AGTGGCTGGTGGACAGACGAAAAAT
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936	CCATTTTTCGTCTGTCCACCAGCCA	2200	TGGCTGGTGGACAGACGAAAAATGG
937	TCCATTTTTCGTCTGTCCACCAGCC	2201	GGCTGGTGGACAGACGAAAAATGGA
938	ATCCATTTTTCGTCTGTCCACCAGC	2202	GCTGGTGGACAGACGAAAAATGGAT
939	CATCCATTTTTCGTCTGTCCACCAG	2203	CTGGTGGACAGACGAAAAATGGATG
940	CCATCCATTTTTCGTCTGTCCACCA	2204	TGGTGGACAGACGAAAAATGGATGG
941	ACCATCCATTTTTCGTCTGTCCACC	2205	GGTGGACAGACGAAAAATGGATGGT
942	AACCATCCATTTTTCGTCTGTCCAC	2206	GTGGACAGACGAAAAATGGATGGTT
943	CAACCATCCATTTTTCGTCTGTCCA	2207	TGGACAGACGAAAAATGGATGGTTG
944	CCAACCATCCATTTTTCGTCTGTCC	2208	GGACAGACGAAAAATGGATGGTTGG
945	TCCAACCATCCATTTTTCGTCTGTC	2209	GACAGACGAAAAATGGATGGTTGGA
946	ATCCAACCATCCATTTTTCGTCTGT	2210	ACAGACGAAAAATGGATGGTTGGAT
947	TATCCAACCATCCATTTTTCGTCTG	2211	CAGACGAAAAATGGATGGTTGGATA
948	TTATCCAACCATCCATTTTTCGTCT	2212	AGACGAAAAATGGATGGTTGGATAA
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953	TCAATTTATCCAACCATCCATTTTT	2217	AAAAATGGATGGTTGGATAAATTGA
954	ATCAATTTATCCAACCATCCATTTT	2218	AAAATGGATGGTTGGATAAATTGAT
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956	CCATCAATTTATCCAACCATCCATT	2220	AATGGATGGTTGGATAAATTGATGG
957	CCCATCAATTTATCCAACCATCCAT	2221	ATGGATGGTTGGATAAATTGATGGG
958	ACCCATCAATTTATCCAACCATCCA	2222	TGGATGGTTGGATAAATTGATGGGT
959	CACCCATCAATTTATCCAACCATCC	2223	GGATGGTTGGATAAATTGATGGGTG

960	CCACCCATCAATTTATCCAACCATC	2224	GATGGTTGGATAAATTGATGGGTGG
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962	ATCCACCCATCAATTTATCCAACCA	2226	TGGTTGGATAAATTGATGGGTGGAT
963	CATCCACCCATCAATTTATCCAACC	2227	GGTTGGATAAATTGATGGGTGGATG
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965	TCCATCCACCCATCAATTTATCCAA	2229	TTGGATAAATTGATGGGTGGATGGA
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967	CATCCATCCACCCATCAATTTATCC	2231	GGATAAATTGATGGGTGGATGGATG
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969	ACCATCCATCCACCCATCAATTTAT	2233	ATAAATTGATGGGTGGATGGATGGT
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974	AACCAACCATCCATCCACCCATCAA	2238	TTGATGGGTGGATGGATGGTTGGTT
975	CAACCAACCATCCATCCACCCATCA	2239	TGATGGGTGGATGGATGGTTGGTTG
976	ACAACCAACCATCCATCCACCCATC	2240	GATGGGTGGATGGATGGTTGGTTGT
977	TACAACCAACCATCCATCCACCCAT	2241	ATGGGTGGATGGATGGTTGGTTGTA
978	ATACAACCAACCATCCATCCACCCA	2242	TGGGTGGATGGATGGTTGGTTGTAT
979	CATACAACCAACCATCCATCCACCC	2243	GGGTGGATGGATGGTTGGTTGTATG
980	TCATACAACCAACCATCCATCCACC	2244	GGTGGATGGATGGTTGGTTGTATGA
981	TTCATACAACCAACCATCCATCCAC	2245	GTGGATGGATGGTTGGTTGTATGAA
982	TTTCATACAACCAACCATCCATCCA	2246	TGGATGGATGGTTGGTTGTATGAAA
983	CTTTCATACAACCAACCATCCATCC	2247	GGATGGATGGTTGGTTGTATGAAAG
984	TCTTTCATACAACCAACCATCCATC	2248	GATGGATGGTTGGTTGTATGAAAGA
985	TTCTTTCATACAACCAACCATCCAT	2249	ATGGATGGTTGGTTGTATGAAAGAA
986	ATTCTTTCATACAACCAACCATCCA	2250	TGGATGGTTGGTTGTATGAAAGAAT
987	CATTCTTTCATACAACCAACCATCC	2251	GGATGGTTGGTTGTATGAAAGAATG
988	TCATTCTTTCATACAACCAACCATC	2252	GATGGTTGGTTGTATGAAAGAATGA
989	TTCATTCTTTCATACAACCAACCAT	2253	ATGGTTGGTTGTATGAAAGAATGAA
990	ATTCATTCTTTCATACAACCAACCA	2254	TGGTTGGTTGTATGAAAGAATGAAT
991	CATTCATTCTTTCATACAACCAACC	2255	GGTTGGTTGTATGAAAGAATGAATG
992	TCATTCATTCTTTCATACAACCAAC	2256	GTTGGTTGTATGAAAGAATGAATGA
993	ATCATTCATTCTTTCATACAACCAA	2257	TTGGTTGTATGAAAGAATGAATGAT
994	AATCATTCATTCTTTCATACAACCA	2258	TGGTTGTATGAAAGAATGAATGATT
995	CAATCATTCATTCTTTCATACAACC	2259	GGTTGTATGAAAGAATGAATGATTG
996	CCAATCATTCATTCTTTCATACAAC	2260	GTTGTATGAAAGAATGAATGATTGG
997	CCCAATCATTCATTCTTTCATACAA	2261	TTGTATGAAAGAATGAATGATTGGG
998	ACCCAATCATTCATTCTTTCATACA	2262	TGTATGAAAGAATGAATGATTGGGT
999	TACCCAATCATTCATTCTTTCATAC	2263	GTATGAAAGAATGAATGATTGGGTA
1000	CTACCCAATCATTCATTCTTTCATA	2264	TATGAAAGAATGAATGATTGGGTAG
1001	CCTACCCAATCATTCATTCTTTCAT	2265	ATGAAAGAATGAATGATTGGGTAGG

1002	ACCTACCCAATCATTCATTCTTTCA	2266	TGAAAGAATGAATGATTGGGTAGGT
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1004	CCACCTACCCAATCATTCATTCTTT	2268	AAAGAATGAATGATTGGGTAGGTGG
1005	TCCACCTACCCAATCATTCATTCTT	2269	AAGAATGAATGATTGGGTAGGTGGA
1006	ATCCACCTACCCAATCATTCATTCT	2270	AGAATGAATGATTGGGTAGGTGGAT
1007	AATCCACCTACCCAATCATTCATTC	2271	GAATGAATGATTGGGTAGGTGGATT
1008	TAATCCACCTACCCAATCATTCATT	2272	AATGAATGATTGGGTAGGTGGATTA
1009	TTAATCCACCTACCCAATCATTCAT	2273	ATGAATGATTGGGTAGGTGGATTAA
1010	CTTAATCCACCTACCCAATCATTCA	2274	TGAATGATTGGGTAGGTGGATTAAG
1011	ACTTAATCCACCTACCCAATCATTC	2275	GAATGATTGGGTAGGTGGATTAAGT
1012	AACTTAATCCACCTACCCAATCATT	2276	AATGATTGGGTAGGTGGATTAAGTT
1013	CAACTTAATCCACCTACCCAATCAT	2277	ATGATTGGGTAGGTGGATTAAGTTG
1014	GCAACTTAATCCACCTACCCAATCA	2278	TGATTGGGTAGGTGGATTAAGTTGC
1015	CGCAACTTAATCCACCTACCCAATC	2279	GATTGGGTAGGTGGATTAAGTTGCG
1016	CCGCAACTTAATCCACCTACCCAAT	2280	ATTGGGTAGGTGGATTAAGTTGCGG
1017	TCCGCAACTTAATCCACCTACCCAA	2281	TTGGGTAGGTGGATTAAGTTGCGGA
1018	ATCCGCAACTTAATCCACCTACCCA	2282	TGGGTAGGTGGATTAAGTTGCGGAT
1019	GATCCGCAACTTAATCCACCTACCC	2283	GGGTAGGTGGATTAAGTTGCGGATC
1020	TGATCCGCAACTTAATCCACCTACC	2284	GGTAGGTGGATTAAGTTGCGGATCA
1021	TTGATCCGCAACTTAATCCACCTAC	2285	GTAGGTGGATTAAGTTGCGGATCAA
1022	ATTGATCCGCAACTTAATCCACCTA	2286	TAGGTGGATTAAGTTGCGGATCAAT
1023	CATTGATCCGCAACTTAATCCACCT	2287	AGGTGGATTAAGTTGCGGATCAATG
1024	ACATTGATCCGCAACTTAATCCACC	2288	GGTGGATTAAGTTGCGGATCAATGT
1025	TACATTGATCCGCAACTTAATCCAC	2289	GTGGATTAAGTTGCGGATCAATGTA
1026	ATACATTGATCCGCAACTTAATCCA	2290	TGGATTAAGTTGCGGATCAATGTAT
1027	CATACATTGATCCGCAACTTAATCC	2291	GGATTAAGTTGCGGATCAATGTATG
1028	CCATACATTGATCCGCAACTTAATC	2292	GATTAAGTTGCGGATCAATGTATGG
1029	CCCATACATTGATCCGCAACTTAAT	2293	ATTAAGTTGCGGATCAATGTATGGG
1030	TCCCATACATTGATCCGCAACTTAA	2294	TTAAGTTGCGGATCAATGTATGGGA
1031	ATCCCATACATTGATCCGCAACTTA	2295	TAAGTTGCGGATCAATGTATGGGAT
1032	CATCCCATACATTGATCCGCAACTT	2296	AAGTTGCGGATCAATGTATGGGATG
1033	CCATCCCATACATTGATCCGCAACT	2297	AGTTGCGGATCAATGTATGGGATGG
1034	TCCATCCCATACATTGATCCGCAAC	2298	GTTGCGGATCAATGTATGGGATGGA
1035	ATCCATCCCATACATTGATCCGCAA	2299	TTGCGGATCAATGTATGGGATGGAT
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1037	TCATCCATCCCATACATTGATCCGC	2301	GCGGATCAATGTATGGGATGGATGA
1038	TTCATCCATCCCATACATTGATCCG	2302	CGGATCAATGTATGGGATGGATGAA
1039	ATTCATCCATCCCATACATTGATCC	2303	GGATCAATGTATGGGATGGATGAAT
1040	CATTCATCCATCCCATACATTGATC	2304	GATCAATGTATGGGATGGATGAATG
1041	CCATTCATCCATCCCATACATTGAT	2305	ATCAATGTATGGGATGGATGAATGG
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1044	CATCCATTCATCCATCCCATACATT	2308	AATGTATGGGATGGATGAATGGATG
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1056	CATCCATCCATCCATCCATTCATCC	2320	GGATGAATGGATGGATGGATGGATG
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1063	AACCACACATCCATCCATCCATCCA	2327	TGGATGGATGGATGGATGTGTGGTT
1064	CAACCACACATCCATCCATCCATCC	2328	GGATGGATGGATGGATGTGTGGTTG
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1066	TTCAACCACACATCCATCCATCCAT	2330	ATGGATGGATGGATGTGTGGTTGAA
1067	ATTCAACCACACATCCATCCATCCA	2331	TGGATGGATGGATGTGTGGTTGAAT
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1070	GTAATTCAACCACACATCCATCCAT	2334	ATGGATGGATGTGTGGTTGAATTAC
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1074	TTCAGTAATTCAACCACACATCCAT	2338	ATGGATGTGTGGTTGAATTACTGAA
1075	TTTCAGTAATTCAACCACACATCCA	2339	TGGATGTGTGGTTGAATTACTGAAA
1076	CTTTCAGTAATTCAACCACACATCC	2340	GGATGTGTGGTTGAATTACTGAAAG
1077	CCTTTCAGTAATTCAACCACACATC	2341	GATGTGTGGTTGAATTACTGAAAGG
1078	ACCTTTCAGTAATTCAACCACACAT	2342	ATGTGTGGTTGAATTACTGAAAGGT
1079	AACCTTTCAGTAATTCAACCACACA	2343	TGTGTGGTTGAATTACTGAAAGGTT
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1082	TCCAACCTTTCAGTAATTCAACCAC	2346	GTGGTTGAATTACTGAAAGGTTGGA
1083	TTCCAACCTTTCAGTAATTCAACCA	2347	TGGTTGAATTACTGAAAGGTTGGAA
1084	CTTCCAACCTTTCAGTAATTCAACC	2348	GGTTGAATTACTGAAAGGTTGGAAG
1085	TCTTCCAACCTTTCAGTAATTCAAC	2349	GTTGAATTACTGAAAGGTTGGAAGA

1086	CTCTTCCAACCTTTCAGTAATTCAA	2350	TTGAATTACTGAAAGGTTGGAAGAG
1087	ACTCTTCCAACCTTTCAGTAATTCA	2351	TGAATTACTGAAAGGTTGGAAGAGT
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1092	CATCCACTCTTCCAACCTTTCAGTA	2356	TACTGAAAGGTTGGAAGAGTGGATG
1093	CCATCCACTCTTCCAACCTTTCAGT	2357	ACTGAAAGGTTGGAAGAGTGGATGG
1094	CCCATCCACTCTTCCAACCTTTCAG	2358	CTGAAAGGTTGGAAGAGTGGATGGG
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1102	AAATTTCACCCATCCACTCTTCCAA	2366	TTGGAAGAGTGGATGGGTGAAATTT
1103	CAAATTTCACCCATCCACTCTTCCA	2367	TGGAAGAGTGGATGGGTGAAATTTG
1104	CCAAATTTCACCCATCCACTCTTCC	2368	GGAAGAGTGGATGGGTGAAATTTGG
1105	CCCAAATTTCACCCATCCACTCTTC	2369	GAAGAGTGGATGGGTGAAATTTGGG
1106	CCCCAAATTTCACCCATCCACTCTT	2370	AAGAGTGGATGGGTGAAATTTGGGG
1107	ACCCCAAATTTCACCCATCCACTCT	2371	AGAGTGGATGGGTGAAATTTGGGGT
1108	TACCCCAAATTTCACCCATCCACTC	2372	GAGTGGATGGGTGAAATTTGGGGTA
1109	CTACCCCAAATTTCACCCATCCACT	2373	AGTGGATGGGTGAAATTTGGGGTAG
1110	ACTACCCCAAATTTCACCCATCCAC	2374	GTGGATGGGTGAAATTTGGGGTAGT
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1112	TAACTACCCCAAATTTCACCCATCC	2376	GGATGGGTGAAATTTGGGGTAGTTA
1113	CTAACTACCCCAAATTTCACCCATC	2377	GATGGGTGAAATTTGGGGTAGTTAG
1114	TCTAACTACCCCAAATTTCACCCAT	2378	ATGGGTGAAATTTGGGGTAGTTAGA
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1116	CATCTAACTACCCCAAATTTCACCC	2380	GGGTGAAATTTGGGGTAGTTAGATG
1117	CCATCTAACTACCCCAAATTTCACC	2381	GGTGAAATTTGGGGTAGTTAGATGG
1118	CCCATCTAACTACCCCAAATTTCAC	2382	GTGAAATTTGGGGTAGTTAGATGGG
1119	ACCCATCTAACTACCCCAAATTTCA	2383	TGAAATTTGGGGTAGTTAGATGGGT
1120	CACCCATCTAACTACCCCAAATTTC	2384	GAAATTTGGGGTAGTTAGATGGGTG
1121	CCACCCATCTAACTACCCCAAATTT	2385	AAATTTGGGGTAGTTAGATGGGTGG
1122	CCCACCCATCTAACTACCCCAAATT	2386	AATTTGGGGTAGTTAGATGGGTGGG
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1126	CACACCCACCCATCTAACTACCCCA	2390	TGGGGTAGTTAGATGGGTGGGTGTG
1127	ACACACCCACCCATCTAACTACCCC	2391	GGGGTAGTTAGATGGGTGGGTGTGT

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1130	TCCACACACCCACCCATCTAACTAC	2394	GTAGTTAGATGGGTGGGTGTGTGGA
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1152	CATTCATCTACTCTTTTATCCATCC	2416	GGATGGATAAAAGAGTAGATGAATG
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1158	TTAATTCATTCATCTACTCTTTTAT	2422	ATAAAAGAGTAGATGAATGAATTAA
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1167	GTTTATTCATTAATTCATTCATCTA	2431	TAGATGAATGAATTAATGAATAAAC
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1243	TGTCATGGAGAGTGCAAGGGGTCGC	2507	GCGACCCCTTGCACTCTCCATGACA
1244	GTGTCATGGAGAGTGCAAGGGGTCG	2508	CGACCCCTTGCACTCTCCATGACAC
1245	AGTGTCATGGAGAGTGCAAGGGGTC	2509	GACCCCTTGCACTCTCCATGACACT
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1251	AGAGAAAGTGTCATGGAGAGTGCAA	2515	TTGCACTCTCCATGACACTTTCTCT
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1253	GGAGAGAAAGTGTCATGGAGAGTGC	2517	GCACTCTCCATGACACTTTCTCTCC

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1256	ATGGGAGAGAAAGTGTCATGGAGAG	2520	CTCTCCATGACACTTTCTCTCCCAT
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1263	TGCCACCATGGGAGAGAAAGTGTCA	2527	TGACACTTTCTCTCCCATGGTGGCA
1264	CTGCCACCATGGGAGAGAAAGTGTC	2528	GACACTTTCTCTCCCATGGTGGCAG

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

UNC13A Transcript

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

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GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
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ATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCAGGTCATCATGGCAGACAGTGAGATCTGTGG
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ACAAGCCCTCAGCCCCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAGGGAAGCTCTCAG
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ACTCCTACCACTCCTGCCACAGCTCGGTCAGCTACCACAAAGACTCGCCTCGCTGGGACCAGGATGAGGA
AGAGCTGGAGGAGGACCTGGAGGACTTCCTGGAGGAGGAGGAGCTGCCTGAAGATGAGGAGGAGCTGGAG
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GAGGAGGAGGAGGAGGTGCCTGACGATTTGGGCAGCTATGCCCAGCGTGAAGACGTAGCTGTGGCTGAGC
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ATATTTTATTAACAGCAGACATTAAAAAAAGAAAAACCACACACA

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

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

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
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CACAAAAGAGAATTTGGGATCCCCTGGTCCCAGGTTTCTCCATCCCTTCTTCCTTTTCCAGAATTTTCCA
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AGAGAGAAACACAAACACAGTGACACAGTGAGAGCTTAGTCTCCAAGAGCCTATTCATTGATTCAAACAC
CCAAGCCACAGGATACCTCAGATGGCCCTCTTGCCAGCTGGAAGCTCTTTCTCCAATGAGCAAAGTTACA
GTGACCTGGCTGGAGTTACCTGGTGCACATAGGACCTTAGGGGAAAGTTCAGCGTGGACTACACTTGCTC
TGGGATCTGCTTTTCCACATGTGTGTATGGCACGCCTTTTTCTGCTGGATTGGGAAGGACAAGATTTTGC
TGTGCTAGGGAGAAATGAAAACGGGGTGAGCTGAGTAGCTGGGTTTCTGGAGGATAGAACATCAGATGGG
GAGGCTTTCCGAGGTGAAGAATGAGAGGGAACCACTTACTAGAGAGAAAAGAGCTCCAGGCCTGGGGAAC
AGCACGTGCGAAGGCCAGGAGAGAAGAACTGTTGAAACAACGAGAAGGGTGGCACGGCTGGAGCTGAGCC
AGCAAGGGGGATCGTGAGGAGCCTTGGGGTTGGGGAGATCTGCAGAAGCATCAGACCAGGCAGGGCCTCG
TACGCAGTCCTGAGGAGTTTTACTTTTATTCTAAGACAGTTGGGGAGCTCCAGGAGCTGTTTTAAGTTGG
GGAGAGACTGGATTCCAGCCTGCAAAAGCTGTTTTGTGAAGACTAAAACCAGTGAGGAGAGGTGGAGGTG
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ACCAGCCTGGCCAACATGGCGAAACCCCATCTCTGCTAAAAATACAAAAATTAGCTGGGTGCAGTGGTGC
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CCCACCAAAAAAAAAAAAAAAATCCTGCCCTTAGATGAGCTCTAGGGCTGCTGAGTACAGTTGTCCCAGTT
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TTGTGACGTTGGTTTCCCGACATGTGAATGGCCCAAGTGTCTGGAAGAAGTGGCGCCACTTTCTAATTTG
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AATGCAAATTCTCATACAGGGTTGGGAAGTTGTAGCCAGGGATAAGCTTATGTGACTGTTATATGGACTG
AGGAGCAGATGTGAATTTCGAACCATGACATGGCTGAGGGTAGGGGTCGGGTGGATGGATGATTCAGGGT
TGTAACCCATAGAGCCCAAAGGGGAAGTGATCTGTGACCTGGGGTGAGGGTGATCTGGAAGATTTTTGGA
TGGCTGGAAAGAAATGGGGAAGTCGAGCTGCCTGAGAGAGCCAAGTTATTTCCCAAAAGATTCCTTAGGA
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TGCAATTTCCACCCTCTTTTCTTTCCCCCAGAGAACTCCTATTCGTCCTTCAAAACCCATCACGGAAACC
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GGGCCTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCCTAAGAATCGTTGAGGACCAAA
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TGCACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGGT
CATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAA
CAGCAGACATTAAAAAAAGAAAAACCACACACA

(**SEQ ID NO: 5058** (SOURCE NCBI Reference Sequence NM_001387021.1)).

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

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
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ATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCAGGTCATCATGGCAGACAGTGAGATCTGTGG
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GGAACTGGGGAACACAAGGTCACAGTGAAAGTGGTGGCTGCCAATGACCTCAAGTGGCAGACTTCTGGCA
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CACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAGGTGGAAATATACAGAGAAAGA
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ACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGGTCAT

GAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAACAG
CAGACATTAAAAAAAGAAAAACCACACACA

(**SEQ ID NO: 5059** (SOURCE NCBI Reference Sequence NM_001387022.1)).

[00175] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 5060.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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(SEQ ID NO: 5060 (SOURCE NCBI Reference Sequence NM_001387023.1)).

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

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ACACAGCCTTGGA

(SEQ ID NO: 5061 (SOURCE NCBI Reference Sequence XM_011527810.2)).

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

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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AGCAGACATTAAAAAAAGAAAAACCACACACAGCCTTGGA

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

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

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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(SEQ ID NO: 5063 (SOURCE NCBI Reference Sequence XM_011527811.2)).

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

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ATGTAACCCCTTTGTTCTGGACAGGTAGAAGGAGAGGAGAATGGTCATCCAGGCCTAATGTAAAGTTTCT
GCAACCC

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

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

UNC13A Transcript with a Cryptic Exon

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

TTCTGCCACCATGGGAGAGAAAGTGTCATGGAGAGTGCAAGGGGTCGCCG
GGGGTCAGAGGTCCCAGGGTCTGGGGCAGCTTACATCATCCATCTGCCTG
TTTATTCATTAATTCATTCATCTACTCTTTTATCCATCCACACACCCACC
CATCTAACTACCCCAAATTTCACCCATCCACTCTTCCAACCTTTCAGTAA
TTCAACCACACATCCATCCATCCATCCATTCATCCATCCCATACATTGAT
CCGCAACTTAATCCACCTACCCAATCATTCATTCTTTCATACAACCAACC
ATCCATCCACCCATCAATTTATCCAACCATCCATTTTTCGTCTGTCCACC
AGCCACTCACAACCATCCATCTAAATATTCAGAAATTATGAACCCAATTA
TCAATACTTGCAATAGTTCAACCACACATCCTTCCATTCATCCACCCACC
CATTCATCCATTTGTCCATCTGCCTATCATCCATCCATCCATCCATCCA
TCTACCTATCTACCCATCTGACTATCAACAAATTCACCTATCTACTCAAT
CTTCCTTCTAATAACTCAACCACACTTCCATCCATCCCATCCAATACAAC
TTAATCTGCTCATCCAACATTTCATCTATCCACCCAGTCAATCATCTATC
CAGCAATCTATCTATCCACTCATCAAGTTATCCATCCATCATTCATCTAT
ACTCATCCATCATCTAACAATTACCCCCAAATTCACCCATCCATACATCT
ATACTTTCAATAGTTCAATCATATATCCATCCATCTGTCCATCCATCCAT
CATCCATCTAGCCACGAATCTACCCACCAACTCATCCATCTATCCATCCA
TGTACTCACCCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTC
ATCTGTTCAATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTT
CCTGGGGATAAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACAT

ACCCAGACACAAACGGCCCAATCCTGAGTGGTTAGGGCTGGAATAGAAGG
AAGAACCTGATGATGAGTAGTGAGAGTCAACCTGGAGGCCAAGGTGGGCT
TCCCAGAGGAGGTGACCCTGAATCTGGACTTTGATGGATAGGGAGGAGTT
TTCCAGGTAAAGGGAATGGCATGGCGGGCAGTCTCAGAGGGCCAGGAGAG
TGTGGATGGTGTGGCCAGAAAGAGGAAGAGCTGGGCAGGCAGGAATGGTG
AGTGGAAGTGGCATGGGAGGGGCCGAGCAATGACCCTCAC
(SEQ ID NO: 5206) where underlined = TDP-43 binding site.

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

CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCATCTGTTCA
ATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTTCCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACATACCCAGACA
CAAACGGCCCAATCCTGAGTGGTTAGGG
(SEQ ID NO: 5207).

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

CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCATCTGTTCA
ATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTTCCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAG
(SEQ ID NO: 5208).

UNC13A Oligonucleotides Targeting Regions of the UNC13A Transcript

[00184] In various embodiments, UNC13A AON disclosed herein are complementary to specific regions of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is complementary to a specific region of the UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is at least 85% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 99% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 95% complementary to a specific region of the UNC13A transcript. In some embodiments, a

UNC13A AON comprises a sequence that is 95 to 99% complementary to a specific region of the UNC13A transcript.

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

UNC13A Oligonucleotide Variants

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

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

parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where two oligonucleotide units were removed from one of the 3' or 5' end of a 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where two oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where four oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and three oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where three oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where five oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where three oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and four oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where four oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where six oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00188] In one embodiment, the corresponding UNC13A AON variant may include a 18mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the

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

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

[00190] In one embodiment, the corresponding UNC13A AON variant may include a 16mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and seven oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 16mer where seven oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may

include a 16mer where nine oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00191] In one embodiment, the corresponding UNC13A AON variant may include a 15mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and eight oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where eight oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where ten oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. Example sequences of UNC13A AON variants are shown below in Table 2A and Table 2B.

Table 2A. Example UNC13A Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
2529	GGAGGGGCCGAGCAATGACCCTC	3793	GAGGGTCATTGCTCGGCCCCTCC
2530	GGGAGGGGCCGAGCAATGACCCT	3794	AGGGTCATTGCTCGGCCCCTCCC
2531	TGGGAGGGGCCGAGCAATGACCC	3795	GGGTCATTGCTCGGCCCCTCCCA
2532	ATGGGAGGGGCCGAGCAATGACC	3796	GGTCATTGCTCGGCCCCTCCCAT
2533	CATGGGAGGGGCCGAGCAATGAC	3797	GTCATTGCTCGGCCCCTCCCATG
2534	GCATGGGAGGGGCCGAGCAATGA	3798	TCATTGCTCGGCCCCTCCCATGC
2535	GGCATGGGAGGGGCCGAGCAATG	3799	CATTGCTCGGCCCCTCCCATGCC
2536	TGGCATGGGAGGGGCCGAGCAAT	3800	ATTGCTCGGCCCCTCCCATGCCA
2537	GTGGCATGGGAGGGGCCGAGCAA	3801	TTGCTCGGCCCCTCCCATGCCAC
2538	AGTGGCATGGGAGGGGCCGAGCA	3802	TGCTCGGCCCCTCCCATGCCACT
2539	AAGTGGCATGGGAGGGGCCGAGC	3803	GCTCGGCCCCTCCCATGCCACTT
2540	GAAGTGGCATGGGAGGGGCCGAG	3804	CTCGGCCCCTCCCATGCCACTTC
2541	GGAAGTGGCATGGGAGGGGCCGA	3805	TCGGCCCCTCCCATGCCACTTCC
2542	TGGAAGTGGCATGGGAGGGGCCG	3806	CGGCCCCTCCCATGCCACTTCCA
2543	GTGGAAGTGGCATGGGAGGGGCC	3807	GGCCCCTCCCATGCCACTTCCAC
2544	AGTGGAAGTGGCATGGGAGGGGC	3808	GCCCCTCCCATGCCACTTCCACT
2545	GAGTGGAAGTGGCATGGGAGGGG	3809	CCCCTCCCATGCCACTTCCACTC
2546	TGAGTGGAAGTGGCATGGGAGGG	3810	CCCTCCCATGCCACTTCCACTCA
2547	GTGAGTGGAAGTGGCATGGGAGG	3811	CCTCCCATGCCACTTCCACTCAC
2548	GGTGAGTGGAAGTGGCATGGGAG	3812	CTCCCATGCCACTTCCACTCACC

2549	TGGTGAGTGGAAGTGGCATGGGA	3813	TCCCATGCCACTTCCACTCACCA
2550	ATGGTGAGTGGAAGTGGCATGGG	3814	CCCATGCCACTTCCACTCACCAT
2551	AATGGTGAGTGGAAGTGGCATGG	3815	CCATGCCACTTCCACTCACCATT
2552	GAATGGTGAGTGGAAGTGGCATG	3816	CATGCCACTTCCACTCACCATTC
2553	GGAATGGTGAGTGGAAGTGGCAT	3817	ATGCCACTTCCACTCACCATTCC
2554	AGGAATGGTGAGTGGAAGTGGCA	3818	TGCCACTTCCACTCACCATTCCT
2555	CAGGAATGGTGAGTGGAAGTGGC	3819	GCCACTTCCACTCACCATTCCTG
2556	GCAGGAATGGTGAGTGGAAGTGG	3820	CCACTTCCACTCACCATTCCTGC
2557	GGCAGGAATGGTGAGTGGAAGTG	3821	CACTTCCACTCACCATTCCTGCC
2558	AGGCAGGAATGGTGAGTGGAAGT	3822	ACTTCCACTCACCATTCCTGCCT
2559	CAGGCAGGAATGGTGAGTGGAAG	3823	CTTCCACTCACCATTCCTGCCTG
2560	GCAGGCAGGAATGGTGAGTGGAA	3824	TTCCACTCACCATTCCTGCCTGC
2561	GGCAGGCAGGAATGGTGAGTGGA	3825	TCCACTCACCATTCCTGCCTGCC
2562	GGGCAGGCAGGAATGGTGAGTGG	3826	CCACTCACCATTCCTGCCTGCCC
2563	TGGGCAGGCAGGAATGGTGAGTG	3827	CACTCACCATTCCTGCCTGCCCA
2564	CTGGGCAGGCAGGAATGGTGAGT	3828	ACTCACCATTCCTGCCTGCCCAG
2565	GCTGGGCAGGCAGGAATGGTGAG	3829	CTCACCATTCCTGCCTGCCCAGC
2566	AGCTGGGCAGGCAGGAATGGTGA	3830	TCACCATTCCTGCCTGCCCAGCT
2567	GAGCTGGGCAGGCAGGAATGGTG	3831	CACCATTCCTGCCTGCCCAGCTC
2568	AGAGCTGGGCAGGCAGGAATGGT	3832	ACCATTCCTGCCTGCCCAGCTCT
2569	AAGAGCTGGGCAGGCAGGAATGG	3833	CCATTCCTGCCTGCCCAGCTCTT
2570	GAAGAGCTGGGCAGGCAGGAATG	3834	CATTCCTGCCTGCCCAGCTCTTC
2571	GGAAGAGCTGGGCAGGCAGGAAT	3835	ATTCCTGCCTGCCCAGCTCTTCC
2572	AGGAAGAGCTGGGCAGGCAGGAA	3836	TTCCTGCCTGCCCAGCTCTTCCT
2573	GAGGAAGAGCTGGGCAGGCAGGA	3837	TCCTGCCTGCCCAGCTCTTCCTC
2574	AGAGGAAGAGCTGGGCAGGCAGG	3838	CCTGCCTGCCCAGCTCTTCCTCT
2575	AAGAGGAAGAGCTGGGCAGGCAG	3839	CTGCCTGCCCAGCTCTTCCTCTT
2576	AAAGAGGAAGAGCTGGGCAGGCA	3840	TGCCTGCCCAGCTCTTCCTCTTT
2577	GAAAGAGGAAGAGCTGGGCAGGC	3841	GCCTGCCCAGCTCTTCCTCTTTC
2578	AGAAAGAGGAAGAGCTGGGCAGG	3842	CCTGCCCAGCTCTTCCTCTTTCT
2579	CAGAAAGAGGAAGAGCTGGGCAG	3843	CTGCCCAGCTCTTCCTCTTTCTG
2580	CCAGAAAGAGGAAGAGCTGGGCA	3844	TGCCCAGCTCTTCCTCTTTCTGG
2581	GCCAGAAAGAGGAAGAGCTGGGC	3845	GCCCAGCTCTTCCTCTTTCTGGC
2582	GGCCAGAAAGAGGAAGAGCTGGG	3846	CCCAGCTCTTCCTCTTTCTGGCC
2583	TGGCCAGAAAGAGGAAGAGCTGG	3847	CCAGCTCTTCCTCTTTCTGGCCA
2584	GTGGCCAGAAAGAGGAAGAGCTG	3848	CAGCTCTTCCTCTTTCTGGCCAC
2585	TGTGGCCAGAAAGAGGAAGAGCT	3849	AGCTCTTCCTCTTTCTGGCCACA
2586	GTGTGGCCAGAAAGAGGAAGAGC	3850	GCTCTTCCTCTTTCTGGCCACAC
2587	GGTGTGGCCAGAAAGAGGAAGAG	3851	CTCTTCCTCTTTCTGGCCACACC
2588	TGGTGTGGCCAGAAAGAGGAAGA	3852	TCTTCCTCTTTCTGGCCACACCA
2589	ATGGTGTGGCCAGAAAGAGGAAG	3853	CTTCCTCTTTCTGGCCACACCAT
2590	GATGGTGTGGCCAGAAAGAGGAA	3854	TTCCTCTTTCTGGCCACACCATC

2591	GGATGGTGTGGCCAGAAAGAGGA	3855	TCCTCTTTCTGGCCACACCATCC
2592	TGGATGGTGTGGCCAGAAAGAGG	3856	CCTCTTTCTGGCCACACCATCCA
2593	GTGGATGGTGTGGCCAGAAAGAG	3857	CTCTTTCTGGCCACACCATCCAC
2594	TGTGGATGGTGTGGCCAGAAAGA	3858	TCTTTCTGGCCACACCATCCACA
2595	GTGTGGATGGTGTGGCCAGAAAG	3859	CTTTCTGGCCACACCATCCACAC
2596	AGTGTGGATGGTGTGGCCAGAAA	3860	TTTCTGGCCACACCATCCACACT
2597	GAGTGTGGATGGTGTGGCCAGAA	3861	TTCTGGCCACACCATCCACACTC
2598	AGAGTGTGGATGGTGTGGCCAGA	3862	TCTGGCCACACCATCCACACTCT
2599	GAGAGTGTGGATGGTGTGGCCAG	3863	CTGGCCACACCATCCACACTCTC
2600	GGAGAGTGTGGATGGTGTGGCCA	3864	TGGCCACACCATCCACACTCTCC
2601	AGGAGAGTGTGGATGGTGTGGCC	3865	GGCCACACCATCCACACTCTCCT
2602	CAGGAGAGTGTGGATGGTGTGGC	3866	GCCACACCATCCACACTCTCCTG
2603	CCAGGAGAGTGTGGATGGTGTGG	3867	CCACACCATCCACACTCTCCTGG
2604	GCCAGGAGAGTGTGGATGGTGTG	3868	CACACCATCCACACTCTCCTGGC
2605	GGCCAGGAGAGTGTGGATGGTGT	3869	ACACCATCCACACTCTCCTGGCC
2606	GGGCCAGGAGAGTGTGGATGGTG	3870	CACCATCCACACTCTCCTGGCCC
2607	AGGGCCAGGAGAGTGTGGATGGT	3871	ACCATCCACACTCTCCTGGCCCT
2608	GAGGGCCAGGAGAGTGTGGATGG	3872	CCATCCACACTCTCCTGGCCCTC
2609	AGAGGGCCAGGAGAGTGTGGATG	3873	CATCCACACTCTCCTGGCCCTCT
2610	CAGAGGGCCAGGAGAGTGTGGAT	3874	ATCCACACTCTCCTGGCCCTCTG
2611	TCAGAGGGCCAGGAGAGTGTGGA	3875	TCCACACTCTCCTGGCCCTCTGA
2612	CTCAGAGGGCCAGGAGAGTGTGG	3876	CCACACTCTCCTGGCCCTCTGAG
2613	TCTCAGAGGGCCAGGAGAGTGTG	3877	CACACTCTCCTGGCCCTCTGAGA
2614	GTCTCAGAGGGCCAGGAGAGTGT	3878	ACACTCTCCTGGCCCTCTGAGAC
2615	AGTCTCAGAGGGCCAGGAGAGTG	3879	CACTCTCCTGGCCCTCTGAGACT
2616	CAGTCTCAGAGGGCCAGGAGAGT	3880	ACTCTCCTGGCCCTCTGAGACTG
2617	GCAGTCTCAGAGGGCCAGGAGAG	3881	CTCTCCTGGCCCTCTGAGACTGC
2618	GGCAGTCTCAGAGGGCCAGGAGA	3882	TCTCCTGGCCCTCTGAGACTGCC
2619	GGGCAGTCTCAGAGGGCCAGGAG	3883	CTCCTGGCCCTCTGAGACTGCCC
2620	CGGGCAGTCTCAGAGGGCCAGGA	3884	TCCTGGCCCTCTGAGACTGCCCG
2621	GCGGGCAGTCTCAGAGGGCCAGG	3885	CCTGGCCCTCTGAGACTGCCCGC
2622	GGCGGGCAGTCTCAGAGGGCCAG	3886	CTGGCCCTCTGAGACTGCCCGCC
2623	TGGCGGGCAGTCTCAGAGGGCCA	3887	TGGCCCTCTGAGACTGCCCGCCA
2624	ATGGCGGGCAGTCTCAGAGGGCC	3888	GGCCCTCTGAGACTGCCCGCCAT
2625	CATGGCGGGCAGTCTCAGAGGGC	3889	GCCCTCTGAGACTGCCCGCCATG
2626	GCATGGCGGGCAGTCTCAGAGGG	3890	CCCTCTGAGACTGCCCGCCATGC
2627	GGCATGGCGGGCAGTCTCAGAGG	3891	CCTCTGAGACTGCCCGCCATGCC
2628	TGGCATGGCGGGCAGTCTCAGAG	3892	CTCTGAGACTGCCCGCCATGCCA
2629	ATGGCATGGCGGGCAGTCTCAGA	3893	TCTGAGACTGCCCGCCATGCCAT
2630	AATGGCATGGCGGGCAGTCTCAG	3894	CTGAGACTGCCCGCCATGCCATT
2631	GAATGGCATGGCGGGCAGTCTCA	3895	TGAGACTGCCCGCCATGCCATTC
2632	GGAATGGCATGGCGGGCAGTCTC	3896	GAGACTGCCCGCCATGCCATTCC

2633	GGGAATGGCATGGCGGGCAGTCT	3897	AGACTGCCCGCCATGCCATTCCC
2634	AGGGAATGGCATGGCGGGCAGTC	3898	GACTGCCCGCCATGCCATTCCCT
2635	AAGGGAATGGCATGGCGGGCAGT	3899	ACTGCCCGCCATGCCATTCCCTT
2636	AAAGGGAATGGCATGGCGGGCAG	3900	CTGCCCGCCATGCCATTCCCTTT
2637	TAAAGGGAATGGCATGGCGGGCA	3901	TGCCCGCCATGCCATTCCCTTTA
2638	GTAAAGGGAATGGCATGGCGGGC	3902	GCCCGCCATGCCATTCCCTTTAC
2639	GGTAAAGGGAATGGCATGGCGGG	3903	CCCGCCATGCCATTCCCTTTACC
2640	AGGTAAAGGGAATGGCATGGCGG	3904	CCGCCATGCCATTCCCTTTACCT
2641	CAGGTAAAGGGAATGGCATGGCG	3905	CGCCATGCCATTCCCTTTACCTG
2642	CCAGGTAAAGGGAATGGCATGGC	3906	GCCATGCCATTCCCTTTACCTGG
2643	TCCAGGTAAAGGGAATGGCATGG	3907	CCATGCCATTCCCTTTACCTGGA
2644	TTCCAGGTAAAGGGAATGGCATG	3908	CATGCCATTCCCTTTACCTGGAA
2645	TTTCCAGGTAAAGGGAATGGCAT	3909	ATGCCATTCCCTTTACCTGGAAA
2646	TTTTCCAGGTAAAGGGAATGGCA	3910	TGCCATTCCCTTTACCTGGAAAA
2647	GTTTTCCAGGTAAAGGGAATGGC	3911	GCCATTCCCTTTACCTGGAAAAC
2648	AGTTTTCCAGGTAAAGGGAATGG	3912	CCATTCCCTTTACCTGGAAAACT
2649	GAGTTTTCCAGGTAAAGGGAATG	3913	CATTCCCTTTACCTGGAAAACTC
2650	GGAGTTTTCCAGGTAAAGGGAAT	3914	ATTCCCTTTACCTGGAAAACTCC
2651	AGGAGTTTTCCAGGTAAAGGGAA	3915	TTCCCTTTACCTGGAAAACTCCT
2652	GAGGAGTTTTCCAGGTAAAGGGA	3916	TCCCTTTACCTGGAAAACTCCTC
2653	GGAGGAGTTTTCCAGGTAAAGGG	3917	CCCTTTACCTGGAAAACTCCTCC
2654	GGGAGGAGTTTTCCAGGTAAAGG	3918	CCTTTACCTGGAAAACTCCTCCC
2655	AGGGAGGAGTTTTCCAGGTAAAG	3919	CTTTACCTGGAAAACTCCTCCCT
2656	TAGGGAGGAGTTTTCCAGGTAAA	3920	TTTACCTGGAAAACTCCTCCCTA
2657	ATAGGGAGGAGTTTTCCAGGTAA	3921	TTACCTGGAAAACTCCTCCCTAT
2658	GATAGGGAGGAGTTTTCCAGGTA	3922	TACCTGGAAAACTCCTCCCTATC
2659	GGATAGGGAGGAGTTTTCCAGGT	3923	ACCTGGAAAACTCCTCCCTATCC
2660	TGGATAGGGAGGAGTTTTCCAGG	3924	CCTGGAAAACTCCTCCCTATCCA
2661	ATGGATAGGGAGGAGTTTTCCAG	3925	CTGGAAAACTCCTCCCTATCCAT
2662	GATGGATAGGGAGGAGTTTTCCA	3926	TGGAAAACTCCTCCCTATCCATC
2663	TGATGGATAGGGAGGAGTTTTCC	3927	GGAAAACTCCTCCCTATCCATCA
2664	TTGATGGATAGGGAGGAGTTTTC	3928	GAAAACTCCTCCCTATCCATCAA
2665	TTTGATGGATAGGGAGGAGTTTT	3929	AAAACTCCTCCCTATCCATCAAA
2666	CTTTGATGGATAGGGAGGAGTTT	3930	AAACTCCTCCCTATCCATCAAAG
2667	ACTTTGATGGATAGGGAGGAGTT	3931	AACTCCTCCCTATCCATCAAAGT
2668	GACTTTGATGGATAGGGAGGAGT	3932	ACTCCTCCCTATCCATCAAAGTC
2669	GGACTTTGATGGATAGGGAGGAG	3933	CTCCTCCCTATCCATCAAAGTCC
2670	TGGACTTTGATGGATAGGGAGGA	3934	TCCTCCCTATCCATCAAAGTCCA
2671	CTGGACTTTGATGGATAGGGAGG	3935	CCTCCCTATCCATCAAAGTCCAG
2672	TCTGGACTTTGATGGATAGGGAG	3936	CTCCCTATCCATCAAAGTCCAGA
2673	ATCTGGACTTTGATGGATAGGGA	3937	TCCCTATCCATCAAAGTCCAGAT
2674	AATCTGGACTTTGATGGATAGGG	3938	CCCTATCCATCAAAGTCCAGATT

2675	GAATCTGGACTTTGATGGATAGG	3939	CCTATCCATCAAAGTCCAGATTC
2676	TGAATCTGGACTTTGATGGATAG	3940	CTATCCATCAAAGTCCAGATTCA
2677	CTGAATCTGGACTTTGATGGATA	3941	TATCCATCAAAGTCCAGATTCAG
2678	CCTGAATCTGGACTTTGATGGAT	3942	ATCCATCAAAGTCCAGATTCAGG
2679	CCCTGAATCTGGACTTTGATGGA	3943	TCCATCAAAGTCCAGATTCAGGG
2680	ACCCTGAATCTGGACTTTGATGG	3944	CCATCAAAGTCCAGATTCAGGGT
2681	GACCCTGAATCTGGACTTTGATG	3945	CATCAAAGTCCAGATTCAGGGTC
2682	TGACCCTGAATCTGGACTTTGAT	3946	ATCAAAGTCCAGATTCAGGGTCA
2683	GTGACCCTGAATCTGGACTTTGA	3947	TCAAAGTCCAGATTCAGGGTCAC
2684	GGTGACCCTGAATCTGGACTTTG	3948	CAAAGTCCAGATTCAGGGTCACC
2685	AGGTGACCCTGAATCTGGACTTT	3949	AAAGTCCAGATTCAGGGTCACCT
2686	GAGGTGACCCTGAATCTGGACTT	3950	AAGTCCAGATTCAGGGTCACCTC
2687	GGAGGTGACCCTGAATCTGGACT	3951	AGTCCAGATTCAGGGTCACCTCC
2688	AGGAGGTGACCCTGAATCTGGAC	3952	GTCCAGATTCAGGGTCACCTCCT
2689	GAGGAGGTGACCCTGAATCTGGA	3953	TCCAGATTCAGGGTCACCTCCTC
2690	AGAGGAGGTGACCCTGAATCTGG	3954	CCAGATTCAGGGTCACCTCCTCT
2691	CAGAGGAGGTGACCCTGAATCTG	3955	CAGATTCAGGGTCACCTCCTCTG
2692	CCAGAGGAGGTGACCCTGAATCT	3956	AGATTCAGGGTCACCTCCTCTGG
2693	CCCAGAGGAGGTGACCCTGAATC	3957	GATTCAGGGTCACCTCCTCTGGG
2694	TCCCAGAGGAGGTGACCCTGAAT	3958	ATTCAGGGTCACCTCCTCTGGGA
2695	TTCCCAGAGGAGGTGACCCTGAA	3959	TTCAGGGTCACCTCCTCTGGGAA
2696	CTTCCCAGAGGAGGTGACCCTGA	3960	TCAGGGTCACCTCCTCTGGGAAG
2697	GCTTCCCAGAGGAGGTGACCCTG	3961	CAGGGTCACCTCCTCTGGGAAGC
2698	GGCTTCCCAGAGGAGGTGACCCT	3962	AGGGTCACCTCCTCTGGGAAGCC
2699	GGGCTTCCCAGAGGAGGTGACCC	3963	GGGTCACCTCCTCTGGGAAGCCC
2700	TGGGCTTCCCAGAGGAGGTGACC	3964	GGTCACCTCCTCTGGGAAGCCCA
2701	GTGGGCTTCCCAGAGGAGGTGAC	3965	GTCACCTCCTCTGGGAAGCCCAC
2702	GGTGGGCTTCCCAGAGGAGGTGA	3966	TCACCTCCTCTGGGAAGCCCACC
2703	AGGTGGGCTTCCCAGAGGAGGTG	3967	CACCTCCTCTGGGAAGCCCACCT
2704	AAGGTGGGCTTCCCAGAGGAGGT	3968	ACCTCCTCTGGGAAGCCCACCTT
2705	CAAGGTGGGCTTCCCAGAGGAGG	3969	CCTCCTCTGGGAAGCCCACCTTG
2706	CCAAGGTGGGCTTCCCAGAGGAG	3970	CTCCTCTGGGAAGCCCACCTTGG
2707	GCCAAGGTGGGCTTCCCAGAGGA	3971	TCCTCTGGGAAGCCCACCTTGGC
2708	GGCCAAGGTGGGCTTCCCAGAGG	3972	CCTCTGGGAAGCCCACCTTGGCC
2709	AGGCCAAGGTGGGCTTCCCAGAG	3973	CTCTGGGAAGCCCACCTTGGCCT
2710	GAGGCCAAGGTGGGCTTCCCAGA	3974	TCTGGGAAGCCCACCTTGGCCTC
2711	GGAGGCCAAGGTGGGCTTCCCAG	3975	CTGGGAAGCCCACCTTGGCCTCC
2712	TGGAGGCCAAGGTGGGCTTCCCA	3976	TGGGAAGCCCACCTTGGCCTCCA
2713	CTGGAGGCCAAGGTGGGCTTCCC	3977	GGGAAGCCCACCTTGGCCTCCAG
2714	CCTGGAGGCCAAGGTGGGCTTCC	3978	GGAAGCCCACCTTGGCCTCCAGG
2715	ACCTGGAGGCCAAGGTGGGCTTC	3979	GAAGCCCACCTTGGCCTCCAGGT
2716	AACCTGGAGGCCAAGGTGGGCTT	3980	AAGCCCACCTTGGCCTCCAGGTT

2717	CAACCTGGAGGCCAAGGTGGGCT	3981	AGCCCACCTTGGCCTCCAGGTTG
2718	TCAACCTGGAGGCCAAGGTGGGC	3982	GCCCACCTTGGCCTCCAGGTTGA
2719	GTCAACCTGGAGGCCAAGGTGGG	3983	CCCACCTTGGCCTCCAGGTTGAC
2720	AGTCAACCTGGAGGCCAAGGTGG	3984	CCACCTTGGCCTCCAGGTTGACT
2721	GAGTCAACCTGGAGGCCAAGGTG	3985	CACCTTGGCCTCCAGGTTGACTC
2722	AGAGTCAACCTGGAGGCCAAGGT	3986	ACCTTGGCCTCCAGGTTGACTCT
2723	GAGAGTCAACCTGGAGGCCAAGG	3987	CCTTGGCCTCCAGGTTGACTCTC
2724	TGAGAGTCAACCTGGAGGCCAAG	3988	CTTGGCCTCCAGGTTGACTCTCA
2725	GTGAGAGTCAACCTGGAGGCCAA	3989	TTGGCCTCCAGGTTGACTCTCAC
2726	AGTGAGAGTCAACCTGGAGGCCA	3990	TGGCCTCCAGGTTGACTCTCACT
2727	TAGTGAGAGTCAACCTGGAGGCC	3991	GGCCTCCAGGTTGACTCTCACTA
2728	GTAGTGAGAGTCAACCTGGAGGC	3992	GCCTCCAGGTTGACTCTCACTAC
2729	AGTAGTGAGAGTCAACCTGGAGG	3993	CCTCCAGGTTGACTCTCACTACT
2730	GAGTAGTGAGAGTCAACCTGGAG	3994	CTCCAGGTTGACTCTCACTACTC
2731	TGAGTAGTGAGAGTCAACCTGGA	3995	TCCAGGTTGACTCTCACTACTCA
2732	ATGAGTAGTGAGAGTCAACCTGG	3996	CCAGGTTGACTCTCACTACTCAT
2733	GATGAGTAGTGAGAGTCAACCTG	3997	CAGGTTGACTCTCACTACTCATC
2734	TGATGAGTAGTGAGAGTCAACCT	3998	AGGTTGACTCTCACTACTCATCA
2735	ATGATGAGTAGTGAGAGTCAACC	3999	GGTTGACTCTCACTACTCATCAT
2736	GATGATGAGTAGTGAGAGTCAAC	4000	GTTGACTCTCACTACTCATCATC
2737	TGATGATGAGTAGTGAGAGTCAA	4001	TTGACTCTCACTACTCATCATCA
2738	CTGATGATGAGTAGTGAGAGTCA	4002	TGACTCTCACTACTCATCATCAG
2739	CCTGATGATGAGTAGTGAGAGTC	4003	GACTCTCACTACTCATCATCAGG
2740	ACCTGATGATGAGTAGTGAGAGT	4004	ACTCTCACTACTCATCATCAGGT
2741	AACCTGATGATGAGTAGTGAGAG	4005	CTCTCACTACTCATCATCAGGTT
2742	GAACCTGATGATGAGTAGTGAGA	4006	TCTCACTACTCATCATCAGGTTC
2743	AGAACCTGATGATGAGTAGTGAG	4007	CTCACTACTCATCATCAGGTTCT
2744	AAGAACCTGATGATGAGTAGTGA	4008	TCACTACTCATCATCAGGTTCTT
2745	GAAGAACCTGATGATGAGTAGTG	4009	CACTACTCATCATCAGGTTCTTC
2746	GGAAGAACCTGATGATGAGTAGT	4010	ACTACTCATCATCAGGTTCTTCC
2747	AGGAAGAACCTGATGATGAGTAG	4011	CTACTCATCATCAGGTTCTTCCT
2748	AAGGAAGAACCTGATGATGAGTA	4012	TACTCATCATCAGGTTCTTCCTT
2749	GAAGGAAGAACCTGATGATGAGT	4013	ACTCATCATCAGGTTCTTCCTTC
2750	AGAAGGAAGAACCTGATGATGAG	4014	CTCATCATCAGGTTCTTCCTTCT
2751	TAGAAGGAAGAACCTGATGATGA	4015	TCATCATCAGGTTCTTCCTTCTA
2752	ATAGAAGGAAGAACCTGATGATG	4016	CATCATCAGGTTCTTCCTTCTAT
2753	AATAGAAGGAAGAACCTGATGAT	4017	ATCATCAGGTTCTTCCTTCTATT
2754	GAATAGAAGGAAGAACCTGATGA	4018	TCATCAGGTTCTTCCTTCTATTC
2755	GGAATAGAAGGAAGAACCTGATG	4019	CATCAGGTTCTTCCTTCTATTCC
2756	TGGAATAGAAGGAAGAACCTGAT	4020	ATCAGGTTCTTCCTTCTATTCCA
2757	CTGGAATAGAAGGAAGAACCTGA	4021	TCAGGTTCTTCCTTCTATTCCAG
2758	GCTGGAATAGAAGGAAGAACCTG	4022	CAGGTTCTTCCTTCTATTCCAGC

2759	GGCTGGAATAGAAGGAAGAACCT	4023	AGGTTCTTCCTTCTATTCCAGCC
2760	GGGCTGGAATAGAAGGAAGAACC	4024	GGTTCTTCCTTCTATTCCAGCCC
2761	AGGGCTGGAATAGAAGGAAGAAC	4025	GTTCTTCCTTCTATTCCAGCCCT
2762	TAGGGCTGGAATAGAAGGAAGAA	4026	TTCTTCCTTCTATTCCAGCCCTA
2763	TTAGGGCTGGAATAGAAGGAAGA	4027	TCTTCCTTCTATTCCAGCCCTAA
2764	GTTAGGGCTGGAATAGAAGGAAG	4028	CTTCCTTCTATTCCAGCCCTAAC
2765	GGTTAGGGCTGGAATAGAAGGAA	4029	TTCCTTCTATTCCAGCCCTAACC
2766	TGGTTAGGGCTGGAATAGAAGGA	4030	TCCTTCTATTCCAGCCCTAACCA
2767	GTGGTTAGGGCTGGAATAGAAGG	4031	CCTTCTATTCCAGCCCTAACCAC
2768	AGTGGTTAGGGCTGGAATAGAAG	4032	CTTCTATTCCAGCCCTAACCACT
2769	GAGTGGTTAGGGCTGGAATAGAA	4033	TTCTATTCCAGCCCTAACCACTC
2770	TGAGTGGTTAGGGCTGGAATAGA	4034	TCTATTCCAGCCCTAACCACTCA
2771	CTGAGTGGTTAGGGCTGGAATAG	4035	CTATTCCAGCCCTAACCACTCAG
2772	CCTGAGTGGTTAGGGCTGGAATA	4036	TATTCCAGCCCTAACCACTCAGG
2773	TCCTGAGTGGTTAGGGCTGGAAT	4037	ATTCCAGCCCTAACCACTCAGGA
2774	ATCCTGAGTGGTTAGGGCTGGAA	4038	TTCCAGCCCTAACCACTCAGGAT
2775	AATCCTGAGTGGTTAGGGCTGGA	4039	TCCAGCCCTAACCACTCAGGATT
2776	CAATCCTGAGTGGTTAGGGCTGG	4040	CCAGCCCTAACCACTCAGGATTG
2777	CCAATCCTGAGTGGTTAGGGCTG	4041	CAGCCCTAACCACTCAGGATTGG
2778	CCCAATCCTGAGTGGTTAGGGCT	4042	AGCCCTAACCACTCAGGATTGGG
2779	GCCCAATCCTGAGTGGTTAGGGC	4043	GCCCTAACCACTCAGGATTGGGC
2780	GGCCCAATCCTGAGTGGTTAGGG	4044	CCCTAACCACTCAGGATTGGGCC
2781	CGGCCCAATCCTGAGTGGTTAGG	4045	CCTAACCACTCAGGATTGGGCCG
2782	ACGGCCCAATCCTGAGTGGTTAG	4046	CTAACCACTCAGGATTGGGCCGT
2783	AACGGCCCAATCCTGAGTGGTTA	4047	TAACCACTCAGGATTGGGCCGTT
2784	AAACGGCCCAATCCTGAGTGGTT	4048	AACCACTCAGGATTGGGCCGTTT
2785	CAAACGGCCCAATCCTGAGTGGT	4049	ACCACTCAGGATTGGGCCGTTTG
2786	ACAAACGGCCCAATCCTGAGTGG	4050	CCACTCAGGATTGGGCCGTTTGT
2787	CACAAACGGCCCAATCCTGAGTG	4051	CACTCAGGATTGGGCCGTTTGTG
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2789	GACACAAACGGCCCAATCCTGAG	4053	CTCAGGATTGGGCCGTTTGTGTC
2790	AGACACAAACGGCCCAATCCTGA	4054	TCAGGATTGGGCCGTTTGTGTCT
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2792	CCAGACACAAACGGCCCAATCCT	4056	AGGATTGGGCCGTTTGTGTCTGG
2793	CCCAGACACAAACGGCCCAATCC	4057	GGATTGGGCCGTTTGTGTCTGGG
2794	ACCCAGACACAAACGGCCCAATC	4058	GATTGGGCCGTTTGTGTCTGGGT
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2796	ATACCCAGACACAAACGGCCCAA	4060	TTGGGCCGTTTGTGTCTGGGTAT
2797	CATACCCAGACACAAACGGCCCA	4061	TGGGCCGTTTGTGTCTGGGTATG
2798	ACATACCCAGACACAAACGGCCC	4062	GGGCCGTTTGTGTCTGGGTATGT
2799	GACATACCCAGACACAAACGGCC	4063	GGCCGTTTGTGTCTGGGTATGTC
2800	AGACATACCCAGACACAAACGGC	4064	GCCGTTTGTGTCTGGGTATGTCT

2801	GAGACATACCCAGACACAAACGG	4065	CCGTTTGTGTCTGGGTATGTCTC
2802	AGAGACATACCCAGACACAAACG	4066	CGTTTGTGTCTGGGTATGTCTCT
2803	AAGAGACATACCCAGACACAAAC	4067	GTTTGTGTCTGGGTATGTCTCTT
2804	GAAGAGACATACCCAGACACAAA	4068	TTTGTGTCTGGGTATGTCTCTTC
2805	GGAAGAGACATACCCAGACACAA	4069	TTGTGTCTGGGTATGTCTCTTCC
2806	TGGAAGAGACATACCCAGACACA	4070	TGTGTCTGGGTATGTCTCTTCCA
2807	CTGGAAGAGACATACCCAGACAC	4071	GTGTCTGGGTATGTCTCTTCCAG
2808	GCTGGAAGAGACATACCCAGACA	4072	TGTCTGGGTATGTCTCTTCCAGC
2809	AGCTGGAAGAGACATACCCAGAC	4073	GTCTGGGTATGTCTCTTCCAGCT
2810	CAGCTGGAAGAGACATACCCAGA	4074	TCTGGGTATGTCTCTTCCAGCTG
2811	GCAGCTGGAAGAGACATACCCAG	4075	CTGGGTATGTCTCTTCCAGCTGC
2812	GGCAGCTGGAAGAGACATACCCA	4076	TGGGTATGTCTCTTCCAGCTGCC
2813	AGGCAGCTGGAAGAGACATACCC	4077	GGGTATGTCTCTTCCAGCTGCCT
2814	CAGGCAGCTGGAAGAGACATACC	4078	GGTATGTCTCTTCCAGCTGCCTG
2815	CCAGGCAGCTGGAAGAGACATAC	4079	GTATGTCTCTTCCAGCTGCCTGG
2816	CCCAGGCAGCTGGAAGAGACATA	4080	TATGTCTCTTCCAGCTGCCTGGG
2817	ACCCAGGCAGCTGGAAGAGACAT	4081	ATGTCTCTTCCAGCTGCCTGGGT
2818	AACCCAGGCAGCTGGAAGAGACA	4082	TGTCTCTTCCAGCTGCCTGGGTT
2819	AAACCCAGGCAGCTGGAAGAGAC	4083	GTCTCTTCCAGCTGCCTGGGTTT
2820	GAAACCCAGGCAGCTGGAAGAGA	4084	TCTCTTCCAGCTGCCTGGGTTTC
2821	GGAAACCCAGGCAGCTGGAAGAG	4085	CTCTTCCAGCTGCCTGGGTTTCC
2822	AGGAAACCCAGGCAGCTGGAAGA	4086	TCTTCCAGCTGCCTGGGTTTCCT
2823	CAGGAAACCCAGGCAGCTGGAAG	4087	CTTCCAGCTGCCTGGGTTTCCTG
2824	CCAGGAAACCCAGGCAGCTGGAA	4088	TTCCAGCTGCCTGGGTTTCCTGG
2825	TCCAGGAAACCCAGGCAGCTGGA	4089	TCCAGCTGCCTGGGTTTCCTGGA
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2827	TTTCCAGGAAACCCAGGCAGCTG	4091	CAGCTGCCTGGGTTTCCTGGAAA
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2831	GTTCTTTCCAGGAAACCCAGGCA	4095	TGCCTGGGTTTCCTGGAAAGAAC
2832	AGTTCTTTCCAGGAAACCCAGGC	4096	GCCTGGGTTTCCTGGAAAGAACT
2833	GAGTTCTTTCCAGGAAACCCAGG	4097	CCTGGGTTTCCTGGAAAGAACTC
2834	AGAGTTCTTTCCAGGAAACCCAG	4098	CTGGGTTTCCTGGAAAGAACTCT
2835	AAGAGTTCTTTCCAGGAAACCCA	4099	TGGGTTTCCTGGAAAGAACTCTT
2836	TAAGAGTTCTTTCCAGGAAACCC	4100	GGGTTTCCTGGAAAGAACTCTTA
2837	ATAAGAGTTCTTTCCAGGAAACC	4101	GGTTTCCTGGAAAGAACTCTTAT
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2839	GGATAAGAGTTCTTTCCAGGAAA	4103	TTTCCTGGAAAGAACTCTTATCC
2840	GGGATAAGAGTTCTTTCCAGGAA	4104	TTCCTGGAAAGAACTCTTATCCC
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2852	AACTAGTTCCTGGGGATAAGAGT	4116	ACTCTTATCCCCAGGAACTAGTT
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2864	ATTTATTCAACAAACTAGTTCCT	4128	AGGAACTAGTTTGTTGAATAAAT
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2868	CAGCATTTATTCAACAAACTAGT	4132	ACTAGTTTGTTGAATAAATGCTG
2869	CCAGCATTTATTCAACAAACTAG	4133	CTAGTTTGTTGAATAAATGCTGG
2870	ACCAGCATTTATTCAACAAACTA	4134	TAGTTTGTTGAATAAATGCTGGT
2871	CACCAGCATTTATTCAACAAACT	4135	AGTTTGTTGAATAAATGCTGGTG
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3000	ATCCATCATCCATCTAGCCACGA	4264	TCGTGGCTAGATGGATGATGGAT
3001	CATCCATCATCCATCTAGCCACG	4265	CGTGGCTAGATGGATGATGGATG
3002	CCATCCATCATCCATCTAGCCAC	4266	GTGGCTAGATGGATGATGGATGG
3003	TCCATCCATCATCCATCTAGCCA	4267	TGGCTAGATGGATGATGGATGGA
3004	ATCCATCCATCATCCATCTAGCC	4268	GGCTAGATGGATGATGGATGGAT
3005	CATCCATCCATCATCCATCTAGC	4269	GCTAGATGGATGATGGATGGATG
3006	CCATCCATCCATCATCCATCTAG	4270	CTAGATGGATGATGGATGGATGG
3007	TCCATCCATCCATCATCCATCTA	4271	TAGATGGATGATGGATGGATGGA
3008	GTCCATCCATCCATCATCCATCT	4272	AGATGGATGATGGATGGATGGAC
3009	TGTCCATCCATCCATCATCCATC	4273	GATGGATGATGGATGGATGGACA
3010	CTGTCCATCCATCCATCATCCAT	4274	ATGGATGATGGATGGATGGACAG

3011	TCTGTCCATCCATCCATCATCCA	4275	TGGATGATGGATGGATGGACAGA
3012	ATCTGTCCATCCATCCATCATCC	4276	GGATGATGGATGGATGGACAGAT
3013	CATCTGTCCATCCATCCATCATC	4277	GATGATGGATGGATGGACAGATG
3014	CCATCTGTCCATCCATCCATCAT	4278	ATGATGGATGGATGGACAGATGG
3015	TCCATCTGTCCATCCATCCATCA	4279	TGATGGATGGATGGACAGATGGA
3016	ATCCATCTGTCCATCCATCCATC	4280	GATGGATGGATGGACAGATGGAT
3017	CATCCATCTGTCCATCCATCCAT	4281	ATGGATGGATGGACAGATGGATG
3018	CCATCCATCTGTCCATCCATCCA	4282	TGGATGGATGGACAGATGGATGG
3019	TCCATCCATCTGTCCATCCATCC	4283	GGATGGATGGACAGATGGATGGA
3020	ATCCATCCATCTGTCCATCCATC	4284	GATGGATGGACAGATGGATGGAT
3021	TATCCATCCATCTGTCCATCCAT	4285	ATGGATGGACAGATGGATGGATA
3022	ATATCCATCCATCTGTCCATCCA	4286	TGGATGGACAGATGGATGGATAT
3023	TATATCCATCCATCTGTCCATCC	4287	GGATGGACAGATGGATGGATATA
3024	ATATATCCATCCATCTGTCCATC	4288	GATGGACAGATGGATGGATATAT
3025	CATATATCCATCCATCTGTCCAT	4289	ATGGACAGATGGATGGATATATG
3026	TCATATATCCATCCATCTGTCCA	4290	TGGACAGATGGATGGATATATGA
3027	ATCATATATCCATCCATCTGTCC	4291	GGACAGATGGATGGATATATGAT
3028	AATCATATATCCATCCATCTGTC	4292	GACAGATGGATGGATATATGATT
3029	CAATCATATATCCATCCATCTGT	4293	ACAGATGGATGGATATATGATTG
3030	TCAATCATATATCCATCCATCTG	4294	CAGATGGATGGATATATGATTGA
3031	TTCAATCATATATCCATCCATCT	4295	AGATGGATGGATATATGATTGAA
3032	GTTCAATCATATATCCATCCATC	4296	GATGGATGGATATATGATTGAAC
3033	AGTTCAATCATATATCCATCCAT	4297	ATGGATGGATATATGATTGAACT
3034	TAGTTCAATCATATATCCATCCA	4298	TGGATGGATATATGATTGAACTA
3035	ATAGTTCAATCATATATCCATCC	4299	GGATGGATATATGATTGAACTAT
3036	AATAGTTCAATCATATATCCATC	4300	GATGGATATATGATTGAACTATT
3037	CAATAGTTCAATCATATATCCAT	4301	ATGGATATATGATTGAACTATTG
3038	TCAATAGTTCAATCATATATCCA	4302	TGGATATATGATTGAACTATTGA
3039	TTCAATAGTTCAATCATATATCC	4303	GGATATATGATTGAACTATTGAA
3040	TTTCAATAGTTCAATCATATATC	4304	GATATATGATTGAACTATTGAAA
3041	CTTTCAATAGTTCAATCATATAT	4305	ATATATGATTGAACTATTGAAAG
3042	ACTTTCAATAGTTCAATCATATA	4306	TATATGATTGAACTATTGAAAGT
3043	TACTTTCAATAGTTCAATCATAT	4307	ATATGATTGAACTATTGAAAGTA
3044	ATACTTTCAATAGTTCAATCATA	4308	TATGATTGAACTATTGAAAGTAT
3045	TATACTTTCAATAGTTCAATCAT	4309	ATGATTGAACTATTGAAAGTATA
3046	CTATACTTTCAATAGTTCAATCA	4310	TGATTGAACTATTGAAAGTATAG
3047	TCTATACTTTCAATAGTTCAATC	4311	GATTGAACTATTGAAAGTATAGA
3048	ATCTATACTTTCAATAGTTCAAT	4312	ATTGAACTATTGAAAGTATAGAT
3049	CATCTATACTTTCAATAGTTCAA	4313	TTGAACTATTGAAAGTATAGATG
3050	ACATCTATACTTTCAATAGTTCA	4314	TGAACTATTGAAAGTATAGATGT
3051	TACATCTATACTTTCAATAGTTC	4315	GAACTATTGAAAGTATAGATGTA
3052	ATACATCTATACTTTCAATAGTT	4316	AACTATTGAAAGTATAGATGTAT

3053	CATACATCTATACTTTCAATAGT	4317	ACTATTGAAAGTATAGATGTATG
3054	CCATACATCTATACTTTCAATAG	4318	CTATTGAAAGTATAGATGTATGG
3055	TCCATACATCTATACTTTCAATA	4319	TATTGAAAGTATAGATGTATGGA
3056	ATCCATACATCTATACTTTCAAT	4320	ATTGAAAGTATAGATGTATGGAT
3057	CATCCATACATCTATACTTTCAA	4321	TTGAAAGTATAGATGTATGGATG
3058	CCATCCATACATCTATACTTTCA	4322	TGAAAGTATAGATGTATGGATGG
3059	CCCATCCATACATCTATACTTTC	4323	GAAAGTATAGATGTATGGATGGG
3060	ACCCATCCATACATCTATACTTT	4324	AAAGTATAGATGTATGGATGGGT
3061	CACCCATCCATACATCTATACTT	4325	AAGTATAGATGTATGGATGGGTG
3062	TCACCCATCCATACATCTATACT	4326	AGTATAGATGTATGGATGGGTGA
3063	TTCACCCATCCATACATCTATAC	4327	GTATAGATGTATGGATGGGTGAA
3064	ATTCACCCATCCATACATCTATA	4328	TATAGATGTATGGATGGGTGAAT
3065	AATTCACCCATCCATACATCTAT	4329	ATAGATGTATGGATGGGTGAATT
3066	AAATTCACCCATCCATACATCTA	4330	TAGATGTATGGATGGGTGAATTT
3067	CAAATTCACCCATCCATACATCT	4331	AGATGTATGGATGGGTGAATTTG
3068	CCAAATTCACCCATCCATACATC	4332	GATGTATGGATGGGTGAATTTGG
3069	CCCAAATTCACCCATCCATACAT	4333	ATGTATGGATGGGTGAATTTGGG
3070	CCCCAAATTCACCCATCCATACA	4334	TGTATGGATGGGTGAATTTGGGG
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3073	TACCCCCAAATTCACCCATCCAT	4337	ATGGATGGGTGAATTTGGGGGTA
3074	TTACCCCCAAATTCACCCATCCA	4338	TGGATGGGTGAATTTGGGGGTAA
3075	ATTACCCCCAAATTCACCCATCC	4339	GGATGGGTGAATTTGGGGGTAAT
3076	AATTACCCCCAAATTCACCCATC	4340	GATGGGTGAATTTGGGGGTAATT
3077	CAATTACCCCCAAATTCACCCAT	4341	ATGGGTGAATTTGGGGGTAATTG
3078	ACAATTACCCCCAAATTCACCCA	4342	TGGGTGAATTTGGGGGTAATTGT
3079	AACAATTACCCCCAAATTCACCC	4343	GGGTGAATTTGGGGGTAATTGTT
3080	TAACAATTACCCCCAAATTCACC	4344	GGTGAATTTGGGGGTAATTGTTA
3081	CTAACAATTACCCCCAAATTCAC	4345	GTGAATTTGGGGGTAATTGTTAG
3082	TCTAACAATTACCCCCAAATTCA	4346	TGAATTTGGGGGTAATTGTTAGA
3083	ATCTAACAATTACCCCCAAATTC	4347	GAATTTGGGGGTAATTGTTAGAT
3084	CATCTAACAATTACCCCCAAATT	4348	AATTTGGGGGTAATTGTTAGATG
3085	TCATCTAACAATTACCCCCAAAT	4349	ATTTGGGGGTAATTGTTAGATGA
3086	ATCATCTAACAATTACCCCCAAA	4350	TTTGGGGGTAATTGTTAGATGAT
3087	CATCATCTAACAATTACCCCCAA	4351	TTGGGGGTAATTGTTAGATGATG
3088	CCATCATCTAACAATTACCCCCA	4352	TGGGGGTAATTGTTAGATGATGG
3089	TCCATCATCTAACAATTACCCCC	4353	GGGGGTAATTGTTAGATGATGGA
3090	ATCCATCATCTAACAATTACCCC	4354	GGGGTAATTGTTAGATGATGGAT
3091	CATCCATCATCTAACAATTACCC	4355	GGGTAATTGTTAGATGATGGATG
3092	TCATCCATCATCTAACAATTACC	4356	GGTAATTGTTAGATGATGGATGA
3093	CTCATCCATCATCTAACAATTAC	4357	GTAATTGTTAGATGATGGATGAG
3094	ACTCATCCATCATCTAACAATTA	4358	TAATTGTTAGATGATGGATGAGT

3095	TACTCATCCATCATCTAACAATT	4359	AATTGTTAGATGATGGATGAGTA
3096	ATACTCATCCATCATCTAACAAT	4360	ATTGTTAGATGATGGATGAGTAT
3097	TATACTCATCCATCATCTAACAA	4361	TTGTTAGATGATGGATGAGTATA
3098	CTATACTCATCCATCATCTAACA	4362	TGTTAGATGATGGATGAGTATAG
3099	TCTATACTCATCCATCATCTAAC	4363	GTTAGATGATGGATGAGTATAGA
3100	ATCTATACTCATCCATCATCTAA	4364	TTAGATGATGGATGAGTATAGAT
3101	CATCTATACTCATCCATCATCTA	4365	TAGATGATGGATGAGTATAGATG
3102	TCATCTATACTCATCCATCATCT	4366	AGATGATGGATGAGTATAGATGA
3103	TTCATCTATACTCATCCATCATC	4367	GATGATGGATGAGTATAGATGAA
3104	ATTCATCTATACTCATCCATCAT	4368	ATGATGGATGAGTATAGATGAAT
3105	CATTCATCTATACTCATCCATCA	4369	TGATGGATGAGTATAGATGAATG
3106	TCATTCATCTATACTCATCCATC	4370	GATGGATGAGTATAGATGAATGA
3107	ATCATTCATCTATACTCATCCAT	4371	ATGGATGAGTATAGATGAATGAT
3108	CATCATTCATCTATACTCATCCA	4372	TGGATGAGTATAGATGAATGATG
3109	CCATCATTCATCTATACTCATCC	4373	GGATGAGTATAGATGAATGATGG
3110	TCCATCATTCATCTATACTCATC	4374	GATGAGTATAGATGAATGATGGA
3111	ATCCATCATTCATCTATACTCAT	4375	ATGAGTATAGATGAATGATGGAT
3112	CATCCATCATTCATCTATACTCA	4376	TGAGTATAGATGAATGATGGATG
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3114	TCCATCCATCATTCATCTATACT	4378	AGTATAGATGAATGATGGATGGA
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3116	TATCCATCCATCATTCATCTATA	4380	TATAGATGAATGATGGATGGATA
3117	TTATCCATCCATCATTCATCTAT	4381	ATAGATGAATGATGGATGGATAA
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3119	AGTTATCCATCCATCATTCATCT	4383	AGATGAATGATGGATGGATAACT
3120	AAGTTATCCATCCATCATTCATC	4384	GATGAATGATGGATGGATAACTT
3121	CAAGTTATCCATCCATCATTCAT	4385	ATGAATGATGGATGGATAACTTG
3122	TCAAGTTATCCATCCATCATTCA	4386	TGAATGATGGATGGATAACTTGA
3123	ATCAAGTTATCCATCCATCATTC	4387	GAATGATGGATGGATAACTTGAT
3124	CATCAAGTTATCCATCCATCATT	4388	AATGATGGATGGATAACTTGATG
3125	TCATCAAGTTATCCATCCATCAT	4389	ATGATGGATGGATAACTTGATGA
3126	CTCATCAAGTTATCCATCCATCA	4390	TGATGGATGGATAACTTGATGAG
3127	ACTCATCAAGTTATCCATCCATC	4391	GATGGATGGATAACTTGATGAGT
3128	CACTCATCAAGTTATCCATCCAT	4392	ATGGATGGATAACTTGATGAGTG
3129	CCACTCATCAAGTTATCCATCCA	4393	TGGATGGATAACTTGATGAGTGG
3130	TCCACTCATCAAGTTATCCATCC	4394	GGATGGATAACTTGATGAGTGGA
3131	ATCCACTCATCAAGTTATCCATC	4395	GATGGATAACTTGATGAGTGGAT
3132	TATCCACTCATCAAGTTATCCAT	4396	ATGGATAACTTGATGAGTGGATA
3133	CTATCCACTCATCAAGTTATCCA	4397	TGGATAACTTGATGAGTGGATAG
3134	TCTATCCACTCATCAAGTTATCC	4398	GGATAACTTGATGAGTGGATAGA
3135	ATCTATCCACTCATCAAGTTATC	4399	GATAACTTGATGAGTGGATAGAT
3136	TATCTATCCACTCATCAAGTTAT	4400	ATAACTTGATGAGTGGATAGATA

3137	CTATCTATCCACTCATCAAGTTA	4401	TAACTTGATGAGTGGATAGATAG
3138	TCTATCTATCCACTCATCAAGTT	4402	AACTTGATGAGTGGATAGATAGA
3139	ATCTATCTATCCACTCATCAAGT	4403	ACTTGATGAGTGGATAGATAGAT
3140	AATCTATCTATCCACTCATCAAG	4404	CTTGATGAGTGGATAGATAGATT
3141	CAATCTATCTATCCACTCATCAA	4405	TTGATGAGTGGATAGATAGATTG
3142	GCAATCTATCTATCCACTCATCA	4406	TGATGAGTGGATAGATAGATTGC
3143	AGCAATCTATCTATCCACTCATC	4407	GATGAGTGGATAGATAGATTGCT
3144	CAGCAATCTATCTATCCACTCAT	4408	ATGAGTGGATAGATAGATTGCTG
3145	CCAGCAATCTATCTATCCACTCA	4409	TGAGTGGATAGATAGATTGCTGG
3146	TCCAGCAATCTATCTATCCACTC	4410	GAGTGGATAGATAGATTGCTGGA
3147	ATCCAGCAATCTATCTATCCACT	4411	AGTGGATAGATAGATTGCTGGAT
3148	TATCCAGCAATCTATCTATCCAC	4412	GTGGATAGATAGATTGCTGGATA
3149	CTATCCAGCAATCTATCTATCCA	4413	TGGATAGATAGATTGCTGGATAG
3150	TCTATCCAGCAATCTATCTATCC	4414	GGATAGATAGATTGCTGGATAGA
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3153	TCATCTATCCAGCAATCTATCTA	4417	TAGATAGATTGCTGGATAGATGA
3154	ATCATCTATCCAGCAATCTATCT	4418	AGATAGATTGCTGGATAGATGAT
3155	AATCATCTATCCAGCAATCTATC	4419	GATAGATTGCTGGATAGATGATT
3156	CAATCATCTATCCAGCAATCTAT	4420	ATAGATTGCTGGATAGATGATTG
3157	TCAATCATCTATCCAGCAATCTA	4421	TAGATTGCTGGATAGATGATTGA
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3159	AGTCAATCATCTATCCAGCAATC	4423	GATTGCTGGATAGATGATTGACT
3160	CAGTCAATCATCTATCCAGCAAT	4424	ATTGCTGGATAGATGATTGACTG
3161	CCAGTCAATCATCTATCCAGCAA	4425	TTGCTGGATAGATGATTGACTGG
3162	CCCAGTCAATCATCTATCCAGCA	4426	TGCTGGATAGATGATTGACTGGG
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3164	CACCCAGTCAATCATCTATCCAG	4428	CTGGATAGATGATTGACTGGGTG
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3169	CTATCCACCCAGTCAATCATCTA	4433	TAGATGATTGACTGGGTGGATAG
3170	TCTATCCACCCAGTCAATCATCT	4434	AGATGATTGACTGGGTGGATAGA
3171	ATCTATCCACCCAGTCAATCATC	4435	GATGATTGACTGGGTGGATAGAT
3172	CATCTATCCACCCAGTCAATCAT	4436	ATGATTGACTGGGTGGATAGATG
3173	TCATCTATCCACCCAGTCAATCA	4437	TGATTGACTGGGTGGATAGATGA
3174	TTCATCTATCCACCCAGTCAATC	4438	GATTGACTGGGTGGATAGATGAA
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3176	ATTTCATCTATCCACCCAGTCAA	4440	TTGACTGGGTGGATAGATGAAAT
3177	CATTTCATCTATCCACCCAGTCA	4441	TGACTGGGTGGATAGATGAAATG
3178	ACATTTCATCTATCCACCCAGTC	4442	GACTGGGTGGATAGATGAAATGT

3179	AACATTTCATCTATCCACCCAGT	4443	ACTGGGTGGATAGATGAAATGTT
3180	CAACATTTCATCTATCCACCCAG	4444	CTGGGTGGATAGATGAAATGTTG
3181	CCAACATTTCATCTATCCACCCA	4445	TGGGTGGATAGATGAAATGTTGG
3182	TCCAACATTTCATCTATCCACCC	4446	GGGTGGATAGATGAAATGTTGGA
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3184	CATCCAACATTTCATCTATCCAC	4448	GTGGATAGATGAAATGTTGGATG
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3198	CAACTTAATCTGCTCATCCAACA	4462	TGTTGGATGAGCAGATTAAGTTG
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3203	CAATACAACTTAATCTGCTCATC	4467	GATGAGCAGATTAAGTTGTATTG
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3231	ACTCAACCACACTTCCATCCATC	4495	GATGGATGGAAGTGTGGTTGAGT
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3239	TTCTAATAACTCAACCACACTTC	4503	GAAGTGTGGTTGAGTTATTAGAA
3240	CTTCTAATAACTCAACCACACTT	4504	AAGTGTGGTTGAGTTATTAGAAG
3241	CCTTCTAATAACTCAACCACACT	4505	AGTGTGGTTGAGTTATTAGAAGG
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3245	TCTTCCTTCTAATAACTCAACCA	4509	TGGTTGAGTTATTAGAAGGAAGA
3246	ATCTTCCTTCTAATAACTCAACC	4510	GGTTGAGTTATTAGAAGGAAGAT
3247	AATCTTCCTTCTAATAACTCAAC	4511	GTTGAGTTATTAGAAGGAAGATT
3248	CAATCTTCCTTCTAATAACTCAA	4512	TTGAGTTATTAGAAGGAAGATTG
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3250	CTCAATCTTCCTTCTAATAACTC	4514	GAGTTATTAGAAGGAAGATTGAG
3251	ACTCAATCTTCCTTCTAATAACT	4515	AGTTATTAGAAGGAAGATTGAGT
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3253	CTACTCAATCTTCCTTCTAATAA	4517	TTATTAGAAGGAAGATTGAGTAG
3254	TCTACTCAATCTTCCTTCTAATA	4518	TATTAGAAGGAAGATTGAGTAGA
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3258	CCTATCTACTCAATCTTCCTTCT	4522	AGAAGGAAGATTGAGTAGATAGG
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3260	CACCTATCTACTCAATCTTCCTT	4524	AAGGAAGATTGAGTAGATAGGTG
3261	TCACCTATCTACTCAATCTTCCT	4525	AGGAAGATTGAGTAGATAGGTGA
3262	TTCACCTATCTACTCAATCTTCC	4526	GGAAGATTGAGTAGATAGGTGAA

3263	ATTCACCTATCTACTCAATCTTC	4527	GAAGATTGAGTAGATAGGTGAAT
3264	AATTCACCTATCTACTCAATCTT	4528	AAGATTGAGTAGATAGGTGAATT
3265	AAATTCACCTATCTACTCAATCT	4529	AGATTGAGTAGATAGGTGAATTT
3266	CAAATTCACCTATCTACTCAATC	4530	GATTGAGTAGATAGGTGAATTTG
3267	ACAAATTCACCTATCTACTCAAT	4531	ATTGAGTAGATAGGTGAATTTGT
3268	AACAAATTCACCTATCTACTCAA	4532	TTGAGTAGATAGGTGAATTTGTT
3269	CAACAAATTCACCTATCTACTCA	4533	TGAGTAGATAGGTGAATTTGTTG
3270	TCAACAAATTCACCTATCTACTC	4534	GAGTAGATAGGTGAATTTGTTGA
3271	ATCAACAAATTCACCTATCTACT	4535	AGTAGATAGGTGAATTTGTTGAT
3272	TATCAACAAATTCACCTATCTAC	4536	GTAGATAGGTGAATTTGTTGATA
3273	CTATCAACAAATTCACCTATCTA	4537	TAGATAGGTGAATTTGTTGATAG
3274	ACTATCAACAAATTCACCTATCT	4538	AGATAGGTGAATTTGTTGATAGT
3275	GACTATCAACAAATTCACCTATC	4539	GATAGGTGAATTTGTTGATAGTC
3276	TGACTATCAACAAATTCACCTAT	4540	ATAGGTGAATTTGTTGATAGTCA
3277	CTGACTATCAACAAATTCACCTA	4541	TAGGTGAATTTGTTGATAGTCAG
3278	TCTGACTATCAACAAATTCACCT	4542	AGGTGAATTTGTTGATAGTCAGA
3279	ATCTGACTATCAACAAATTCACC	4543	GGTGAATTTGTTGATAGTCAGAT
3280	CATCTGACTATCAACAAATTCAC	4544	GTGAATTTGTTGATAGTCAGATG
3281	CCATCTGACTATCAACAAATTCA	4545	TGAATTTGTTGATAGTCAGATGG
3282	CCCATCTGACTATCAACAAATTC	4546	GAATTTGTTGATAGTCAGATGGG
3283	ACCCATCTGACTATCAACAAATT	4547	AATTTGTTGATAGTCAGATGGGT
3284	TACCCATCTGACTATCAACAAAT	4548	ATTTGTTGATAGTCAGATGGGTA
3285	CTACCCATCTGACTATCAACAAA	4549	TTTGTTGATAGTCAGATGGGTAG
3286	TCTACCCATCTGACTATCAACAA	4550	TTGTTGATAGTCAGATGGGTAGA
3287	ATCTACCCATCTGACTATCAACA	4551	TGTTGATAGTCAGATGGGTAGAT
3288	TATCTACCCATCTGACTATCAAC	4552	GTTGATAGTCAGATGGGTAGATA
3289	CTATCTACCCATCTGACTATCAA	4553	TTGATAGTCAGATGGGTAGATAG
3290	CCTATCTACCCATCTGACTATCA	4554	TGATAGTCAGATGGGTAGATAGG
3291	ACCTATCTACCCATCTGACTATC	4555	GATAGTCAGATGGGTAGATAGGT
3292	TACCTATCTACCCATCTGACTAT	4556	ATAGTCAGATGGGTAGATAGGTA
3293	CTACCTATCTACCCATCTGACTA	4557	TAGTCAGATGGGTAGATAGGTAG
3294	TCTACCTATCTACCCATCTGACT	4558	AGTCAGATGGGTAGATAGGTAGA
3295	ATCTACCTATCTACCCATCTGAC	4559	GTCAGATGGGTAGATAGGTAGAT
3296	CATCTACCTATCTACCCATCTGA	4560	TCAGATGGGTAGATAGGTAGATG
3297	CCATCTACCTATCTACCCATCTG	4561	CAGATGGGTAGATAGGTAGATGG
3298	TCCATCTACCTATCTACCCATCT	4562	AGATGGGTAGATAGGTAGATGGA
3299	ATCCATCTACCTATCTACCCATC	4563	GATGGGTAGATAGGTAGATGGAT
3300	CATCCATCTACCTATCTACCCAT	4564	ATGGGTAGATAGGTAGATGGATG
3301	CCATCCATCTACCTATCTACCCA	4565	TGGGTAGATAGGTAGATGGATGG
3302	TCCATCCATCTACCTATCTACCC	4566	GGGTAGATAGGTAGATGGATGGA
3303	ATCCATCCATCTACCTATCTACC	4567	GGTAGATAGGTAGATGGATGGAT
3304	CATCCATCCATCTACCTATCTAC	4568	GTAGATAGGTAGATGGATGGATG

3305	CCATCCATCCATCTACCTATCTA	4569	TAGATAGGTAGATGGATGGATGG
3306	TCCATCCATCCATCTACCTATCT	4570	AGATAGGTAGATGGATGGATGGA
3307	ATCCATCCATCCATCTACCTATC	4571	GATAGGTAGATGGATGGATGGAT
3308	CATCCATCCATCCATCTACCTAT	4572	ATAGGTAGATGGATGGATGGATG
3309	CCATCCATCCATCCATCTACCTA	4573	TAGGTAGATGGATGGATGGATGG
3310	TCCATCCATCCATCCATCTACCT	4574	AGGTAGATGGATGGATGGATGGA
3311	ATCCATCCATCCATCCATCTACC	4575	GGTAGATGGATGGATGGATGGAT
3312	CATCCATCCATCCATCCATCTAC	4576	GTAGATGGATGGATGGATGGATG
3313	CCATCCATCCATCCATCCATCTA	4577	TAGATGGATGGATGGATGGATGG
3314	TCCATCCATCCATCCATCCATCT	4578	AGATGGATGGATGGATGGATGGA
3315	ATCCATCCATCCATCCATCCATC	4579	GATGGATGGATGGATGGATGGAT
3316	CATCCATCCATCCATCCATCCAT	4580	ATGGATGGATGGATGGATGGATG
3317	ACATCCATCCATCCATCCATCCA	4581	TGGATGGATGGATGGATGGATGT
3318	TACATCCATCCATCCATCCATCC	4582	GGATGGATGGATGGATGGATGTA
3319	ATACATCCATCCATCCATCCATC	4583	GATGGATGGATGGATGGATGTAT
3320	TATACATCCATCCATCCATCCAT	4584	ATGGATGGATGGATGGATGTATA
3321	CTATACATCCATCCATCCATCCA	4585	TGGATGGATGGATGGATGTATAG
3322	CCTATACATCCATCCATCCATCC	4586	GGATGGATGGATGGATGTATAGG
3323	GCCTATACATCCATCCATCCATC	4587	GATGGATGGATGGATGTATAGGC
3324	TGCCTATACATCCATCCATCCAT	4588	ATGGATGGATGGATGTATAGGCA
3325	CTGCCTATACATCCATCCATCCA	4589	TGGATGGATGGATGTATAGGCAG
3326	TCTGCCTATACATCCATCCATCC	4590	GGATGGATGGATGTATAGGCAGA
3327	ATCTGCCTATACATCCATCCATC	4591	GATGGATGGATGTATAGGCAGAT
3328	CATCTGCCTATACATCCATCCAT	4592	ATGGATGGATGTATAGGCAGATG
3329	CCATCTGCCTATACATCCATCCA	4593	TGGATGGATGTATAGGCAGATGG
3330	TCCATCTGCCTATACATCCATCC	4594	GGATGGATGTATAGGCAGATGGA
3331	GTCCATCTGCCTATACATCCATC	4595	GATGGATGTATAGGCAGATGGAC
3332	TGTCCATCTGCCTATACATCCAT	4596	ATGGATGTATAGGCAGATGGACA
3333	TTGTCCATCTGCCTATACATCCA	4597	TGGATGTATAGGCAGATGGACAA
3334	TTTGTCCATCTGCCTATACATCC	4598	GGATGTATAGGCAGATGGACAAA
3335	ATTTGTCCATCTGCCTATACATC	4599	GATGTATAGGCAGATGGACAAAT
3336	CATTTGTCCATCTGCCTATACAT	4600	ATGTATAGGCAGATGGACAAATG
3337	CCATTTGTCCATCTGCCTATACA	4601	TGTATAGGCAGATGGACAAATGG
3338	TCCATTTGTCCATCTGCCTATAC	4602	GTATAGGCAGATGGACAAATGGA
3339	ATCCATTTGTCCATCTGCCTATA	4603	TATAGGCAGATGGACAAATGGAT
3340	CATCCATTTGTCCATCTGCCTAT	4604	ATAGGCAGATGGACAAATGGATG
3341	TCATCCATTTGTCCATCTGCCTA	4605	TAGGCAGATGGACAAATGGATGA
3342	TTCATCCATTTGTCCATCTGCCT	4606	AGGCAGATGGACAAATGGATGAA
3343	ATTCATCCATTTGTCCATCTGCC	4607	GGCAGATGGACAAATGGATGAAT
3344	CATTCATCCATTTGTCCATCTGC	4608	GCAGATGGACAAATGGATGAATG
3345	CCATTCATCCATTTGTCCATCTG	4609	CAGATGGACAAATGGATGAATGG
3346	CCCATTCATCCATTTGTCCATCT	4610	AGATGGACAAATGGATGAATGGG

3347	ACCCATTCATCCATTTGTCCATC	4611	GATGGACAAATGGATGAATGGGT
3348	CACCCATTCATCCATTTGTCCAT	4612	ATGGACAAATGGATGAATGGGTG
3349	CCACCCATTCATCCATTTGTCCA	4613	TGGACAAATGGATGAATGGGTGG
3350	CCCACCCATTCATCCATTTGTCC	4614	GGACAAATGGATGAATGGGTGGG
3351	ACCCACCCATTCATCCATTTGTC	4615	GACAAATGGATGAATGGGTGGGT
3352	CACCCACCCATTCATCCATTTGT	4616	ACAAATGGATGAATGGGTGGGTG
3353	CCACCCACCCATTCATCCATTTG	4617	CAAATGGATGAATGGGTGGGTGG
3354	TCCACCCACCCATTCATCCATTT	4618	AAATGGATGAATGGGTGGGTGGA
3355	ATCCACCCACCCATTCATCCATT	4619	AATGGATGAATGGGTGGGTGGAT
3356	CATCCACCCACCCATTCATCCAT	4620	ATGGATGAATGGGTGGGTGGATG
3357	TCATCCACCCACCCATTCATCCA	4621	TGGATGAATGGGTGGGTGGATGA
3358	TTCATCCACCCACCCATTCATCC	4622	GGATGAATGGGTGGGTGGATGAA
3359	ATTCATCCACCCACCCATTCATC	4623	GATGAATGGGTGGGTGGATGAAT
3360	CATTCATCCACCCACCCATTCAT	4624	ATGAATGGGTGGGTGGATGAATG
3361	CCATTCATCCACCCACCCATTCA	4625	TGAATGGGTGGGTGGATGAATGG
3362	TCCATTCATCCACCCACCCATTC	4626	GAATGGGTGGGTGGATGAATGGA
3363	TTCCATTCATCCACCCACCCATT	4627	AATGGGTGGGTGGATGAATGGAA
3364	CTTCCATTCATCCACCCACCCAT	4628	ATGGGTGGGTGGATGAATGGAAG
3365	CCTTCCATTCATCCACCCACCCA	4629	TGGGTGGGTGGATGAATGGAAGG
3366	TCCTTCCATTCATCCACCCACCC	4630	GGGTGGGTGGATGAATGGAAGGA
3367	ATCCTTCCATTCATCCACCCACC	4631	GGTGGGTGGATGAATGGAAGGAT
3368	CATCCTTCCATTCATCCACCCAC	4632	GTGGGTGGATGAATGGAAGGATG
3369	ACATCCTTCCATTCATCCACCCA	4633	TGGGTGGATGAATGGAAGGATGT
3370	CACATCCTTCCATTCATCCACCC	4634	GGGTGGATGAATGGAAGGATGTG
3371	ACACATCCTTCCATTCATCCACC	4635	GGTGGATGAATGGAAGGATGTGT
3372	CACACATCCTTCCATTCATCCAC	4636	GTGGATGAATGGAAGGATGTGTG
3373	CCACACATCCTTCCATTCATCCA	4637	TGGATGAATGGAAGGATGTGTGG
3374	ACCACACATCCTTCCATTCATCC	4638	GGATGAATGGAAGGATGTGTGGT
3375	AACCACACATCCTTCCATTCATC	4639	GATGAATGGAAGGATGTGTGGTT
3376	CAACCACACATCCTTCCATTCAT	4640	ATGAATGGAAGGATGTGTGGTTG
3377	TCAACCACACATCCTTCCATTCA	4641	TGAATGGAAGGATGTGTGGTTGA
3378	TTCAACCACACATCCTTCCATTC	4642	GAATGGAAGGATGTGTGGTTGAA
3379	GTTCAACCACACATCCTTCCATT	4643	AATGGAAGGATGTGTGGTTGAAC
3380	AGTTCAACCACACATCCTTCCAT	4644	ATGGAAGGATGTGTGGTTGAACT
3381	TAGTTCAACCACACATCCTTCCA	4645	TGGAAGGATGTGTGGTTGAACTA
3382	ATAGTTCAACCACACATCCTTCC	4646	GGAAGGATGTGTGGTTGAACTAT
3383	AATAGTTCAACCACACATCCTTC	4647	GAAGGATGTGTGGTTGAACTATT
3384	CAATAGTTCAACCACACATCCTT	4648	AAGGATGTGTGGTTGAACTATTG
3385	GCAATAGTTCAACCACACATCCT	4649	AGGATGTGTGGTTGAACTATTGC
3386	TGCAATAGTTCAACCACACATCC	4650	GGATGTGTGGTTGAACTATTGCA
3387	TTGCAATAGTTCAACCACACATC	4651	GATGTGTGGTTGAACTATTGCAA
3388	CTTGCAATAGTTCAACCACACAT	4652	ATGTGTGGTTGAACTATTGCAAG

3389	ACTTGCAATAGTTCAACCACACA	4653	TGTGTGGTTGAACTATTGCAAGT
3390	TACTTGCAATAGTTCAACCACAC	4654	GTGTGGTTGAACTATTGCAAGTA
3391	ATACTTGCAATAGTTCAACCACA	4655	TGTGGTTGAACTATTGCAAGTAT
3392	AATACTTGCAATAGTTCAACCAC	4656	GTGGTTGAACTATTGCAAGTATT
3393	CAATACTTGCAATAGTTCAACCA	4657	TGGTTGAACTATTGCAAGTATTG
3394	TCAATACTTGCAATAGTTCAACC	4658	GGTTGAACTATTGCAAGTATTGA
3395	ATCAATACTTGCAATAGTTCAAC	4659	GTTGAACTATTGCAAGTATTGAT
3396	TATCAATACTTGCAATAGTTCAA	4660	TTGAACTATTGCAAGTATTGATA
3397	TTATCAATACTTGCAATAGTTCA	4661	TGAACTATTGCAAGTATTGATAA
3398	ATTATCAATACTTGCAATAGTTC	4662	GAACTATTGCAAGTATTGATAAT
3399	AATTATCAATACTTGCAATAGTT	4663	AACTATTGCAAGTATTGATAATT
3400	CAATTATCAATACTTGCAATAGT	4664	ACTATTGCAAGTATTGATAATTG
3401	CCAATTATCAATACTTGCAATAG	4665	CTATTGCAAGTATTGATAATTGG
3402	CCCAATTATCAATACTTGCAATA	4666	TATTGCAAGTATTGATAATTGGG
3403	ACCCAATTATCAATACTTGCAAT	4667	ATTGCAAGTATTGATAATTGGGT
3404	AACCCAATTATCAATACTTGCAA	4668	TTGCAAGTATTGATAATTGGGTT
3405	GAACCCAATTATCAATACTTGCA	4669	TGCAAGTATTGATAATTGGGTTC
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3407	ATGAACCCAATTATCAATACTTG	4671	CAAGTATTGATAATTGGGTTCAT
3408	TATGAACCCAATTATCAATACTT	4672	AAGTATTGATAATTGGGTTCATA
3409	TTATGAACCCAATTATCAATACT	4673	AGTATTGATAATTGGGTTCATAA
3410	ATTATGAACCCAATTATCAATAC	4674	GTATTGATAATTGGGTTCATAAT
3411	AATTATGAACCCAATTATCAATA	4675	TATTGATAATTGGGTTCATAATT
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3413	GAAATTATGAACCCAATTATCAA	4677	TTGATAATTGGGTTCATAATTTC
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3415	CAGAAATTATGAACCCAATTATC	4679	GATAATTGGGTTCATAATTTCTG
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3419	TATTCAGAAATTATGAACCCAAT	4683	ATTGGGTTCATAATTTCTGAATA
3420	ATATTCAGAAATTATGAACCCAA	4684	TTGGGTTCATAATTTCTGAATAT
3421	AATATTCAGAAATTATGAACCCA	4685	TGGGTTCATAATTTCTGAATATT
3422	AAATATTCAGAAATTATGAACCC	4686	GGGTTCATAATTTCTGAATATTT
3423	TAAATATTCAGAAATTATGAACC	4687	GGTTCATAATTTCTGAATATTTA
3424	CTAAATATTCAGAAATTATGAAC	4688	GTTCATAATTTCTGAATATTTAG
3425	TCTAAATATTCAGAAATTATGAA	4689	TTCATAATTTCTGAATATTTAGA
3426	ATCTAAATATTCAGAAATTATGA	4690	TCATAATTTCTGAATATTTAGAT
3427	CATCTAAATATTCAGAAATTATG	4691	CATAATTTCTGAATATTTAGATG
3428	CCATCTAAATATTCAGAAATTAT	4692	ATAATTTCTGAATATTTAGATGG
3429	TCCATCTAAATATTCAGAAATTA	4693	TAATTTCTGAATATTTAGATGGA
3430	ATCCATCTAAATATTCAGAAATT	4694	AATTTCTGAATATTTAGATGGAT

3431	CATCCATCTAAATATTCAGAAAT	4695	ATTTCTGAATATTTAGATGGATG
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3433	ACCATCCATCTAAATATTCAGAA	4697	TTCTGAATATTTAGATGGATGGT
3434	AACCATCCATCTAAATATTCAGA	4698	TCTGAATATTTAGATGGATGGTT
3435	CAACCATCCATCTAAATATTCAG	4699	CTGAATATTTAGATGGATGGTTG
3436	ACAACCATCCATCTAAATATTCA	4700	TGAATATTTAGATGGATGGTTGT
3437	CACAACCATCCATCTAAATATTC	4701	GAATATTTAGATGGATGGTTGTG
3438	TCACAACCATCCATCTAAATATT	4702	AATATTTAGATGGATGGTTGTGA
3439	CTCACAACCATCCATCTAAATAT	4703	ATATTTAGATGGATGGTTGTGAG
3440	ACTCACAACCATCCATCTAAATA	4704	TATTTAGATGGATGGTTGTGAGT
3441	CACTCACAACCATCCATCTAAAT	4705	ATTTAGATGGATGGTTGTGAGTG
3442	CCACTCACAACCATCCATCTAAA	4706	TTTAGATGGATGGTTGTGAGTGG
3443	GCCACTCACAACCATCCATCTAA	4707	TTAGATGGATGGTTGTGAGTGGC
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3447	ACCAGCCACTCACAACCATCCAT	4711	ATGGATGGTTGTGAGTGGCTGGT
3448	CACCAGCCACTCACAACCATCCA	4712	TGGATGGTTGTGAGTGGCTGGTG
3449	CCACCAGCCACTCACAACCATCC	4713	GGATGGTTGTGAGTGGCTGGTGG
3450	TCCACCAGCCACTCACAACCATC	4714	GATGGTTGTGAGTGGCTGGTGGA
3451	GTCCACCAGCCACTCACAACCAT	4715	ATGGTTGTGAGTGGCTGGTGGAC
3452	TGTCCACCAGCCACTCACAACCA	4716	TGGTTGTGAGTGGCTGGTGGACA
3453	CTGTCCACCAGCCACTCACAACC	4717	GGTTGTGAGTGGCTGGTGGACAG
3454	TCTGTCCACCAGCCACTCACAAC	4718	GTTGTGAGTGGCTGGTGGACAGA
3455	GTCTGTCCACCAGCCACTCACAA	4719	TTGTGAGTGGCTGGTGGACAGAC
3456	CGTCTGTCCACCAGCCACTCACA	4720	TGTGAGTGGCTGGTGGACAGACG
3457	TCGTCTGTCCACCAGCCACTCAC	4721	GTGAGTGGCTGGTGGACAGACGA
3458	TTCGTCTGTCCACCAGCCACTCA	4722	TGAGTGGCTGGTGGACAGACGAA
3459	TTTCGTCTGTCCACCAGCCACTC	4723	GAGTGGCTGGTGGACAGACGAAA
3460	TTTTCGTCTGTCCACCAGCCACT	4724	AGTGGCTGGTGGACAGACGAAAA
3461	TTTTTCGTCTGTCCACCAGCCAC	4725	GTGGCTGGTGGACAGACGAAAAA
3462	ATTTTTCGTCTGTCCACCAGCCA	4726	TGGCTGGTGGACAGACGAAAAAT
3463	CATTTTTCGTCTGTCCACCAGCC	4727	GGCTGGTGGACAGACGAAAAATG
3464	CCATTTTTCGTCTGTCCACCAGC	4728	GCTGGTGGACAGACGAAAAATGG
3465	TCCATTTTTCGTCTGTCCACCAG	4729	CTGGTGGACAGACGAAAAATGGA
3466	ATCCATTTTTCGTCTGTCCACCA	4730	TGGTGGACAGACGAAAAATGGAT
3467	CATCCATTTTTCGTCTGTCCACC	4731	GGTGGACAGACGAAAAATGGATG
3468	CCATCCATTTTTCGTCTGTCCAC	4732	GTGGACAGACGAAAAATGGATGG
3469	ACCATCCATTTTTCGTCTGTCCA	4733	TGGACAGACGAAAAATGGATGGT
3470	AACCATCCATTTTTCGTCTGTCC	4734	GGACAGACGAAAAATGGATGGTT
3471	CAACCATCCATTTTTCGTCTGTC	4735	GACAGACGAAAAATGGATGGTTG
3472	CCAACCATCCATTTTTCGTCTGT	4736	ACAGACGAAAAATGGATGGTTGG

3473	TCCAACCATCCATTTTTCGTCTG	4737	CAGACGAAAAATGGATGGTTGGA
3474	ATCCAACCATCCATTTTTCGTCT	4738	AGACGAAAAATGGATGGTTGGAT
3475	TATCCAACCATCCATTTTTCGTC	4739	GACGAAAAATGGATGGTTGGATA
3476	TTATCCAACCATCCATTTTTCGT	4740	ACGAAAAATGGATGGTTGGATAA
3477	TTTATCCAACCATCCATTTTTCG	4741	CGAAAAATGGATGGTTGGATAAA
3478	ATTTATCCAACCATCCATTTTTC	4742	GAAAAATGGATGGTTGGATAAAT
3479	AATTTATCCAACCATCCATTTTT	4743	AAAAATGGATGGTTGGATAAATT
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3482	ATCAATTTATCCAACCATCCATT	4746	AATGGATGGTTGGATAAATTGAT
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3484	CCATCAATTTATCCAACCATCCA	4748	TGGATGGTTGGATAAATTGATGG
3485	CCCATCAATTTATCCAACCATCC	4749	GGATGGTTGGATAAATTGATGGG
3486	ACCCATCAATTTATCCAACCATC	4750	GATGGTTGGATAAATTGATGGGT
3487	CACCCATCAATTTATCCAACCAT	4751	ATGGTTGGATAAATTGATGGGTG
3488	CCACCCATCAATTTATCCAACCA	4752	TGGTTGGATAAATTGATGGGTGG
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3493	TCCATCCACCCATCAATTTATCC	4757	GGATAAATTGATGGGTGGATGGA
3494	ATCCATCCACCCATCAATTTATC	4758	GATAAATTGATGGGTGGATGGAT
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3499	CAACCATCCATCCACCCATCAAT	4763	ATTGATGGGTGGATGGATGGTTG
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3502	AACCAACCATCCATCCACCCATC	4766	GATGGGTGGATGGATGGTTGGTT
3503	CAACCAACCATCCATCCACCCAT	4767	ATGGGTGGATGGATGGTTGGTTG
3504	ACAACCAACCATCCATCCACCCA	4768	TGGGTGGATGGATGGTTGGTTGT
3505	TACAACCAACCATCCATCCACCC	4769	GGGTGGATGGATGGTTGGTTGTA
3506	ATACAACCAACCATCCATCCACC	4770	GGTGGATGGATGGTTGGTTGTAT
3507	CATACAACCAACCATCCATCCAC	4771	GTGGATGGATGGTTGGTTGTATG
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3509	TTCATACAACCAACCATCCATCC	4773	GGATGGATGGTTGGTTGTATGAA
3510	TTTCATACAACCAACCATCCATC	4774	GATGGATGGTTGGTTGTATGAAA
3511	CTTTCATACAACCAACCATCCAT	4775	ATGGATGGTTGGTTGTATGAAAG
3512	TCTTTCATACAACCAACCATCCA	4776	TGGATGGTTGGTTGTATGAAAGA
3513	TTCTTTCATACAACCAACCATCC	4777	GGATGGTTGGTTGTATGAAAGAA
3514	ATTCTTTCATACAACCAACCATC	4778	GATGGTTGGTTGTATGAAAGAAT

3515	CATTCTTTCATACAACCAACCAT	4779	ATGGTTGGTTGTATGAAAGAATG
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3517	TTCATTCTTTCATACAACCAACC	4781	GGTTGGTTGTATGAAAGAATGAA
3518	ATTCATTCTTTCATACAACCAAC	4782	GTTGGTTGTATGAAAGAATGAAT
3519	CATTCATTCTTTCATACAACCAA	4783	TTGGTTGTATGAAAGAATGAATG
3520	TCATTCATTCTTTCATACAACCA	4784	TGGTTGTATGAAAGAATGAATGA
3521	ATCATTCATTCTTTCATACAACC	4785	GGTTGTATGAAAGAATGAATGAT
3522	AATCATTCATTCTTTCATACAAC	4786	GTTGTATGAAAGAATGAATGATT
3523	CAATCATTCATTCTTTCATACAA	4787	TTGTATGAAAGAATGAATGATTG
3524	CCAATCATTCATTCTTTCATACA	4788	TGTATGAAAGAATGAATGATTGG
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3526	ACCCAATCATTCATTCTTTCATA	4790	TATGAAAGAATGAATGATTGGGT
3527	TACCCAATCATTCATTCTTTCAT	4791	ATGAAAGAATGAATGATTGGGTA
3528	CTACCCAATCATTCATTCTTTCA	4792	TGAAAGAATGAATGATTGGGTAG
3529	CCTACCCAATCATTCATTCTTTC	4793	GAAAGAATGAATGATTGGGTAGG
3530	ACCTACCCAATCATTCATTCTTT	4794	AAAGAATGAATGATTGGGTAGGT
3531	CACCTACCCAATCATTCATTCTT	4795	AAGAATGAATGATTGGGTAGGTG
3532	CCACCTACCCAATCATTCATTCT	4796	AGAATGAATGATTGGGTAGGTGG
3533	TCCACCTACCCAATCATTCATTC	4797	GAATGAATGATTGGGTAGGTGGA
3534	ATCCACCTACCCAATCATTCATT	4798	AATGAATGATTGGGTAGGTGGAT
3535	AATCCACCTACCCAATCATTCAT	4799	ATGAATGATTGGGTAGGTGGATT
3536	TAATCCACCTACCCAATCATTCA	4800	TGAATGATTGGGTAGGTGGATTA
3537	TTAATCCACCTACCCAATCATTC	4801	GAATGATTGGGTAGGTGGATTAA
3538	CTTAATCCACCTACCCAATCATT	4802	AATGATTGGGTAGGTGGATTAAG
3539	ACTTAATCCACCTACCCAATCAT	4803	ATGATTGGGTAGGTGGATTAAGT
3540	AACTTAATCCACCTACCCAATCA	4804	TGATTGGGTAGGTGGATTAAGTT
3541	CAACTTAATCCACCTACCCAATC	4805	GATTGGGTAGGTGGATTAAGTTG
3542	GCAACTTAATCCACCTACCCAAT	4806	ATTGGGTAGGTGGATTAAGTTGC
3543	CGCAACTTAATCCACCTACCCAA	4807	TTGGGTAGGTGGATTAAGTTGCG
3544	CCGCAACTTAATCCACCTACCCA	4808	TGGGTAGGTGGATTAAGTTGCGG
3545	TCCGCAACTTAATCCACCTACCC	4809	GGGTAGGTGGATTAAGTTGCGGA
3546	ATCCGCAACTTAATCCACCTACC	4810	GGTAGGTGGATTAAGTTGCGGAT
3547	GATCCGCAACTTAATCCACCTAC	4811	GTAGGTGGATTAAGTTGCGGATC
3548	TGATCCGCAACTTAATCCACCTA	4812	TAGGTGGATTAAGTTGCGGATCA
3549	TTGATCCGCAACTTAATCCACCT	4813	AGGTGGATTAAGTTGCGGATCAA
3550	ATTGATCCGCAACTTAATCCACC	4814	GGTGGATTAAGTTGCGGATCAAT
3551	CATTGATCCGCAACTTAATCCAC	4815	GTGGATTAAGTTGCGGATCAATG
3552	ACATTGATCCGCAACTTAATCCA	4816	TGGATTAAGTTGCGGATCAATGT
3553	TACATTGATCCGCAACTTAATCC	4817	GGATTAAGTTGCGGATCAATGTA
3554	ATACATTGATCCGCAACTTAATC	4818	GATTAAGTTGCGGATCAATGTAT
3555	CATACATTGATCCGCAACTTAAT	4819	ATTAAGTTGCGGATCAATGTATG
3556	CCATACATTGATCCGCAACTTAA	4820	TTAAGTTGCGGATCAATGTATGG

3557	CCCATACATTGATCCGCAACTTA	4821	TAAGTTGCGGATCAATGTATGGG
3558	TCCCATACATTGATCCGCAACTT	4822	AAGTTGCGGATCAATGTATGGGA
3559	ATCCCATACATTGATCCGCAACT	4823	AGTTGCGGATCAATGTATGGGAT
3560	CATCCCATACATTGATCCGCAAC	4824	GTTGCGGATCAATGTATGGGATG
3561	CCATCCCATACATTGATCCGCAA	4825	TTGCGGATCAATGTATGGGATGG
3562	TCCATCCCATACATTGATCCGCA	4826	TGCGGATCAATGTATGGGATGGA
3563	ATCCATCCCATACATTGATCCGC	4827	GCGGATCAATGTATGGGATGGAT
3564	CATCCATCCCATACATTGATCCG	4828	CGGATCAATGTATGGGATGGATG
3565	TCATCCATCCCATACATTGATCC	4829	GGATCAATGTATGGGATGGATGA
3566	TTCATCCATCCCATACATTGATC	4830	GATCAATGTATGGGATGGATGAA
3567	ATTCATCCATCCCATACATTGAT	4831	ATCAATGTATGGGATGGATGAAT
3568	CATTCATCCATCCCATACATTGA	4832	TCAATGTATGGGATGGATGAATG
3569	CCATTCATCCATCCCATACATTG	4833	CAATGTATGGGATGGATGAATGG
3570	TCCATTCATCCATCCCATACATT	4834	AATGTATGGGATGGATGAATGGA
3571	ATCCATTCATCCATCCCATACAT	4835	ATGTATGGGATGGATGAATGGAT
3572	CATCCATTCATCCATCCCATACA	4836	TGTATGGGATGGATGAATGGATG
3573	CCATCCATTCATCCATCCCATAC	4837	GTATGGGATGGATGAATGGATGG
3574	TCCATCCATTCATCCATCCCATA	4838	TATGGGATGGATGAATGGATGGA
3575	ATCCATCCATTCATCCATCCCAT	4839	ATGGGATGGATGAATGGATGGAT
3576	CATCCATCCATTCATCCATCCCA	4840	TGGGATGGATGAATGGATGGATG
3577	CCATCCATCCATTCATCCATCCC	4841	GGGATGGATGAATGGATGGATGG
3578	TCCATCCATCCATTCATCCATCC	4842	GGATGGATGAATGGATGGATGGA
3579	ATCCATCCATCCATTCATCCATC	4843	GATGGATGAATGGATGGATGGAT
3580	CATCCATCCATCCATTCATCCAT	4844	ATGGATGAATGGATGGATGGATG
3581	CCATCCATCCATCCATTCATCCA	4845	TGGATGAATGGATGGATGGATGG
3582	TCCATCCATCCATCCATTCATCC	4846	GGATGAATGGATGGATGGATGGA
3583	ATCCATCCATCCATCCATTCATC	4847	GATGAATGGATGGATGGATGGAT
3584	CATCCATCCATCCATCCATTCAT	4848	ATGAATGGATGGATGGATGGATG
3585	ACATCCATCCATCCATCCATTCA	4849	TGAATGGATGGATGGATGGATGT
3586	CACATCCATCCATCCATCCATTC	4850	GAATGGATGGATGGATGGATGTG
3587	ACACATCCATCCATCCATCCATT	4851	AATGGATGGATGGATGGATGTGT
3588	CACACATCCATCCATCCATCCAT	4852	ATGGATGGATGGATGGATGTGTG
3589	CCACACATCCATCCATCCATCCA	4853	TGGATGGATGGATGGATGTGTGG
3590	ACCACACATCCATCCATCCATCC	4854	GGATGGATGGATGGATGTGTGGT
3591	AACCACACATCCATCCATCCATC	4855	GATGGATGGATGGATGTGTGGTT
3592	CAACCACACATCCATCCATCCAT	4856	ATGGATGGATGGATGTGTGGTTG
3593	TCAACCACACATCCATCCATCCA	4857	TGGATGGATGGATGTGTGGTTGA
3594	TTCAACCACACATCCATCCATCC	4858	GGATGGATGGATGTGTGGTTGAA
3595	ATTCAACCACACATCCATCCATC	4859	GATGGATGGATGTGTGGTTGAAT
3596	AATTCAACCACACATCCATCCAT	4860	ATGGATGGATGTGTGGTTGAATT
3597	TAATTCAACCACACATCCATCCA	4861	TGGATGGATGTGTGGTTGAATTA
3598	GTAATTCAACCACACATCCATCC	4862	GGATGGATGTGTGGTTGAATTAC

3599	AGTAATTCAACCACACATCCATC	4863	GATGGATGTGTGGTTGAATTACT
3600	CAGTAATTCAACCACACATCCAT	4864	ATGGATGTGTGGTTGAATTACTG
3601	TCAGTAATTCAACCACACATCCA	4865	TGGATGTGTGGTTGAATTACTGA
3602	TTCAGTAATTCAACCACACATCC	4866	GGATGTGTGGTTGAATTACTGAA
3603	TTTCAGTAATTCAACCACACATC	4867	GATGTGTGGTTGAATTACTGAAA
3604	CTTTCAGTAATTCAACCACACAT	4868	ATGTGTGGTTGAATTACTGAAAG
3605	CCTTTCAGTAATTCAACCACACA	4869	TGTGTGGTTGAATTACTGAAAGG
3606	ACCTTTCAGTAATTCAACCACAC	4870	GTGTGGTTGAATTACTGAAAGGT
3607	AACCTTTCAGTAATTCAACCACA	4871	TGTGGTTGAATTACTGAAAGGTT
3608	CAACCTTTCAGTAATTCAACCAC	4872	GTGGTTGAATTACTGAAAGGTTG
3609	CCAACCTTTCAGTAATTCAACCA	4873	TGGTTGAATTACTGAAAGGTTGG
3610	TCCAACCTTTCAGTAATTCAACC	4874	GGTTGAATTACTGAAAGGTTGGA
3611	TTCCAACCTTTCAGTAATTCAAC	4875	GTTGAATTACTGAAAGGTTGGAA
3612	CTTCCAACCTTTCAGTAATTCAA	4876	TTGAATTACTGAAAGGTTGGAAG
3613	TCTTCCAACCTTTCAGTAATTCA	4877	TGAATTACTGAAAGGTTGGAAGA
3614	CTCTTCCAACCTTTCAGTAATTC	4878	GAATTACTGAAAGGTTGGAAGAG
3615	ACTCTTCCAACCTTTCAGTAATT	4879	AATTACTGAAAGGTTGGAAGAGT
3616	CACTCTTCCAACCTTTCAGTAAT	4880	ATTACTGAAAGGTTGGAAGAGTG
3617	CCACTCTTCCAACCTTTCAGTAA	4881	TTACTGAAAGGTTGGAAGAGTGG
3618	TCCACTCTTCCAACCTTTCAGTA	4882	TACTGAAAGGTTGGAAGAGTGGA
3619	ATCCACTCTTCCAACCTTTCAGT	4883	ACTGAAAGGTTGGAAGAGTGGAT
3620	CATCCACTCTTCCAACCTTTCAG	4884	CTGAAAGGTTGGAAGAGTGGATG
3621	CCATCCACTCTTCCAACCTTTCA	4885	TGAAAGGTTGGAAGAGTGGATGG
3622	CCCATCCACTCTTCCAACCTTTC	4886	GAAAGGTTGGAAGAGTGGATGGG
3623	ACCCATCCACTCTTCCAACCTTT	4887	AAAGGTTGGAAGAGTGGATGGGT
3624	CACCCATCCACTCTTCCAACCTT	4888	AAGGTTGGAAGAGTGGATGGGTG
3625	TCACCCATCCACTCTTCCAACCT	4889	AGGTTGGAAGAGTGGATGGGTGA
3626	TTCACCCATCCACTCTTCCAACC	4890	GGTTGGAAGAGTGGATGGGTGAA
3627	TTTCACCCATCCACTCTTCCAAC	4891	GTTGGAAGAGTGGATGGGTGAAA
3628	ATTTCACCCATCCACTCTTCCAA	4892	TTGGAAGAGTGGATGGGTGAAAT
3629	AATTTCACCCATCCACTCTTCCA	4893	TGGAAGAGTGGATGGGTGAAATT
3630	AAATTTCACCCATCCACTCTTCC	4894	GGAAGAGTGGATGGGTGAAATTT
3631	CAAATTTCACCCATCCACTCTTC	4895	GAAGAGTGGATGGGTGAAATTTG
3632	CCAAATTTCACCCATCCACTCTT	4896	AAGAGTGGATGGGTGAAATTTGG
3633	CCCAAATTTCACCCATCCACTCT	4897	AGAGTGGATGGGTGAAATTTGGG
3634	CCCCAAATTTCACCCATCCACTC	4898	GAGTGGATGGGTGAAATTTGGGG
3635	ACCCCAAATTTCACCCATCCACT	4899	AGTGGATGGGTGAAATTTGGGGT
3636	TACCCCAAATTTCACCCATCCAC	4900	GTGGATGGGTGAAATTTGGGGTA
3637	CTACCCCAAATTTCACCCATCCA	4901	TGGATGGGTGAAATTTGGGGTAG
3638	ACTACCCCAAATTTCACCCATCC	4902	GGATGGGTGAAATTTGGGGTAGT
3639	AACTACCCCAAATTTCACCCATC	4903	GATGGGTGAAATTTGGGGTAGTT
3640	TAACTACCCCAAATTTCACCCAT	4904	ATGGGTGAAATTTGGGGTAGTTA

3641	CTAACTACCCCAAATTTCACCCA	4905	TGGGTGAAATTTGGGGTAGTTAG
3642	TCTAACTACCCCAAATTTCACCC	4906	GGGTGAAATTTGGGGTAGTTAGA
3643	ATCTAACTACCCCAAATTTCACC	4907	GGTGAAATTTGGGGTAGTTAGAT
3644	CATCTAACTACCCCAAATTTCAC	4908	GTGAAATTTGGGGTAGTTAGATG
3645	CCATCTAACTACCCCAAATTTCA	4909	TGAAATTTGGGGTAGTTAGATGG
3646	CCCATCTAACTACCCCAAATTTC	4910	GAAATTTGGGGTAGTTAGATGGG
3647	ACCCATCTAACTACCCCAAATTT	4911	AAATTTGGGGTAGTTAGATGGGT
3648	CACCCATCTAACTACCCCAAATT	4912	AATTTGGGGTAGTTAGATGGGTG
3649	CCACCCATCTAACTACCCCAAAT	4913	ATTTGGGGTAGTTAGATGGGTGG
3650	CCCACCCATCTAACTACCCCAAA	4914	TTTGGGGTAGTTAGATGGGTGGG
3651	ACCCACCCATCTAACTACCCCAA	4915	TTGGGGTAGTTAGATGGGTGGGT
3652	CACCCACCCATCTAACTACCCCA	4916	TGGGGTAGTTAGATGGGTGGGTG
3653	ACACCCACCCATCTAACTACCCC	4917	GGGGTAGTTAGATGGGTGGGTGT
3654	CACACCCACCCATCTAACTACCC	4918	GGGTAGTTAGATGGGTGGGTGTG
3655	ACACACCCACCCATCTAACTACC	4919	GGTAGTTAGATGGGTGGGTGTGT
3656	CACACACCCACCCATCTAACTAC	4920	GTAGTTAGATGGGTGGGTGTGTG
3657	CCACACACCCACCCATCTAACTA	4921	TAGTTAGATGGGTGGGTGTGTGG
3658	TCCACACACCCACCCATCTAACT	4922	AGTTAGATGGGTGGGTGTGTGGA
3659	ATCCACACACCCACCCATCTAAC	4923	GTTAGATGGGTGGGTGTGTGGAT
3660	CATCCACACACCCACCCATCTAA	4924	TTAGATGGGTGGGTGTGTGGATG
3661	CCATCCACACACCCACCCATCTA	4925	TAGATGGGTGGGTGTGTGGATGG
3662	TCCATCCACACACCCACCCATCT	4926	AGATGGGTGGGTGTGTGGATGGA
3663	ATCCATCCACACACCCACCCATC	4927	GATGGGTGGGTGTGTGGATGGAT
3664	TATCCATCCACACACCCACCCAT	4928	ATGGGTGGGTGTGTGGATGGATA
3665	TTATCCATCCACACACCCACCCA	4929	TGGGTGGGTGTGTGGATGGATAA
3666	TTTATCCATCCACACACCCACCC	4930	GGGTGGGTGTGTGGATGGATAAA
3667	TTTTATCCATCCACACACCCACC	4931	GGTGGGTGTGTGGATGGATAAAA
3668	CTTTTATCCATCCACACACCCAC	4932	GTGGGTGTGTGGATGGATAAAAG
3669	TCTTTTATCCATCCACACACCCA	4933	TGGGTGTGTGGATGGATAAAAGA
3670	CTCTTTTATCCATCCACACACCC	4934	GGGTGTGTGGATGGATAAAAGAG
3671	ACTCTTTTATCCATCCACACACC	4935	GGTGTGTGGATGGATAAAAGAGT
3672	TACTCTTTTATCCATCCACACAC	4936	GTGTGTGGATGGATAAAAGAGTA
3673	CTACTCTTTTATCCATCCACACA	4937	TGTGTGGATGGATAAAAGAGTAG
3674	TCTACTCTTTTATCCATCCACAC	4938	GTGTGGATGGATAAAAGAGTAGA
3675	ATCTACTCTTTTATCCATCCACA	4939	TGTGGATGGATAAAAGAGTAGAT
3676	CATCTACTCTTTTATCCATCCAC	4940	GTGGATGGATAAAAGAGTAGATG
3677	TCATCTACTCTTTTATCCATCCA	4941	TGGATGGATAAAAGAGTAGATGA
3678	TTCATCTACTCTTTTATCCATCC	4942	GGATGGATAAAAGAGTAGATGAA
3679	ATTCATCTACTCTTTTATCCATC	4943	GATGGATAAAAGAGTAGATGAAT
3680	CATTCATCTACTCTTTTATCCAT	4944	ATGGATAAAAGAGTAGATGAATG
3681	TCATTCATCTACTCTTTTATCCA	4945	TGGATAAAAGAGTAGATGAATGA
3682	TTCATTCATCTACTCTTTTATCC	4946	GGATAAAAGAGTAGATGAATGAA

3683	ATTCATTCATCTACTCTTTTATC	4947	GATAAAAGAGTAGATGAATGAAT
3684	AATTCATTCATCTACTCTTTTAT	4948	ATAAAAGAGTAGATGAATGAATT
3685	TAATTCATTCATCTACTCTTTTA	4949	TAAAAGAGTAGATGAATGAATTA
3686	TTAATTCATTCATCTACTCTTTT	4950	AAAAGAGTAGATGAATGAATTAA
3687	ATTAATTCATTCATCTACTCTTT	4951	AAAGAGTAGATGAATGAATTAAT
3688	CATTAATTCATTCATCTACTCTT	4952	AAGAGTAGATGAATGAATTAATG
3689	TCATTAATTCATTCATCTACTCT	4953	AGAGTAGATGAATGAATTAATGA
3690	TTCATTAATTCATTCATCTACTC	4954	GAGTAGATGAATGAATTAATGAA
3691	ATTCATTAATTCATTCATCTACT	4955	AGTAGATGAATGAATTAATGAAT
3692	TATTCATTAATTCATTCATCTAC	4956	GTAGATGAATGAATTAATGAATA
3693	TTATTCATTAATTCATTCATCTA	4957	TAGATGAATGAATTAATGAATAA
3694	TTTATTCATTAATTCATTCATCT	4958	AGATGAATGAATTAATGAATAAA
3695	GTTTATTCATTAATTCATTCATC	4959	GATGAATGAATTAATGAATAAAC
3696	TGTTTATTCATTAATTCATTCAT	4960	ATGAATGAATTAATGAATAAACA
3697	CTGTTTATTCATTAATTCATTCA	4961	TGAATGAATTAATGAATAAACAG
3698	CCTGTTTATTCATTAATTCATTC	4962	GAATGAATTAATGAATAAACAGG
3699	GCCTGTTTATTCATTAATTCATT	4963	AATGAATTAATGAATAAACAGGC
3700	TGCCTGTTTATTCATTAATTCAT	4964	ATGAATTAATGAATAAACAGGCA
3701	CTGCCTGTTTATTCATTAATTCA	4965	TGAATTAATGAATAAACAGGCAG
3702	TCTGCCTGTTTATTCATTAATTC	4966	GAATTAATGAATAAACAGGCAGA
3703	ATCTGCCTGTTTATTCATTAATT	4967	AATTAATGAATAAACAGGCAGAT
3704	CATCTGCCTGTTTATTCATTAAT	4968	ATTAATGAATAAACAGGCAGATG
3705	CCATCTGCCTGTTTATTCATTAA	4969	TTAATGAATAAACAGGCAGATGG
3706	TCCATCTGCCTGTTTATTCATTA	4970	TAATGAATAAACAGGCAGATGGA
3707	ATCCATCTGCCTGTTTATTCATT	4971	AATGAATAAACAGGCAGATGGAT
3708	CATCCATCTGCCTGTTTATTCAT	4972	ATGAATAAACAGGCAGATGGATG
3709	TCATCCATCTGCCTGTTTATTCA	4973	TGAATAAACAGGCAGATGGATGA
3710	ATCATCCATCTGCCTGTTTATTC	4974	GAATAAACAGGCAGATGGATGAT
3711	CATCATCCATCTGCCTGTTTATT	4975	AATAAACAGGCAGATGGATGATG
3712	ACATCATCCATCTGCCTGTTTAT	4976	ATAAACAGGCAGATGGATGATGT
3713	TACATCATCCATCTGCCTGTTTA	4977	TAAACAGGCAGATGGATGATGTA
3714	TTACATCATCCATCTGCCTGTTT	4978	AAACAGGCAGATGGATGATGTAA
3715	CTTACATCATCCATCTGCCTGTT	4979	AACAGGCAGATGGATGATGTAAG
3716	GCTTACATCATCCATCTGCCTGT	4980	ACAGGCAGATGGATGATGTAAGC
3717	AGCTTACATCATCCATCTGCCTG	4981	CAGGCAGATGGATGATGTAAGCT
3718	CAGCTTACATCATCCATCTGCCT	4982	AGGCAGATGGATGATGTAAGCTG
3719	GCAGCTTACATCATCCATCTGCC	4983	GGCAGATGGATGATGTAAGCTGC
3720	GGCAGCTTACATCATCCATCTGC	4984	GCAGATGGATGATGTAAGCTGCC
3721	GGGCAGCTTACATCATCCATCTG	4985	CAGATGGATGATGTAAGCTGCCC
3722	GGGGCAGCTTACATCATCCATCT	4986	AGATGGATGATGTAAGCTGCCCC
3723	TGGGGCAGCTTACATCATCCATC	4987	GATGGATGATGTAAGCTGCCCCA
3724	CTGGGGCAGCTTACATCATCCAT	4988	ATGGATGATGTAAGCTGCCCCAG

3725	TCTGGGGCAGCTTACATCATCCA	4989	TGGATGATGTAAGCTGCCCCAGA
3726	GTCTGGGGCAGCTTACATCATCC	4990	GGATGATGTAAGCTGCCCCAGAC
3727	GGTCTGGGGCAGCTTACATCATC	4991	GATGATGTAAGCTGCCCCAGACC
3728	GGGTCTGGGGCAGCTTACATCAT	4992	ATGATGTAAGCTGCCCCAGACCC
3729	AGGGTCTGGGGCAGCTTACATCA	4993	TGATGTAAGCTGCCCCAGACCCT
3730	CAGGGTCTGGGGCAGCTTACATC	4994	GATGTAAGCTGCCCCAGACCCTG
3731	CCAGGGTCTGGGGCAGCTTACAT	4995	ATGTAAGCTGCCCCAGACCCTGG
3732	CCCAGGGTCTGGGGCAGCTTACA	4996	TGTAAGCTGCCCCAGACCCTGGG
3733	TCCCAGGGTCTGGGGCAGCTTAC	4997	GTAAGCTGCCCCAGACCCTGGGA
3734	GTCCCAGGGTCTGGGGCAGCTTA	4998	TAAGCTGCCCCAGACCCTGGGAC
3735	GGTCCCAGGGTCTGGGGCAGCTT	4999	AAGCTGCCCCAGACCCTGGGACC
3736	AGGTCCCAGGGTCTGGGGCAGCT	5000	AGCTGCCCCAGACCCTGGGACCT
3737	GAGGTCCCAGGGTCTGGGGCAGC	5001	GCTGCCCCAGACCCTGGGACCTC
3738	AGAGGTCCCAGGGTCTGGGGCAG	5002	CTGCCCCAGACCCTGGGACCTCT
3739	CAGAGGTCCCAGGGTCTGGGGCA	5003	TGCCCCAGACCCTGGGACCTCTG
3740	TCAGAGGTCCCAGGGTCTGGGGC	5004	GCCCCAGACCCTGGGACCTCTGA
3741	GTCAGAGGTCCCAGGGTCTGGGG	5005	CCCCAGACCCTGGGACCTCTGAC
3742	GGTCAGAGGTCCCAGGGTCTGGG	5006	CCCAGACCCTGGGACCTCTGACC
3743	GGGTCAGAGGTCCCAGGGTCTGG	5007	CCAGACCCTGGGACCTCTGACCC
3744	GGGGTCAGAGGTCCCAGGGTCTG	5008	CAGACCCTGGGACCTCTGACCCC
3745	GGGGGTCAGAGGTCCCAGGGTCT	5009	AGACCCTGGGACCTCTGACCCCC
3746	CGGGGGTCAGAGGTCCCAGGGTC	5010	GACCCTGGGACCTCTGACCCCCG
3747	CCGGGGGTCAGAGGTCCCAGGGT	5011	ACCCTGGGACCTCTGACCCCCGG
3748	GCCGGGGGTCAGAGGTCCCAGGG	5012	CCCTGGGACCTCTGACCCCCGGC
3749	CGCCGGGGGTCAGAGGTCCCAGG	5013	CCTGGGACCTCTGACCCCCGGCG
3750	TCGCCGGGGGTCAGAGGTCCCAG	5014	CTGGGACCTCTGACCCCCGGCGA
3751	GTCGCCGGGGGTCAGAGGTCCCA	5015	TGGGACCTCTGACCCCCGGCGAC
3752	GGTCGCCGGGGGTCAGAGGTCCC	5016	GGGACCTCTGACCCCCGGCGACC
3753	GGGTCGCCGGGGGTCAGAGGTCC	5017	GGACCTCTGACCCCCGGCGACCC
3754	GGGGTCGCCGGGGGTCAGAGGTC	5018	GACCTCTGACCCCCGGCGACCCC
3755	AGGGGTCGCCGGGGGTCAGAGGT	5019	ACCTCTGACCCCCGGCGACCCCT
3756	AAGGGGTCGCCGGGGGTCAGAGG	5020	CCTCTGACCCCCGGCGACCCCTT
3757	CAAGGGGTCGCCGGGGGTCAGAG	5021	CTCTGACCCCCGGCGACCCCTTG
3758	GCAAGGGGTCGCCGGGGGTCAGA	5022	TCTGACCCCCGGCGACCCCTTGC
3759	TGCAAGGGGTCGCCGGGGGTCAG	5023	CTGACCCCCGGCGACCCCTTGCA
3760	GTGCAAGGGGTCGCCGGGGGTCA	5024	TGACCCCCGGCGACCCCTTGCAC
3761	AGTGCAAGGGGTCGCCGGGGGTC	5025	GACCCCCGGCGACCCCTTGCACT
3762	GAGTGCAAGGGGTCGCCGGGGGT	5026	ACCCCCGGCGACCCCTTGCACTC
3763	AGAGTGCAAGGGGTCGCCGGGGG	5027	CCCCCGGCGACCCCTTGCACTCT
3764	GAGAGTGCAAGGGGTCGCCGGGG	5028	CCCCGGCGACCCCTTGCACTCTC
3765	GGAGAGTGCAAGGGGTCGCCGGG	5029	CCCGGCGACCCCTTGCACTCTCC
3766	TGGAGAGTGCAAGGGGTCGCCGG	5030	CCGGCGACCCCTTGCACTCTCCA

3767	ATGGAGAGTGCAAGGGGTCGCCG	5031	CGGCGACCCCTTGCACTCTCCAT
3768	CATGGAGAGTGCAAGGGGTCGCC	5032	GGCGACCCCTTGCACTCTCCATG
3769	TCATGGAGAGTGCAAGGGGTCGC	5033	GCGACCCCTTGCACTCTCCATGA
3770	GTCATGGAGAGTGCAAGGGGTCG	5034	CGACCCCTTGCACTCTCCATGAC
3771	TGTCATGGAGAGTGCAAGGGGTC	5035	GACCCCTTGCACTCTCCATGACA
3772	GTGTCATGGAGAGTGCAAGGGGT	5036	ACCCCTTGCACTCTCCATGACAC
3773	AGTGTCATGGAGAGTGCAAGGGG	5037	CCCCTTGCACTCTCCATGACACT
3774	AAGTGTCATGGAGAGTGCAAGGG	5038	CCCTTGCACTCTCCATGACACTT
3775	AAAGTGTCATGGAGAGTGCAAGG	5039	CCTTGCACTCTCCATGACACTTT
3776	GAAAGTGTCATGGAGAGTGCAAG	5040	CTTGCACTCTCCATGACACTTTC
3777	AGAAAGTGTCATGGAGAGTGCAA	5041	TTGCACTCTCCATGACACTTTCT
3778	GAGAAAGTGTCATGGAGAGTGCA	5042	TGCACTCTCCATGACACTTTCTC
3779	AGAGAAAGTGTCATGGAGAGTGC	5043	GCACTCTCCATGACACTTTCTCT
3780	GAGAGAAAGTGTCATGGAGAGTG	5044	CACTCTCCATGACACTTTCTCTC
3781	GGAGAGAAAGTGTCATGGAGAGT	5045	ACTCTCCATGACACTTTCTCTCC
3782	GGGAGAGAAAGTGTCATGGAGAG	5046	CTCTCCATGACACTTTCTCTCCC
3783	TGGGAGAGAAAGTGTCATGGAGA	5047	TCTCCATGACACTTTCTCTCCCA
3784	ATGGGAGAGAAAGTGTCATGGAG	5048	CTCCATGACACTTTCTCTCCCAT
3785	CATGGGAGAGAAAGTGTCATGGA	5049	TCCATGACACTTTCTCTCCCATG
3786	CCATGGGAGAGAAAGTGTCATGG	5050	CCATGACACTTTCTCTCCCATGG
3787	ACCATGGGAGAGAAAGTGTCATG	5051	CATGACACTTTCTCTCCCATGGT
3788	CACCATGGGAGAGAAAGTGTCAT	5052	ATGACACTTTCTCTCCCATGGTG
3789	CCACCATGGGAGAGAAAGTGTCA	5053	TGACACTTTCTCTCCCATGGTGG
3790	GCCACCATGGGAGAGAAAGTGTC	5054	GACACTTTCTCTCCCATGGTGGC
3791	TGCCACCATGGGAGAGAAAGTGT	5055	ACACTTTCTCTCCCATGGTGGCA
3792	CTGCCACCATGGGAGAGAAAGTG	5056	CACTTTCTCTCCCATGGTGGCAG

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Table 2B. Example UNC13A Oligonucleotide Variant Sequences

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

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

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

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

[00193] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more locked nucleic acids (LNAs). In particular embodiments, an antisense oligonucleotide includes one LNA. In particular embodiments, an antisense oligonucleotide includes two LNAs. In particular

embodiments, an antisense oligonucleotide includes three LNAs. Generally, a LNA refers to nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar.

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

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

[00196] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise three LNAs located at three different positions of the antisense oligonucleotide. In some embodiments, an antisense

oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 4th position of the antisense oligonucleotide, a second LNA at a 12th position of the antisense oligonucleotide, and a third LNA at a 20th position of the antisense oligonucleotide.

Antisense Oligonucleotides with One or more Spacers

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

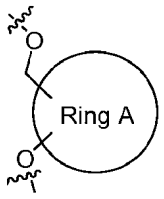
[00198] In certain embodiments, an oligonucleotide with one or more spacers, such as disclosed herein, may be an oligonucleotide with 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length, or 18, 19, 20, 21, 22, 23, 24, or 25 oligonucleotide units in length. As used herein, an "oligonucleotide unit" refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide.

[00199] In particular embodiments, oligonucleotides with one or more spacers are 25 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 21

oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 25 oligonucleotide units in length.

[00200] In various embodiments, a UNC13A AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5. In various embodiments, a UNC13A AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

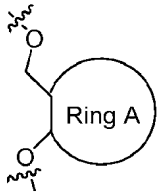
[00201] In some embodiments, the spacer is of Formula (X):



Formula (X)

wherein ring A is as defined herein.

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



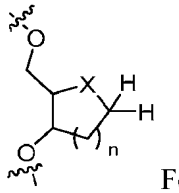
Formula (Xa)

wherein ring A is as defined herein and the -CH_2-O- group is on a ring A atom adjacent to the -O- group.

[00203] As generally defined herein, ring A of formulae (X) and (Xa), is an optionally substituted 4-8 member monocyclic cycloalkyl group (*e.g.* ring A is cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl) or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N (*e.g.* ring A is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl). In some embodiments, ring A is tetrahydrofuranyl. In some embodiments, ring A is tetrahydropyranyl. In some embodiments, ring A is pyrrolidinyl. In some embodiments, ring A is cyclopentyl. In some embodiments, the monocyclic cycloalkyl or monocyclic heterocyclyl is not further substituted. In some embodiments, the cycloalkyl or heterocyclyl is further substituted with 0, 1, 2 or 3 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN.

[00204] In some embodiments, tetrahydrofuranyl is substituted with 1 or 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 1 substituent selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with -O(CH_2)$_2$OMe.

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

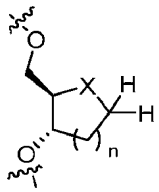


Formula (I)

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

n is 0, 1, 2 or 3.

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

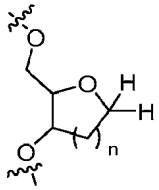


Formula (I')

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

n is 0, 1, 2 or 3.

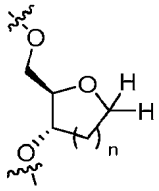
[00207] In some embodiments, the spacer is represented by Formula (Ia), wherein:



Formula (Ia)

and n is 0, 1, 2 or 3.

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



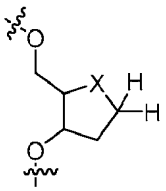
Formula (Ia')

and n is 0, 1, 2 or 3.

[00209] As generally defined herein, X is selected from -CH_2- and -O-. In some embodiments, X is -CH_2-. In other embodiments, X is -O-.

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

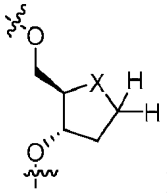
[00211] In some embodiments, the spacer is represented by Formula (II), wherein:



Formula (II)

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

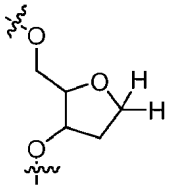
[00212] In some embodiments, the spacer is represented by Formula (II'), wherein:



Formula (II')

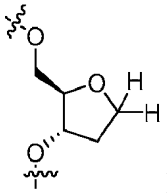
X is selected from -CH_2-and -O.

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



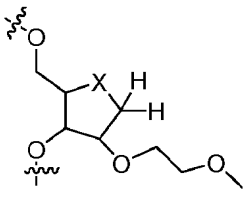
Formula (Iia).

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



Formula (Iia').

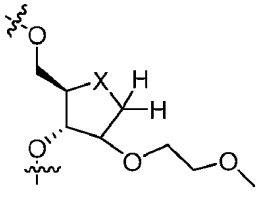
[00215] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

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

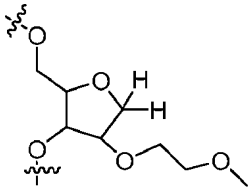
[00216] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

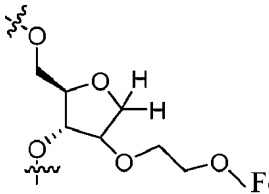
X is selected from -CH_2-and -O.

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



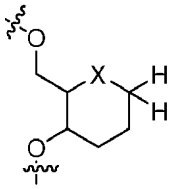
Formula (IIib).

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



Formula (IIib').

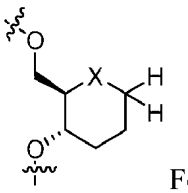
[00219] In some embodiments, the spacer is represented by Formula (III), wherein:



Formula (III)

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

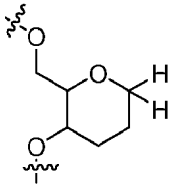
[00220] In some embodiments, the spacer is represented by Formula (III'), wherein:



Formula (III')

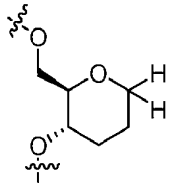
X is selected from -CH_2-and -O.

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



Formula (IIIa).

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



Formula (IIIa').

[00223] In some embodiments, the open positions of Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') (*i.e.*, the positions not specifically depicted as bearing exclusively hydrogen atoms, including the -CH_2- group of X) are further substituted with 0-3 substituents independently selected from halo (*e.g.*, -F, -Cl), - OMe, -OEt -$O(CH_2)$OMe, -$O(CH_2)_2$OMe and CN. In some embodiments, Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') are not further substituted.

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

[00225] In various embodiments, a UNC13A oligonucleotide includes one spacer that replaces a nucleoside in the UNC13A oligonucleotide (e.g., one spacer replaces one nucleoside of the UNC13A oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between

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

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

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

[00228] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20,

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

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

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

[00231] In various embodiments, the three spacers in a UNC13A oligonucleotide are positioned such that each of the four segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. For example, a UNC13A oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides

connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

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

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

embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

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

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

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

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

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

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

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

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

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

Sequence name	**Relation to UNC13A oligonucleotide variant**		**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A parent oligonucleotide	N/A		XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
UNC13A Oligonucleotide (25mer) with Spacer at position 15 (UNC13A AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer		XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
UNC13A oligonucleotide variant (23mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Oligonucleotide (23mer) with Spacer at position 12 (UNC13A AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer		XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A		XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Oligonucleotide (21mer) with Spacer at position 11 (UNC13A AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX
UNC13A oligonucleotide variant (19mer)	N/A		XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Oligonucleotide (19mer) with Spacer at position 10 (UNC13A AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer		XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate

(*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

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

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

Sequence name	**Relation to UNC13A parent oligonucleotide**		**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A parent oligonucleotide	N/A		XXXXXXXXXXXXXXXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 22 (UNC13A AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14 (UNC13A AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer		XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 19 (UNC13A AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 14 (UNC13A AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 14 (UNC13A AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 14 (UNC13A AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 14 (UNC13A AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 15 (UNC13A AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 15 (UNC13A AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 15 (UNC13A AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 15 (UNC13A AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 16 (UNC13A AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 16 (UNC13A AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 16 (UNC13A AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 16 (UNC13A AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 17 (UNC13A AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 17 (UNC13A AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 17 (UNC13A AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 17 (UNC13A AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 18 (UNC13A ATON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 18 (UNC13A AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 18 (UNC13A AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 18 (UNC13A AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 19 (UNC13A AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 19 (UNC13A AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 19 (UNC13A AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 20 (UNC13A AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 20 (UNC13A AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX$\mathbf{S_{20}}$XXXXX

UNC13A Oligonucleotide with Spacers at positions 11 and 20 (UNC13A AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 21 (UNC13A AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers		XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 21 (UNC13A AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers		XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 15 (UNC13A AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers		XXXS_4XXXXXXXXXXS_{15}XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 19 (UNC13A AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers		XXXXXX$\mathbf{S_7}$XXXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 18 (UNC13A AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers		XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{18}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 21 (UNC13A AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers		XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate

(*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00242] In various embodiments, UNC13A oligonucleotides include three spacers. The inclusion of three spacers divides up the UNC13A oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the UNC13A oligonucleotide such that each of the segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. Example UNC13A AONs with three spacers are documented below in Table 4.

Table 4: Identification of UNC13A AONs or AON variants with three spacers. Here, each UNC13A AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A parent oligonucleotide**		**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 24 (UNC13A AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 23 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
UNC13A Oligonucleotide with Spacers at positions 2 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers		X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 3 and 10	Nucleosides at positions 3 and 10 and 18		XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX

and 18 (UNC13A AON 25_sp8sp16sp23)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 4 and 12 and 19 (UNC13A AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers		XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 13 and 18 (UNC13A AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 5 and 13 and 21 (UNC13A AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers		XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 13 and 19 (UNC13A AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers		XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 6 and 13 and 20 (UNC13A AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers		XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 19 (UNC13A AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11	Nucleosides at positions 8 and 11 and 16		XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXX

and 16 (UNC13A AON 23_sp8sp11sp16)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 7 and 14 and 22 (UNC13A AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers		XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00243] In various embodiments, UNC13A AONs with one or more spacers are reduced in length in comparison to the UNC13A AONs described above in Tables 3B and 4. For example, such UNC13A AONs may be UNC13A oligonucleotide variants with one or more spacers. In various embodiments, the UNC13A oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, UNC13A oligonucleotide variants include two spacers such that the UNC13A oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nueclosides. Example UNC13A oligonucleotide variants with one or more spacers are shown below in Table 5.

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

Sequence name	**Relation to UNC13A oligonucleotide variant**		**Sequence* (where *X* indicates a nucleoside of the UNC13A oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')

UNC13A oligonucleotide variant (23mer)	N/A		XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (UNC13A AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A		XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (UNC13A AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers		XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (UNC13A AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (UNC13A AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers		XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A	Nucleosides at positions 8 and 14 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX

AON variant 21_sp8sp14)			
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A AON variant 21_sp8sp14)	Nucleosides at positions 6 and 20 are substituted with spacers		XXXXX$\mathbf{S_6}$XXXXXXXXXXXXX$\mathbf{S_{20}}$X
UNC13A oligonucleotide variant (19mer)	N/A		XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (UNC13A AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers		XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (UNC13A AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers		XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00244] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more spacers

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

[00245] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00246] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

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

can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

Performance of UNC13A Oligonucleotides

[00248] Generally, UNC13A oligonucleotides and/or UNC13A parent oligonucleotides (*e.g.*, UNC13A oligonucleotides with sequences of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5) target UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208 in order to increase, restore, rescue, or stabilize levels of expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein (*e.g.*, full length UNC13A). In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of mis-spliced UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A protein. In some embodiments, the percent increase of the full length UNC13A protein is an increase in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length UNC13A protein followed by increase of the full length UNC13A protein using a UNC13A AON.

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

[00250] In various embodiments, UNC13A AONs can exhibit at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon. In various embodiments, UNC13A AONs can exhibit at least a 100% reduction of an UNC13A transcript with a cryptic exon. In various embodiments, reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide. In various embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

Modifications

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

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

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

Modified Internucleoside Linkages

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

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

[00256] In certain embodiments, antisense compounds targeted to a UNC13A nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a UNC13A nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Modified Sugar Moieties

[00257] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (*see* PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl

ring oxygen atom with S with further substitution at the 2'-position (*see* published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (*see* PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[00258] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or 5), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-O CH_2 CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2S$ CH_3, $O(CH_2)_2$—O—$N(R_m)(R_n)$, O—CH_2—C(=O)—$N(R_m)(R_n)$, and O—CH_2—C(=O)—$N(R_1)$—($CH_2)_2$—$N(R_m)(R_n)$- , where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00259] Additional examples of modified sugar moieties include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00260] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)—O-2' (LNA); 4'-(CH_2)—S-2'; 4'-$(CH_2)_2$—O-2' (ENA); 4'-$CH(CH_3)$—O-2' and 4'-$CH(CH_2OCH_3)$—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-$C(CH_3)(CH_3)$—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—$N(OCH_3)$-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH_2—O—$N(CH_3)$-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'- CH_2—N(R)—O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH_2—$C(H)(CH_3)$-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH_2—C—$(=CH_2)$-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[00261] Further reports related to bicyclic nucleosides can also be found in published literature (*see* for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron,

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

[00262] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $—[C(R_a)(R_b)]_n—$, $—C(R_a)=C(R_b)—$, $—C(R_a)=N—$, $—C(=O)—$, $—C(=NR_a)—$, $—C(=S)—$, $—O—$, $—Si(R_a)_2—$, $—S(=O)_x—$, and $—N(R_a)—$; wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

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

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

[00263] In certain embodiments, the bridge of a bicyclic sugar moiety is $—[C(R_a)(R_b)]_n—$, $—[—[C(R_a)(R_b)]_n—O—$, $—C(R_aR_b)—N(R)—O—$ or $—C(R_aR_b)—O—N(R)—$. In certain

embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—N(R)-2' and 4'-CH_2—N(R)—O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl, each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)—H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group; and R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00264] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2—O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00265] In certain embodiments, bicyclic nucleosides include, but are not limited to, α-L-methyleneoxy (4'-CH_2—O-2') BNA, β-D-methyleneoxy (4'-CH_2—O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$—O-2) BNA, aminooxy (4'-CH_2—O—N(R)-2') BNA, oxyamino (4'-CH_2—N(R)—O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$—O-2') BNA, methylene-thio (4'-CH_2—S-2') BNA, methylene-amino (4'-CH_2—N(R)-2') BNA, methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, and propylene carbocyclic (4'-$(CH_2)_3$-2') BNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

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

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

[00268] The present disclosure also provides a pharmaceutical composition comprising a UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a UNC13A AON that includes a sequence of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5).

[00269] The present disclosure also provides methods that include the use of pharmaceutical compositions comprising a UNC13A AON is formulated together with one or more pharmaceutically acceptable excipients. Exemplary compositions provided herein include compositions comprising a UNC13A AON, and one or more pharmaceutically acceptable excipients. Formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use. The most suitable form of administration in any given case will depend on the clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition that one is trying to prevent in a subject; the state, disorder, disease, or condition one is trying to prevent in a subject; and/or on the nature of the particular compound and/or the composition being used.

Additional Chemically Modified UNC13A Oligonucleotides

[00270] UNC13A AONs described herein, can include chemically modified nucleosides, including modified ribonucleosides and modified deoxyribonucleosides. Chemically modified

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

[00271] UNC13A AONs described herein can include chemical modifications that promote stabilization of an oligonucleotide's terminal 5'-phosphate and phosphatase-resistant analogs of 5′-phosphate. Chemical modifications that promote oligonucleotide terminal 5'-phosphate stabilization or which are phosphatase-resistant analogs of 5′-phosphate include, but are not limited to, 5′-methyl phosphonate, 5′-methylenephosphonate, 5′-methylenephosphonate analogs, 5′-*E*-vinyl phosphonate (5′-*E*-VP), 5′-phosphorothioate, and 5′-*C*-methyl analogs. Chemical modifications that promote AON terminal 5'-phosphate stabilization and phosphatase-resistant analogues of 5′-phosphate are described in Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of which are incorporated by reference herein.

[00272] In some embodiments described herein, UNC13A AONs described herein can include chemically modified nucleosides, for example, 2' O-methyl ribonucleosides, for example, 2' O-methyl cytidine, 2' O-methyl guanosine, 2' O-methyl uridine, and/or 2' O-methyl adenosine. UNC13A AONs described herein can include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methylcytosine, and/or a 5-methylpurine, for example, 5-methylguanine. Chemically modified nucleosides can further include pseudo-uridine or 5'methoxyuridine. UNC13A AONs described herein can include any of the following chemically modified nucleosides: 5-methyl-2'-O-methylcytidine, 5-methyl-2'-O-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl 2'-deoxycytidine.

[00273] UNC13A AONs described herein can include a phosphate backbone where one or more of the oligonucleoside linkages is a phosphate linkage. UNC13A AONs described herein may include a modified oligonucleotide backbone, where one or more of the nucleoside linkages of the sequence is selected from the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments of UNC13A AONs described herein, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. For example, in some embodiments of UNC13A AONs described herein, one, two, three, or more internucleoside linkages of the oligonucleotide is a phosphorothioate linkage. In preferred embodiments of UNC13A AONs described herein, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. Thus, in some embodiments, all of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 are phosphorothioate linkages.

[00274] In various embodiments, nucleotide linkages of UNC13A AON described herein such as any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 include a mix of phosphodiester and phosphorothioate linkages.

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

XXoDoXXXXXXXXXXXXXXXXXXXXX

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

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

XXoDXXXXXXXXXXXXXXXXXXXXX

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

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

XXDoXXXXXXXXXXXXXXXXXXXXX

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

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

XxoD$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

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

XXDoXXXXXXX$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

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

XXXoDoXXXXXXXXXXXXXXXXXXXXX

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

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

XXXoDXXXXXXXXXXXXXXXXXXXXX

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

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

XXXDoXXXXXXXXXXXXXXXXXXXXX

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

[00283] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXX

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

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

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

[00286] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the UNC13A AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

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

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

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

XXXXoDo**S$_1$**oEoXXXXXXXXXXX**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

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

XXXXX**S$_1$**XXXXXXXXXXXoDo**S$_2$**oDoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

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

XXXXXXo**S$_1$**XXXXXXXXXXX**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

XXXXXX**S$_1$**XXXXXXXXXXXo**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXXXo\mathbf{S}_1XXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXXX\mathbf{S}_1XXXXXo\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXEoDo\mathbf{S}_1XXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXX\mathbf{S}_1XXXXEoDo\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00296] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer UNC13A AON can be denoted as:

$$XXXEoD\mathbf{S}_1XXXXXXo\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXo\mathbf{S}_1XXXXEoD\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXX\mathbf{S}_1oXXXXXXXXXXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXX\mathbf{S}_1XXXXXXXXXXX\mathbf{S}_2oXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$oXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

XXXXXXX**S**$_1$XXXXX**S**$_2$oXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

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

XXXXoDo**S**$_1$oEoXXXXXXXXXXoFo**S**$_2$oHoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

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

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

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

$$XXXXXXXX\mathbf{S}_1XXXXoDoEoFoHoXXX\mathbf{S}_2XXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

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

$$XXXXXXX\mathbf{S}_1XXXoDoEoXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

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

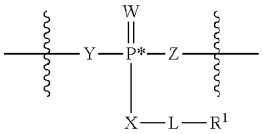
[00308] UNC13A AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR,

NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-Ome modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

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

[00310] In some embodiments, UNC13A AONs with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00311] For example, a UNC13A AON with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of the at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of the at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of the at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



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

W is O, S or Se; each of X, Y and Z is independently —O—, —S—, —N(-L-R^1)—, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; each R′ is independently —R, —C(O)R, —CO$_2$R, or —SO$_2$R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally

substituted group selected from C_1-C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each  independently represents a connection to a nucleoside. In some embodiments, a UNC13A AON with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

Motor Neuron Diseases

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

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

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

Amyotrophic Lateral Sclerosis

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

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

Frontotemporal Dementia

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

Amyotrophic lateral sclerosis with frontotemporal dementia

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

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

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

Methods of Treatment

[00320] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism) in a patient in need thereof comprising administering a UNC13A AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed UNC13A AON. In some embodiments of the disclosure, an effective amount of a disclosed UNC13A oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein, thereby increase, restore, or stabilize UNC13A activity and/or function.

[00321] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS, FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed UNC13A AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

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

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

[00324] Patients treated using an above method may experience an increase, restoration of, or stabilization of UNC13A mRNA expression, which is capable of translation to produce a functional UNC13A protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize UNC13A activity and/or function in a target cell (for example, a motor neuron) after administering a UNC13A oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a UNC13A oligonucleotide may be on, *e.g.*, at least a daily basis. The UNC13A oligonucleotide may be administered orally. In some embodiments, the UNC13A oligonucleotide is administered intrathecally, intrathalamically, or intracisternally. For example, in an embodiment described herein, a UNC13A oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a UNC13A oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as

compared to a patient who is not administered a UNC13A oligonucleotide, such as one disclosed herein.

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

[00326] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00327] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or

SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00328] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one

(*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Treatment and Evaluation

[00329] A patient, as described herein, refers to any animal at risk for, suffering from or diagnosed with a neurological disease, including, but not limited to, mammals, primates, and humans. In certain embodiments, the patient may be a non-human mammal such as, for example, a cat, a dog, or a horse. A patient may be an individual diagnosed with a high risk of developing a neurological disease, someone who has been diagnosed with a neurological disease, someone who previously suffered from a neurological disease, or an individual evaluated for symptoms or indications of a neurological disease, for example, any of the signs or symptoms associated with neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

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

[00331] "Effective amount," as used herein, refers to the amount of an agent that is sufficient to at least partially treat a condition when administered to a patient. The therapeutically effective amount will vary depending on the severity of the condition, the route of administration of the component, and the age, weight, etc. of the patient being treated. Accordingly, an effective amount of a disclosed UNC13A oligonucleotide is the amount of the UNC13A oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease.

[00332] Efficacy of treatment may be evaluated by means of evaluation of gross symptoms associated with a neurological disease, analysis of tissue histology, biochemical assay, imaging methods such as, for example, magnetic resonance imaging, or other known methods. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed UNC13A oligonucleotide.

[00333] Efficacy of treatment may also be evaluated at the tissue or cellular level, for example, by means of obtaining a tissue biopsy (*e.g.*, a brain, spinal, muscle, motor neuron tissue biopsy, or olfactory neurosphere cell biopsy) and evaluating gross tissue or cell morphology or staining properties. Biochemical assays that examine protein or RNA expression may also be used to evaluate efficacy of treatment. For instance, one may evaluate levels of a protein or gene product indicative of a neurological disease, in dissociated cells or non-dissociated tissue via immunocytochemical, immunohistochemical, Western blotting, or Northern blotting methods, or methods useful for evaluating RNA levels such as quantitative or semi-quantitative polymerase chain (*e.g.*, digital PCR (DigitalPCR, dPCR, or dePCR), qPCR etc.) reaction. One may also evaluate the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43 or p75 extracellular domain ($p75^{ECD}$)) found in spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, exosome-like cerebrospinal fluid extracellular vesicles ("CSF exosomes"), such as those described in Welton *et al.*, (2017) "Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery in neurological disease; multiple sclerosis" *J Extracell Vesicles.*, 6(1):1-10; and Street *et al.*, (2012) "Identification and proteomic profiling of exosomes in human cerebrospinal fluid" *J*

Transl. Med., 10:5), urine, fecal matter, lymphatic fluid, blood, plasma, or serum to evaluate disease state and efficacy of treatment. One may also evaluate the presence or level of expression of useful biomarkers found in the plasma, neuronal extracellular vesicles/exosomes. Additional measurements of efficacy may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential (CMAP), and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

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

[00335] Validation of UNC13A oligonucleotides may be determined by direct or indirect assessment of UNC13A expression levels or activity. For instance, biochemical assays that measure UNC13A protein or RNA expression may be used to evaluate overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to

any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. For instance, one may measure UNC13A protein levels in cells or tissue by Western blot to evaluate overall UNC13A levels. One may also measure UNC13A mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. One may also evaluate UNC13A protein levels or levels of another protein indicative of UNC13A signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00336] Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease

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

[00337] The disclosure also provides methods of restoring expression of full length UNC13A transcripts in cells of a patient suffering from a neurological disease. Full length UNC13A transcripts may be restored in any cell in which UNC13A expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

Pharmaceutical Compositions and Routes of Administration

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

[00339] As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings,

isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. In one embodiment the pharmaceutical composition is administered orally and includes an enteric coating suitable for regulating the site of absorption of the encapsulated substances within the digestive system or gut. For example, an enteric coating can include an ethylacrylate-methacrylic acid copolymer.

[00340] In one embodiment, a disclosed UNC13A oligonucleotide and any pharmaceutical composition thereof may be administered by one or several routes, including topically, intrathecally, intrathalamically, intracisternally, intracerebroventricularly, parenterally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. The term parenteral as used herein includes subcutaneous injections, intrapancreatic administration, intravenous, intracisternal, intracerebroventricular, intrathecal, intrathalamic, intramuscular, intraperitoneal, intrasternal injection or infusion techniques. For example, a disclosed UNC13A oligonucleotide may be administered subcutaneously to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered orally to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered directly to the nervous system, or specific regions or cells of the nervous system (*e.g.*, the brain, brain stem, lower motor neurons, spinal cord, upper motor neurons) via parenteral administration, for example, a disclosed UNC13A oligonucleotide may be administered intrathecally, intrathalamically intracisternally, or intracerebroventricularly.

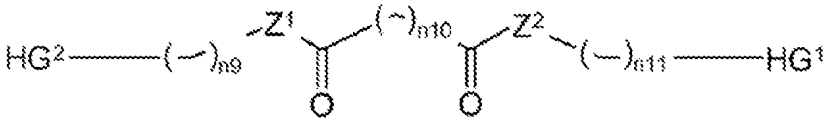
[00341] In various embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be exposed to calcium-containing buffers prior to administration. Such calcium-containing buffers can mitigate toxicity adverse effects of the UNC13A oligonucleotide. Further details of exposing an example antisense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

[00342] In some embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be encapsulated in a nanoparticle coating. It is believed that nanoparticle encapsulation prevents AON degradation and enhances cellular uptake. For example, in some embodiments a UNC13A oligonucleotide is encapsulated in a coating of a cationic polymer, for example, a synthetic polymer (*e.g.*, poly-L-lysine, polyamidoamine, a poly(β-amino ester), and polyethyleneimine) or a naturally occurring polymer (*e.g.*, chitosan and a protamine). In some embodiments, a

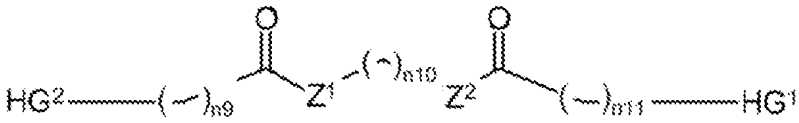
UNC13A oligonucleotide is encapsulated in a lipid or lipid-like material, for example, a cationic lipid, a cationic lipid-like material, or an ionizable lipid that is positively charged only at an acidic pH. An example of a lipid nanoparticle nucleotide therapy includes Exicure's XCUR-FXN, a lipid-nanoparticle spherical nucleic acid (SNA)-based therapeutic candidate. For example, in some embodiments, a UNC13A oligonucleotide is encapsulated in a lipid nanoparticle that includes hydrophobic moieties, *e.g.*, cholesterol and/or a polyethylene glycol (PEG) lipid.

[00343] In various embodiments, a pharmaceutical composition comprising a disclosed UNC13A oligonucleotide may further comprise a bolaamphiphilic compound. Example bolaamphiphilic compounds are described in WO2014039493A1, WO2014039500A1, WO2014039502A1, WO2014039503A1, and WO2014039504A1, each of which is hereby incorporated by reference in its entirety. In particular embodiments, a bolaamphiphilic compound is a compound according to formula I: HG^2 L^1 HG^1, or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, isotopic variant, or N-oxide thereof, or a combination thereof; wherein: each HG^1 and HG^2 is independently a hydrophilic head group; and L^1 is alkylene, alkenyl, heteroalkylene, or heteroalkenyl linker; unsubstituted or substituted with C1-C20 alkyl, hydroxyl, or oxo.

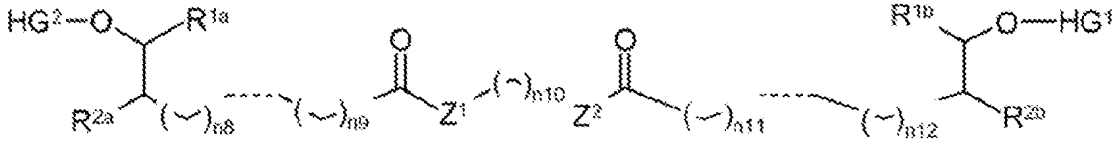
[00344] In one embodiment, with respect to the bolaamphiphilic compound of formula I, the bolaamphiphilic compound is a compound according to formula II, III, IV, V, or VI:



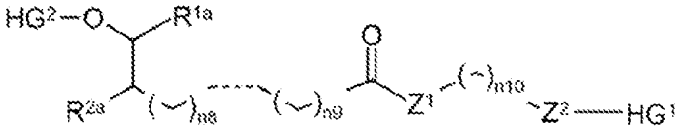
II



III

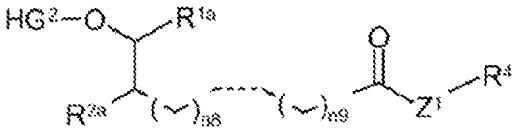


IV



V

; or



VI

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

wherein:

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

each Z^1 and Z^2 is independently $-C(R^3)_2-$, $-N(R^3)-$ or -0-;

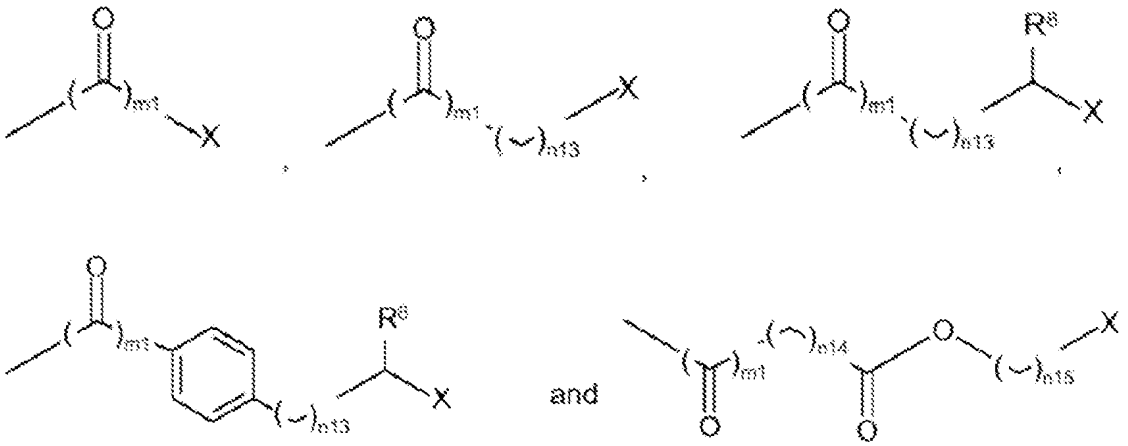
each R^{la}, R^{lb}, R^3, and R^4 is independently H or Ci-C8 alkyl;

each R^{2a} and R^{2b} is independently H , Ci-C8 alkyl, OH, alkoxy, or O-HG^1 or O-HG^2; each n8, n9, n11, and n12 is independently an integer from 1-20;

n10 is an integer from 2-20; and

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

[00346] In one embodiment, with respect to the bolaamphiphilic compound of formula I, II, III, IV, V, or VI, each HG^1 and HG^2 is independently selected from:



[00347] wherein: X is $-NR^{5a}R^{5b}$, or $-N^{+}R^{5a}R^{5b}R^{5c}$; each R^{5a}, and R^{5b} is independently H or substituted or unsubstituted C_1-C_{20} alkyl or R^{5a} and R^{5b} may join together to form an N containing substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl; each R^{5c} is independently substituted or unsubstituted C_1-C_{20} alkyl; each R^8 is independently H, substituted or unsubstituted C_1-C_{20} alkyl, alkoxy, or carboxy; ml is 0 or 1; and each n13, n14, and n15 is independently an integer from 1-20.

[00348] In various embodiments, pharmaceutical compositions disclosed herein comprise complexes between bolaamphiphiles and pharmacologically or biologically active compounds (e.g., an UNC13A oligonucleotide disclosed herein). In various embodiments, the pharmaceutical compositions disclosed herein comprise a bolaamphiphile vesicle complexes comprising one or more bolaamphiphilic compounds and the biologically active compound is an oligonucleotide (e.g., an UNC13A oligonucleotide disclosed herein).

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

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

Parenteral Administration

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

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

[00353] Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In one embodiment, a disclosed UNC13A antisense oligonucleotide may be suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethylcellulose and 0.1% (v/v) TWEEN™ 80. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00354] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and

the required other ingredients from those enumerated above. Sterile injectable solutions of the disclosure may be prepared by incorporating a disclosed UNC13A antisense oligonucleotide in the required amount of the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter.

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

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

Oral Administration

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

[00358] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed UNC13A oligonucleotide, *e.g.*, a

UNC13A oligonucleotide represented by any SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00359] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable filler. For example, a disclosed UNC13A oligonucleotide and a filler may be blended together, optionally, with other excipients, and formed into granules. In some embodiments, the intragranular phase may be formed using wet granulation, *e.g.*, a liquid (*e.g.*, water) is added to the blended UNC13A oligonucleotide and filler, and then the combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intragranular phase.

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

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

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

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

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

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

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

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

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

[00369] In another contemplated embodiment, a pharmaceutical tablet formulation for oral administration of a disclosed UNC13A oligonucleotide comprises an intra-granular phase, wherein the intra-granular phase includes a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and which may also include an extra-granular phase, that may include a pharmaceutically acceptable excipient such as a disintegrant. The extra-granular phase may include components chosen from microcrystalline cellulose, magnesium stearate, and mixtures thereof. The pharmaceutical

composition may also include an enteric coating of about 12% to 20% by weight of the tablet. For example, a pharmaceutically acceptable tablet for oral use may comprise about 0.5% to 10% by weight of a disclosed UNC13A AON, *e.g.*, a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof, about 30% to 50% by weight mannitol, about 10% to 30% by weight microcrystalline cellulose, and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

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

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

[00372] The rate at which the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the UNC13A oligonucleotide releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. In another embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in diluted HCl with a pH of 1.0, where substantially none of the UNC13A oligonucleotide is released after 120 minutes. A contemplated tablet, in another embodiment, may have a dissolution profile, *e.g.*, when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 6.6, of about 10% to about 30%, or not more than about 50% of the UNC13A oligonucleotide releasing after 30 minutes.

[00373] In some embodiments, methods provided herein may further include administering at least one other agent that is directed to treatment of diseases and disorders disclosed herein. In

one embodiment, contemplated other agents may be co-administered (*e.g.*, sequentially or simultaneously).

Dosage and Frequency of Administration

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

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

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

frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once per day for 7 days. In some embodiments, dosing is once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In some embodiments, dosing is once a month to every three months. In some embodiments, dosing is once every 2 weeks for three dose, then monthly, bimonthly, or every three or four months.

Combination Therapies

[00377] In various embodiments, a UNC13A AON as disclosed herein can be administered in combination with one or more additional therapies. The combination therapy of the disclosed oligonucleotide and the one or more additional therapies can, in some embodiments, be synergistic in treating any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Parkinson's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

[00378] Non-limiting examples of therapies for Parkinson's disease (PD) include: deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, Nuplazid, and embryonic dopamine cell implantation.

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

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

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

[00382] Non-limiting examples of therapies for epilepsy include Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and zonisamide (zonegran).

[00383] Example additional therapies include any of Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, 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), medroxyprosterone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents. Additional therapies can further include breathing care, physical therapy, occupational therapy, speech therapy, and nutritional support. Further non-limiting examples of additional therapies include any of deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, 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 zonisamide (zonegran). In various embodiments, an additional therapy can be a second antisense oligonucleotide. As an example, the second antisense oligonucleotide may target a UNC13A transcript (*e.g.*, UNC13A pre-mRNA, mature UNC13A mRNA) to modulate the expression levels of full length UNC13A protein.

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

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

Conjugates

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

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

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

Conjugate Groups

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

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

Conjugate Moieties

[00389] Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, dyes, bile acids, and phenylbutyric acid. In particular embodiments, conjugate moieties are selected from a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, lipoic acid, panthothenic acid, polyethylene glycol, an antibody (*e.g.*, an antibody for crossing the blood brain barrier such as anti-transferrin receptor antibody), or a cell-penetrating peptide (*e.g.*, transactivator of transcription (TAT) and penetratine).

[00390] In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

Conjugate Linkers

[00391] Conjugate moieties are attached to a UNC13A AON through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbon chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

[00392] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino,

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

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

[00394] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane- l-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

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

[00396] In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N -benzoyl-5 -methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is

typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

[00397] Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

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

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

[00400] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain

embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxy adenosine.

Terminal Groups

[00401] In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside. In various embodiments, terminal groups comprise one or more spacers.

Diagnostic Methods

[00402] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of UNC13A expression signal in one or more biological samples of a patient. As used herein, the term "UNC13A expression signal" can refer to any indication of UNC13A gene expression, or gene or gene product activity. UNC13A gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of UNC13A gene expression that can be assessed include, but are not limited to, UNC13A gene or chromatin state, UNC13A gene interaction with cellular components that regulate gene expression, UNC13A gene product expression levels (*e.g.*, expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, or interaction of UNC13A RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00403] Detection of UNC13A expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of UNC13A

transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, plasma, or serum. Methods of detection include assays that measure levels of UNC13A gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Modifications in General

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

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

"AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

[00406] Certain compounds described herein (*e.g.*, modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that contain stereocenters that are drawn or described with undefined stereochemistry included all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

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

EXAMPLES

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

Example 1: Design and Selection of UNC13A Oligonucleotides

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

Additionally, each of the internucleoside linkages between the nucleosides of the UNC13A oligonucleotides are phosphorothioate internucleoside linkages.

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

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

SEQ ID No:	Oligonucleotide Sequence (where S indicates presence of a Spacer)* (5' → 3')	Length
5133	GGGCAGSCAGGAATGGTGSGTGGAA	25
5134	AGGGAGSAGTTTTCCAGGSAAAGGG	25
5135	GCAGCTSGAAGAGACATASCCAGAC	25
5136	TCCACCSGCCACTCACAASCATCCA	25
5137	GAAAGTSTCATGGAGAGTSCAAGGG	25
5138	GGGCAGGCSGGAATGGTGSGTGGAA	25
5139	AGGGAGGASTTTTCCAGGSAAAGGG	25
5140	GCAGCTGGSAGAGACATASCCAGAC	25
5141	TCCACCAGSCACTCACAASCATCCA	25
5142	GAAAGTGTSATGGAGAGTSCAAGGG	25
5143	GCAGGCASGAATGGTSAGTGGAA	23
5144	GGGCAGGSAGGAATGSTGAGTGG	23
5145	GGCAGGCSGGAATGGSGAGTGGA	23
5146	GTAAAGGSAATGGCASGGCGGGC	23
5147	AGGTAAASGGAATGGSATGGCGG	23
5148	GGTAAAGSGAATGGCSTGGCGGG	23
5149	AGGAGGTSACCCTGASTCTGGAC	23
5150	AGAGGAGSTGACCCTSAATCTGG	23
5151	GAGGAGGSGACCCTGSATCTGGA	23
5152	ACAAACGSCCCAATCSTGAGTGG	23

5153	ACACAAASGGCCCAASCCTGAGT	23
5154	CACAAACSGCCCAATSCTGAGTG	23
5155	TCTTTCCSGGAAACCSAGGCAGC	23
5156	GTTCTTTSCAGGAAASCCAGGCA	23
5157	TTCTTTCSAGGAAACSCAGGCAG	23
5158	TCCGCAASTTAATCCSCCTACCC	23
5159	GATCCGCSACTTAATSCACCTAC	23
5160	ATCCGCASCTTAATCSACCTACC	23
5161	CCCACCCSTCTAACTSCCCCAAA	23
5162	CACCCACSCATCTAASTACCCCA	23
5163	ACCCACCSATCTAACSACCCCAA	23
5164	AAGTGTCSTGGAGAGSGCAAGGG	23
5165	GAAAGTGSCATGGAGSGTGCAAG	23
5166	AAAGTGTSATGGAGASTGCAAGG	23

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

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

SEQ ID No:	Oligonucleotide Sequence (where **S** indicates presence of a Spacer)* (5' → 3')	Length
5168	AGTTCASCCACACATCCTSCCATTC	25
5169	AGTTCAACSACACATCCTSCCATTC	25
5170	GTTCAACSACACATCSTTCCATT	23
5171	AGTTCAASCACACATSCTTCCAT	23
5172	TTCAACCSCACATCCSTCCATTC	23
5173	CTTGCASTAGTTCAACCASACATCC	25
5174	CTTGCAATSGTTCAACCASACATCC	25

5175	TTGCAATSGTTCAACSACACATC	23
5176	CTTGCAASAGTTCAASCACACAT	23
5177	TGCAATASTTCAACCSCACATCC	23
5178	ACACATSCATCCATCCATSCATTCA	25
5179	ACACATCCSTCCATCCATSCATTCA	25
5180	CACATCCSTCCATCCSTCCATTC	23
5181	ACACATCSATCCATCSATCCATT	23
5182	ACATCCASCCATCCASCCATTCA	23
5183	CAGTAASTCAACCACACASCCATCC	25
5184	CAGTAATTSAACCACACASCCATCC	25
5185	AGTAATTSAACCACASATCCATC	23
5186	CAGTAATSCAACCACSCATCCAT	23
5187	GTAATTCSACCACACSTCCATCC	23
5188	ACCTTTSAGTAATTCAACSACACAT	25
5189	ACCTTTCASTAATTCAACSACACAT	25
5190	CCTTTCASTAATTCASCCACACA	23
5191	ACCTTTCSGTAATTCSACCACAC	23
5192	CTTTCAGSAATTCAASCACACAT	23
5193	CTCTTTSATCCATCCACASACCCAC	25
5194	CTCTTTTASCCATCCACASACCCAC	25
5195	TCTTTTASCCATCCASACACCCA	23
5196	CTCTTTTSTCCATCCSCACACCC	23
5197	CTTTTATSCATCCACSCACCCAC	23
5198	ATCTACSCTTTTATCCATSCACACA	25
5199	ATCTACTCSTTTATCCATSCACACA	25
5200	TCTACTCSTTTATCCSTCCACAC	23
5201	ATCTACTSTTTTATCSATCCACA	23
5202	CTACTCTSTTATCCASCCACACA	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages.

A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (Iia') as disclosed herein.

Example 2: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00413] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 50,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13a transcript. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

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

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

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

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

[00418] UNC13A-FL (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-FL), the normalized UNC13A-FL signal was further

normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A FL were normalized using the following formula:

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

[00419] Table 7 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons. UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers were tested for their ability to increase or restore full-length UNC13A mRNA (*i.e.*, mRNA from which full-length UNC13A protein is translated) levels. In some cases, UNC13A AONs with spacers increased full-length UNC13A mRNA ("UNC13A FL"), also referred to herein as correctly spliced UNC13A (UNC13A CS). In some cases, UNC13A AONs without spacers increased full-length UNC13A mRNA or correctly spliced UNC13A mRNA (UNC13A CS)). Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00420] As shown in Table 7, a 500 nM dose of SEQ ID NO: 5326 (ACACAAASGGCCCAASCCTGAGT with two spacers) rescued full length UNC13A mRNA to 55.69%. Comparatively, a 500 nM dose of SEQ ID NO: 5325 (ACACAAACGGCCCAATCCTGAGT with no spacers) rescued full length UNC13A mRNA to 41.87%. This indicates that the addition of spacers of SEQ ID NO: 5326 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5325).

[00421] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5352 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 55.88%. A 500 nM dose of SEQ ID NO: 5352 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 66.62%. Comparatively, a 200 nM dose of SEQ ID NO: 3547 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 43.88%. A 500 nM dose of SEQ ID NO: 5351 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 66.98%. This indicates that at 200 nM and 500 nM doses, the performance of an AON with SEQ ID NO: 5352 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5351).

[00422] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5359 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to

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

[00423] Additionally shown in Table 7, a 500 nM dose of SEQ ID NO: 5361 (CCCACCCSTCTAACTSCCCCAAA with two spacers) rescued full length UNC13A mRNA to 43.10%. Comparatively, a 500 nM dose of SEQ ID NO: 5360 (CCCACCCATCTAACTACCCCAAA with no spacers) rescued full length UNC13A mRNA to 23.37%. This indicates that at a 500 nM dose, the addition of spacers improves the performance of an AON with SEQ ID NO: 5361 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 5360).

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

[00425] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5370 (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 67.77%. A 500 nM dose of SEQ ID NO: 5370 (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 84.79%. Comparatively, a 200 nM dose of SEQ ID NO: 5362 (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A

mRNA to 22.48%. A 500 nM dose of SEQ ID NO: 5362 (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 24.84%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 5142 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 1248).

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

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

SEQ ID NO:	Oligonucleotide Sequence* (where **S** indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	500 nM	500 nM
		Normalized CS	Normalized CS SD	Normalized CS	Normalized CS SD
5293	GAAGAGCTGGGCAGGCAGGAATGGT	3.79367	0.480565	-63.053	0.19433
5294	TGTGGATGGTGTGGCCAGAAAGAGG	60.6986	0.724229	-23.435	0.36397
5295	GGCCAGGAGAGTGTGGATGGTGTGG	154.828	1.127288	434.631	2.32539
5296	ATGGCATGGCGGGCAGTCTCAGAGG	37.1601	0.448286	12.6634	0.41631
5297	AAAGGGAATGGCATGGCGGGCAGTC	-26.139	0.13718	22.9464	0.49028
5298	AGGTAAAGGGAATGGCATGGCGGGC	-5.3242	0.383369	-37.199	0.17903
5299	GGTAAAGGGAATGGCATGGCGGG	-29.228	0.227001	-33.566	0.20089
5300	GGTAAAG**S**GAATGGC**S**TGGCGGG	-16.331	0.304608	-29.739	0.22392
5301	AGGTAAAGGGAATGGCATGGCGG	-13.385	0.322337	-40.436	0.15956
5302	AGGTAAA**S**GGAATGG**S**ATGGCGG	-13.664	0.320657	-24.027	0.2583
5303	GTAAAGGGAATGGCATGGCGGGC	-29.989	0.222419	-26.677	0.24235
5304	GTAAAGG**S**AATGGCA**S**GGCGGGC	25.771	0.557959	-18.428	0.29199
5305	TCCAGGTAAAGGGAATGGCATGGCG	-7.8349	0.268854	40.2877	0.61503
5306	AGGGAGGAGTTTTCCAGGTAAAGGG	-32.255	0.392785	-25.109	0.4256
5307	AGGGAG**S**AGTTTTCCAGG**S**AAAGGG	6.97605	0.572906	-3.6889	0.52394
5308	AGGGAGGA**S**TTTTCCAGGSAAAGGG	-70.51	0.217148	-78.696	0.17957
5309	AGAGGAGGTGACCCTGAATCTGGAC	129.033	0.93262	110.34	1.0505

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5310	GAGGAGGTGACCCTGAATCTGGA	169.855	1.024819	164.814	1.30762
5311	GAGGAGGSGACCCTGSATCTGGA	-72.457	0.658323	138.629	1.28191
5312	AGAGGAGGTGACCCTGAATCTGG	171.498	1.135638	3.26987	0.54512
5313	AGAGGAGSTGACCCTSAATCTGG	7.49253	0.565048	-57.946	0.25617
5314	AGGAGGTGACCCTGAATCTGGAC	44.7095	0.740715	125.001	1.1197
5315	AGGAGGTSACCCTGASTCTGGAC	-44.26	0.320771	12.8179	0.59018
5316	GAGAGTCAACCTGGAGGCCAAGGTG	32.5688	0.559505	57.0338	0.7355
5317	GTAGTGAGAGTCAACCTGGAGGCCA	70.681	0.905428	67.6819	0.88671
5318	TGAGTAGTGAGAGTCAACCTGGAGG	91.2119	1.033573	59.7857	0.83742
5319	CCTGAGTGGTTAGGGCTGGAATAGA	46.7792	0.756244	-24.332	0.3124
5320	CAATCCTGAGTGGTTAGGGCTGGAA	-8.5	0.411217	73.8646	0.9253
5321	ACGGCCCAATCCTGAGTGGTTAGGG	66.8521	0.88153	45.3726	0.74746
5322	ACACAAACGGCCCAATCCTGAGTGG	-11.42	0.462541	75.8487	0.8839
5323	CACAAACGGCCCAATCCTGAGTG	-11.128	0.463949	-41.939	0.31518
5324	CACAAACSGCCCAATSCTGAGTG	50.7872	0.762897	-14.314	0.44857
5325	ACACAAACGGCCCAATCCTGAGT	-27.43	0.385239	41.8694	0.71984
5326	ACACAAASGGCCCAASCCTGAGT	-14.732	0.44655	55.6902	0.78657
5327	ACAAACGGCCCAATCCTGAGTGG	-49.751	0.277462	-20.306	0.41964
5328	ACAAACGSCCCAATCSTGAGTGG	105.349	1.026341	47.8744	0.74883
5329	CAGACACAAACGGCCCAATCCTGAG	-40.7843	0.3272	-5.4793	0.5486
5330	CATACCCAGACACAAACGGCCCAAT	-21.2475	0.3317	14.4015	0.5542
5331	GAGACATACCCAGACACAAACGGCC	47.2141	0.7590	116.3656	1.1906

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5332	GCAGCTGGAAGAGACATACCCAGAC	4.7146	0.5625	-66.6389	0.2349
5333	GCAGCTSGAAGAGACATASCCAGAC	33.7840	0.6960	-6.4957	0.5111
5334	GCAGCTGGSAGAGACATASCCAGAC	3.7461	0.5581	35.3538	0.7032
5335	TCTTTCCAGGAAACCCAGGCAGCTG	17.5514	0.5395	30.5680	0.5952
5336	GTTCTTTCCAGGAAACCCAGGCAGC	41.1141	0.5932	-27.3254	0.2666
5337	TTCTTTCCAGGAAACCCAGGCAG	-31.8396	0.2450	-7.7732	0.3599
5338	TTCTTTCSAGGAAACSCAGGCAG	-72.0800	0.0530	-37.1813	0.2196
5339	GTTCTTTCCAGGAAACCCAGGCA	-14.5643	0.3275	44.7209	0.6104
5340	GTTCTTTSCAGGAAASCCAGGCA	-38.7597	0.2120	-22.4863	0.2897
5341	TCTTTCCAGGAAACCCAGGCAGC	2.0002	0.4065	-15.1244	0.3248
5342	TCTTTCCSGGAAACCSAGGCAGC	-59.9899	0.1107	-64.5153	0.0891
5343	CACGAATCTACCCACCAACTCATCC	-39.5824	0.2948	-56.2924	0.2233
5344	TCTAGCCACGAATCTACCCACCAAC	75.4170	0.7873	-12.0685	0.4126
5345	GTCTGTCCACCAGCCACTCACAACC	121.2337	0.9834	-62.7895	0.1955
5346	TTCGTCTGTCCACCAGCCACTCACA	-18.2285	0.3863	-45.7096	0.2686
5347	TCCATTTTTCGTCTGTCCACCAGCC	-63.8195	0.2479	-54.2647	0.2917
5348	GATCCGCAACTTAATCCACCTACCC	88.0305	0.9091	44.9905	0.5436
5349	ATCCGCAACTTAATCCACCTACC	30.7027	0.4223	45.1113	0.5446
5350	ATCCGCASCTTAATCSACCTACC	38.8278	0.4913	50.8796	0.5936
5351	GATCCGCAACTTAATCCACCTAC	43.8789	0.5342	66.9823	0.7303
5352	GATCCGCSACTTAATSCACCTAC	**55.8768**	**0.6360**	**66.6162**	**0.7272**
5353	TCCGCAACTTAATCCACCTACCC	64.3790	0.7082	67.3066	0.7331

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5354	TCCGCAASTTAATCCSCCTACCC	53.4236	0.6152	51.3988	0.5980
5355	CACCCACCCATCTAACTACCCCAAA	64.1844	0.6729	44.6783	0.4941
5356	ACCCACCCATCTAACTACCCCAA	41.2908	0.4631	64.1844	0.6729
5357	ACCCACCSATCTAACSACCCCAA	46.9810	0.4070	58.8250	0.6238
5358	CACCCACCCATCTAACTACCCCA	47.6810	0.5217	41.0564	0.4609
5359	CACCCACSCATCTAASTACCCCA	47.9432	0.5241	83.1895	0.8471
5360	CCCACCCATCTAACTACCCCAAA	72.0651	0.5775	23.3677	0.2988
5361	CCCACCCSTCTAACTSCCCCAAA	41.8445	0.4682	43.0965	0.4796
5362	GAAAGTGTCATGGAGAGTGCAAGGG	22.4754	0.5041	24.8358	0.5167
5363	AAAGTGTCATGGAGAGTGCAAGG	82.5919	0.8245	7.0300	0.4218
5364	AAAGTGTSATGGAGASTGCAAGG	61.0070	0.7095	-4.8799	0.3583
5365	GAAAGTGTCATGGAGAGTGCAAG	55.7844	0.6816	-19.7864	0.2789
5366	GAAAGTGSCATGGAGSGTGCAAG	40.0402	0.5977	3.6974	0.4040
5367	AAGTGTCATGGAGAGTGCAAGGG	19.0435	0.4858	-34.5807	0.2001
5368	AAGTGTCSTGGAGAGSGCAAGGG	35.3880	0.5729	6.6020	0.4195
5369	GAAAGTSTCATGGAGAGTSCAAGGG	-10.6183	0.3278	50.6900	0.6545
5370	GAAAGTGTSATGGAGAGTSCAAGGG	67.7691	0.7455	84.7852	0.8362
5371	CACCATGGGAGAGAAAGTGTCATGG	17.7544	0.4529	64.3335	0.7880

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

Example 3: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00427] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00428] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C"is 5-MeC.

[00429] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[00430] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detect using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 5203)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 5204)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 5203)

[00431] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00432] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

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

[00433] Table 8 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[00434] As shown in Table 8, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00435] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5372 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 4.4%. A 50 nM dose of SEQ ID NO: 5372 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 20.3%.

[00436] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5373 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 5.1%. A 50 nM dose of SEQ ID NO: 5373 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 26.0%.

[00437] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5374 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 6.6%. A 50 nM dose of SEQ ID NO: 5374 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 41.2%.

[00438] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5375 (GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 8.3%. A 50 nM dose of SEQ ID NO: 5375 (GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 31.0%.

[00439] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5376 (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 8.8%. A 50 nM dose of SEQ ID NO: 5376 (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 35.4%.

[00440] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5377 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 11.8%. A 50 nM dose of SEQ ID NO: 5377 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 30.6%.

[00441] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5378 (GCAGCTGGAAGAGACATACCCAGACwith no spacers) reduced UNC13A cryptic exon levels to 13.8%. A 50 nM dose of SEQ ID NO: 53787 (GCAGCTGGAAGAGACATACCCAGACwith no spacers) reduced UNC13A cryptic exon levels to 66.0%.

[00442] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5379 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 15.2%. A 50 nM dose of SEQ ID NO: 5379 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 34.4%.

[00443] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5380 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 15.8%. A 50 nM dose of SEQ ID NO: 5380 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 45.4%.

[00444] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5381 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 18.2%. A 50 nM dose of SEQ ID NO: 5381 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 41.9%.

[00445] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5382 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 20.1%. A 50 nM dose of SEQ ID NO: 5382 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 42.8%.

[00446] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5383 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 23.1%. A 50 nM dose of SEQ ID NO: 5383 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 50.2%.

[00447] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5384 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 25%. A 50 nM dose of SEQ ID NO: 5384 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 40.6%.

[00448] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5385 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 27.2%. A 50 nM dose of SEQ ID NO: 5385 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 43.4%.

[00449] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5386 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 34.4%. A 50 nM dose of SEQ ID NO: 5386 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 64.3%.

[00450] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5387 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 40.5%. A 50 nM dose of SEQ ID NO: 5387 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 82.2%.

[00451] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5388 (TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 41.6%. A 50 nM dose of SEQ ID NO: 5388 (TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 54.2%.

[00452] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5389 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 42.0%. A 50 nM dose of SEQ ID NO: 5389 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 54.0%.

[00453] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5390 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 44.5%. A 50 nM dose of SEQ ID NO: 5390 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 45.5%.

[00454] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5391 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 46.4%. A 50 nM dose of SEQ ID NO: 5391 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 69.7%.

[00455] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5392 (ACACATCCATCCATCCATCCATT with no spacers) reduced UNC13A cryptic exon levels to 47.8%.

[00456] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5393 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.1%. A 50 nM dose of SEQ ID NO: 5393 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 76.5%.

[00457] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5394 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.2%. A 50 nM dose of SEQ ID NO: 5394 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 62.8%.

[00458] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5395 (CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 49.6%. A 50 nM dose of SEQ ID NO: 5395 (CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 70.9%.

[00459] As shown in Table 8, a 200 nM dose of SEQ ID NO: 5396 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 49.8%. A 50 nM dose of SEQ ID NO: 5396 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 67.0%.

Table 8. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	50 nM	50 nM
		Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon	Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon
5372	GAGACATACCCAGACACAAACGGCC	4.38	4.41	20.3	14.4
5373	GTTCTTTCCAGGAAACCCAGGCA	5.11	4.14	26	15.2
5374	GTTCTTTSCAGGAAASCCAGGCA	6.62	6.06	41.2	15.2
5375	GCAGCTGGSAGAGACATASCCAGAC	8.3	7.86	31	26.4
5376	GTTCTTTCCAGGAAACCCAGGCAGC	8.84	7.85	35.4	22.4
5377	GCAGCTSGAAGAGACATASCCAGAC	11.8	10.7	30.6	13
5378	GCAGCTGGAAGAGACATACCCAGAC	13.8	7.11	66	45.9
5379	TTCTTTCCAGGAAACCCAGGCAG	15.2	7.39	34.4	25.1
5380	ACATCCATCCATCCATCCATTCA	15.8	8.84	45.4	14
5381	TCTTTCCSGGAAACCSAGGCAGC	18.2	9.18	41.9	24.2
5382	TTCTTTCSAGGAAACSCAGGCAG	20.1	9.33	42.8	27.7
5383	ACACATCCATCCATCCATCCATTCA	23.1	15.7	50.2	21.5
5384	TCTTTCCAGGAAACCCAGGCAGC	25	11.7	40.6	22.9
5385	CATACCCAGACACAAACGGCCCAAT	27.2	20.6	43.4	28
5386	CTCTTTTATCCATCCACACACCCAC	34.4	20.1	64.3	34.7

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5387	CTCTTTTATCCATCCACACACCC	40.5	15.2	82.2	45.5
5388	TCTTTCCAGGAAACCCAGGCAGCTG	41.6	30.5	54.2	20.8
5389	GAAAGTGSCATGGAGSGTGCAAG	42	38.1	54	32.5
5390	ATCTACSCTTTTATCCATSCACACA	44.5	22.4	45.5	34.4
5391	ATCTACTCTTTTATCCATCCACACA	46.4	29.9	69.7	47.6
5392	ACACATCCATCCATCCATCCATT	47.8	24.9	122	41.9
5393	CTACTCTSTTATCCASCCACACA	48.1	35.4	76.5	37.9
5394	ATCTACTCSTTTATCCATSCACACA	48.2	21.5	62.8	44.3
5395	CTTTCAGSAATTCAASCACACAT	49.6	39.2	70.9	46.3
5396	AAGTGTCATGGAGAGTGCAAGGG	49.8	39.3	67	59.7
5397	CACATCCATCCATCCATCCATTC	51.6	14.2	80.3	41.4
5398	CAATCCTGAGTGGTTAGGGCTGGAA	54.2	18.8	59.6	16.2
5399	CAGACACAAACGGCCCAATCCTGAG	54.4	19.2	73.2	43.7
5400	CTTTTATCCATCCACACACCCAC	55.4	30.5	59	34.2
5401	TCTTTTATCCATCCACACACCCA	55.7	29.2	61.1	45.6
5402	CTCTTTTSTCCATCCSCACACCC	55.9	29.8	83.8	50.9
5403	GGGCAGGCAGGAATGGTGAGTGG	56.6	41	73.6	47.2
5404	TCCACCAGSCACTCACAASCATCCA	58	17.7	86.1	36.5
5405	CACCCACCCATCTAACTACCCCAAA	58.2	42.7	91	34.4
5406	GGCAGGCAGGAATGGTGAGTGGA	59.1	43.9	57.9	41.1
5407	TCTTTTASCCATCCASACACCCA	63.1	23.5	54.3	40.7

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5408	CACCCACCCATCTAACTACCCCA	63.1	44.6	74.3	51.2
5409	AAAGTGTSATGGAGASTGCAAGG	63.7	39.2	55.5	53
5410	TGCAATASTTCAACCSCACATCC	64.1	25.7	75.7	42.9
5411	GGGCAGGCSGGAATGGTGSGTGGAA	64.2	32	73	39
5412	GGGCAGGCAGGAATGGTGAGTGGAA	64.6	42.2	91.2	48.4
5413	GGCAGGCSGGAATGGSGAGTGGA	64.6	49.5	92.8	65
5414	CTCTTTSATCCATCCACASACCCAC	65.1	34.1	53	32.2
5415	AAAGTGTCATGGAGAGTGCAAGG	65.3	45.4	71.2	64.2
5416	CAGTAATSCAACCACSCATCCAT	65.5	23.7	92.7	24.1
5417	CTCTTTTASCCATCCACASACCCAC	65.6	37.8	67.8	29.5
5418	CTACTCTTTTATCCATCCACACA	67.1	32	50.5	34
5419	ACCTTTCAGTAATTCAACCACACAT	67.5	52.3	87.4	58
5420	GAAAGTGTCATGGAGAGTGCAAG	68.3	52.7	52.7	38.7
5421	CTTTTATSCATCCACSCACCCAC	68.7	58.9	59.2	33.2
5422	ACCTTTCASTAATTCAACSACACAT	69.2	35.5	115	79.8
5423	ACACAAASGGCCCAASCCTGAGT	69.3	54.9	114	67.4
5424	CACCCACSCATCTAASTACCCCA	71.4	65.7	111	77.3
5425	AGTAATTSAACCACASATCCATC	72	16	58	21.7
5426	AAGTGTCSTGGAGAGSGCAAGGG	72.1	51.9	70.7	59.6
5427	ACACAAACGGCCCAATCCTGAGT	72.4	18.3	99.8	34.6
5428	TGCAATAGTTCAACCACACATCC	74	35.8	124	53.6

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5429	CTTTCAGTAATTCAACCACACAT	74.1	39.5	65.7	57.3
5430	ACACAAACGGCCCAATCCTGAGTGG	74.3	16.6	109	53.2
5431	CCTGAGTGGTTAGGGCTGGAATAGA	75.2	42.7	92.4	35.7
5432	CCTTTCAGTAATTCAACCACACA	76.2	42.9	145	138
5433	CACAAACGGCCCAATCCTGAGTG	76.8	37.3	91.2	46.8
5434	ACCCACCCATCTAACTACCCCAA	77.1	52.6	87.2	59.1
5435	TCTACTCSTTTATCCSTCCACAC	78.2	43.6	88.6	71.7
5436	CACAAACSGCCCAATSCTGAGTG	78.2	45.6	86.8	45.4
5437	ACAAACGSCCCAATCSTGAGTGG	78.3	38.8	66.1	35
5438	TCCACCSGCCACTCACAASCATCCA	78.7	73.6	120	50.9
5439	CCCACCCATCTAACTACCCCAAA	78.9	50.3	71.8	60.4
5440	GGGCAGGSAGGAATGSTGAGTGG	82.7	67.3	142	100
5441	CTTGCASTAGTTCAACCASACATCC	86	34.4	140	132
5442	ATCTACTSTTTTATCSATCCACA	86.3	55.6	117	68.8
5443	ACGGCCCAATCCTGAGTGGTTAGGG	86.9	44.1	108	78
5444	GATCCGCAACTTAATCCACCTAC	88.3	76.5	115	86.5
5445	GAAAGTSTCATGGAGAGTSCAAGGG	89.6	50.5	107	42.8
5446	ATCTACTCTTTTATCCATCCACA	91.1	60.9	89.8	70.4
5447	ACAAACGGCCCAATCCTGAGTGG	92.9	43.5	78.5	47.3
5448	GCAGGCAGGAATGGTGAGTGGAA	94	74.1	118	82.7
5449	ACCTTTCSGTAATTCSACCACAC	95.2	44.9	60.6	52.1

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5450	AGGTAAAGGGAATGGCATGGCGGGC	96	49.3	115	57
5451	TCCGCAACTTAATCCACCTACCC	96	82.6	111	77.3
5452	GAAAGTGTCATGGAGAGTGCAAGGG	96.3	58.9	118	77.8
5453	CTTGCAASAGTTCAASCACACAT	98.9	42.4	90.8	40.8
5454	CTTGCAATAGTTCAACCACACAT	99.5	39	95.7	46.1
5455	CCCACCCSTCTAACTSCCCCAAA	99.7	71.7	112	82.8
5456	CAGTAATTSAACCACACASCCATCC	101	95.2	128	130
5457	TTGCAATAGTTCAACCACACATC	102	54.4	138	55.5
5458	ACCTTTCAGTAATTCAACCACAC	105	105	120	108
5459	GTAATTCSACCACACSTCCATCC	106	60.1	116	48.6
5460	GTAGTGAGAGTCAACCTGGAGGCCA	107	21.8	92.6	27.2
5461	TCTACTCTTTTATCCATCCACAC	107	71.4	83.2	56.9
5462	CACCATGGGAGAGAAAGTGTCATGG	108	103	67.4	60.1
5463	AGGGAGGAGTTTTCCAGGTAAAGGG	109	50.5	95.7	21.4
5464	GCAGGCASGAATGGTSAGTGGAA	109	74.8	150	98.2
5465	ACCCACCSATCTAACSACCCCAA	112	74.4	81.6	45.8
5466	ACACATSCATCCATCCATSCATTCA	114	36.7	135	39.5
5467	TTGCAATSGTTCAACSACACATC	115	54.7	98.6	51.2
5468	AGGGAGSAGTTTTCCAGGSAAAGGG	116	30	110	29.8
5469	ACATCCASCCATCCASCCATTCA	116	50.6	111	38
5470	ACCTTTSAGTAATTCAACSACACAT	116	81.4	101	74.7

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5471	GAAAGTGTSATGGAGAGTSCAAGGG	117	40.6	115	66.2
5472	AGGGAGGASTTTTCCAGGSAAAGGG	118	30.4	111	22.7
5473	GAGAGTCAACCTGGAGGCCAAGGTG	118	43.8	96.1	17.9
5474	GTTCAACCACACATCCTTCCATT	119	70.8	186	142
5475	CTTGCAATAGTTCAACCACACATCC	120	57.3	140	70.5
5476	GTCTGTCCACCAGCCACTCACAACC	120	104	154	122
5477	AGTTCAACCACACATCCTTCCAT	121	55	161	77.7
5478	AGTTCAACSACACATCCTSCCATTC	122	71.7	129	96.7
5479	ACACATCSATCCATCSATCCATT	123	40.6	108	40.9
5480	TTCAACCACACATCCTTCCATTC	124	9.97	143	48.5
5481	GAGGAGGSGACCCTGSATCTGGA	124	33.6	117	67.2
5482	GGTAAAGGGAATGGCATGGCGGG	125	50.2	110	68.5
5483	AGTTCAASCACACATSCTTCCAT	125	81.5	142	155
5484	CACATCCSTCCATCCSTCCATTC	128	67	89.1	32
5485	AGGTAAASGGAATGGSATGGCGG	128	77.5	149	85.4
5486	GGGCAGSCAGGAATGGTGSGTGGAA	129	72.2	105	58.4
5487	GATCCGCSACTTAATSCACCTAC	136	111	152	102
5488	GTAATTCAACCACACATCCATCC	137	54	107	52.1
5489	AGAGGAGSTGACCCTSAATCTGG	139	55.6	118	48.1
5490	GTTCAACSACACATCSTTCCATT	145	80.5	138	84.8
5491	CAGTAATTCAACCACACATCCAT	146	47.3	119	22.7

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5492	ATCCGCASCTTAATCSACCTACC	147	63.2	132	76.5
5493	AGGTAAAGGGAATGGCATGGCGG	147	82.1	148	92.8
5494	TCCGCAASTTAATCCSCCTACCC	148	97	180	93.3
5495	AGGAGGTSACCCTGASTCTGGAC	149	47.3	101	58.2
5496	AGTTCASCCACACATCCTSCCATTC	149	79	132	60.8
5497	CAGTAASTCAACCACACASCCATCC	149	84.3	116	53.3
5498	AGTTCAACCACACATCCTTCCATTC	151	106	137	114
5499	GGTAAAGSGAATGGCSTGGCGGG	151	111	106	63.6
5500	CAGTAATTCAACCACACATCCATCC	155	85.5	133	58.7
5501	TTCAACCSCACATCCSTCCATTC	156	159	139	80.1
5502	CTTGCAATSGTTCAACCASACATCC	157	99.7	123	77
5503	GAAGAGCTGGGCAGGCAGGAATGGT	158	99.8	160	79.5
5504	GATCCGCAACTTAATCCACCTACCC	161	73	154	72
5505	ACACATCCSTCCATCCATSCATTCA	163	45.7	163	44.5
5506	TGAGTAGTGAGAGTCAACCTGGAGG	164	54.7	108	59.6
5507	ATGGCATGGCGGGCAGTCTCAGAGG	168	99.2	166	76.5
5508	AGTAATTCAACCACACATCCATC	173	58.2	107	51.4
5509	TCCACCAGCCACTCACAACCATCCA	173	134	84.3	45.9
5510	AGGAGGTGACCCTGAATCTGGAC	176	46.2	85.1	44.1
5511	CACGAATCTACCCACCAACTCATCC	178	116	140	49.4
5512	GAGGAGGTGACCCTGAATCTGGA	182	60.1	108	36.8

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5513	CCTTTCASTAATTCASCCACACA	182	192	114	61.7
5514	TGTGGATGGTGTGGCCAGAAAGAGG	185	70.1	156	70.7
5515	ATCCGCAACTTAATCCACCTACC	186	58.2	149	63.5
5516	GTAAAGGSAATGGCASGGCGGGC	193	116	161	79.1
5517	TTCGTCTGTCCACCAGCCACTCACA	193	125	119	81.2
5518	TCCATTTTTCGTCTGTCCACCAGCC	196	122	113	51.4
5519	AGAGGAGGTGACCCTGAATCTGG	197	67.6	108	41.2
5520	AGAGGAGGTGACCCTGAATCTGGAC	197	92.2	119	37.6
5521	GGCCAGGAGAGTGTGGATGGTGTGG	200	74.8	162	83.3
5522	GTAAAGGGAATGGCATGGCGGGC	205	79.8	80	52
5523	TCCAGGTAAAGGGAATGGCATGGCG	215	102	149	127
5524	AAAGGGAATGGCATGGCGGGCAGTC	226	99.9	178	113
5525	GGAAGAGACATACCCAGACACAAAC	0.02	0.00	11.43	6.56
5526	CAGCTGGAAGAGACATACCCAGACA	0.03	0.02	16.20	7.83
5527	GAAGAGACATACCCAGACACAAACG	0.94	1.59	0.61	1.01
5528	AGAGTTCTTTCCAGGAAACCCAGGC	1.47	2.28	19.61	9.44
5529	AAGAGTTCTTTCCAGGAAACCCAGG	3.01	2.16	21.95	5.43
5530	GAGTTCTTTCCAGGAAACCCAGGCA	3.49	2.07	29.80	2.76
5531	AGTTCTTTCCAGGAAACCCAGGCAG	3.62	3.79	38.61	18.71
5532	AGGCAGCTGGAAGAGACATACCCAG	4.63	5.37	32.99	2.70
5533	AGAGACATACCCAGACACAAACGGC	5.98	6.18	12.51	6.77

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5534	CTGGAAGAGACATACCCAGACACAA	6.26	10.82	58.24	12.87
5535	AAGAGACATACCCAGACACAAACGG	9.32	5.24	16.02	3.73
5536	AGACATACCCAGACACAAACGGCCC	12.07	2.14	29.94	15.81
5537	GGCAGCTGGAAGAGACATACCCAGA	12.92	4.64	50.87	17.93
5538	CAGGCAGCTGGAAGAGACATACCCA	14.04	2.17	32.22	17.05
5539	GCTGGAAGAGACATACCCAGACACA	15.74	19.34	36.35	14.55
5540	AGCTGGAAGAGACATACCCAGACAC	18.82	10.27	20.31	17.71
5541	GCAGCTGGAAGAGACATACCCAGAC	18.87	22.30	55.59	34.27
5542	GACATACCCAGACACAAACGGCCCA	19.96	11.08	28.25	4.42
5543	GAGACATACCCAGACACAAACGGCC	21.01	9.29	26.91	8.72
5544	ACATCCATCCATCCATCCATTCATC	21.36	5.97	63.61	8.59
5545	CACATCCATCCATCCATCCATTCAT	23.52	1.80	108.40	54.14
5546	CCAGGCAGCTGGAAGAGACATACCC	25.02	3.34	60.96	5.29
5547	ATCCATCCATCCATCCATTCATCCA	25.59	10.98	86.98	36.11
5548	ACACATCCATCCATCCATCCATTCA	27.76	4.11	72.26	37.32
5549	TTCTTTCCAGGAAACCCAGGCAGCT	30.66	1.40	86.91	11.41
5550	TCTTTCCAGGAAACCCAGGCAGCTG	31.13	5.45	52.43	7.09
5551	CATCCATCCATCCATCCATTCATCC	35.45	4.51	75.99	10.37
5552	CACACATCCATCCATCCATCCATTC	38.25	19.28	96.63	22.67
5553	ACATACCCAGACACAAACGGCCCAA	38.57	4.68	44.89	1.89
5554	ACCACACATCCATCCATCCATCCAT	39.40	7.68	71.32	18.18

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5555	CCACACATCCATCCATCCATCCATT	39.80	8.88	77.72	2.82
5556	AACCACACATCCATCCATCCATCCA	41.07	10.10	97.41	24.31
5557	CTTTCCAGGAAACCCAGGCAGCTGG	42.16	22.26	77.70	9.85
5558	TTTCCAGGAAACCCAGGCAGCTGGA	51.84	9.47	72.21	10.14
5559	CATACCCAGACACAAACGGCCCAAT	60.89	6.26	84.01	23.09

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

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Example 4: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00460] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00461] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C"is 5-MeC.

[00462] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[00463] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detected using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 5203)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 5204)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 5203)

[00464] To evaluate UNC13A AON ability to reduce UNC13A correctly spliced (CS)exon junction 20/21 levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was

isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A CS exon 20/21 junction, and reference GAPDH quantification.

[00465] Transcript levels (e.g., UNC13A exon junction 20/21, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a exon 20/21 junction was detect using TaqMan Gene Expression Assay Hs01000584_m1.

[00466] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00467] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt).

[00468] Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

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

[00469] Table 9 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[00470] As shown in Table 9, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00471] Correctly spliced UNC13A (Ct) was also normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % increase of correctly spliced UNC13A), the normalized correctly spliced UNC13A signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt).

[00472] Relative quantity (RQ) of transcript level was calculated using the equation RQ=2^(-deltadeltaCt) and is used to describe the treatment condition comparison to normal, healthy

levels (1.0). RQ values for UNC13A corrected splicing were normalized using the following formula:

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

Table 9. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

		UNC13A Corrected Splicing Normalized RQ				UNC13A Cryptic Splicing Normalized RQ			
		200nM		50nM		200nM		50nM	
SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	Mean	STD	Mean	STD	Mean	STD	Mean	STD
5566	GAAGAGACATACCCAGACACAAACG	41.82	18.84	-27.56	73.08	3.16	1.03	18.87	12.38
5565	GAAGAGACATACCCAGACACAAA	8.93	7.32	-7.13	7.81	15.78	7.41	42.31	31.11
5563	AAGAGACATACCCAGACACAAAC	-28.45	72.83	-12.62	12.84	12.06	9.62	57.27	34.91
5564	AGAGACATACCCAGACACAAACG	13.03	15.19	9.48	11.41	14.78	6.73	61.44	25.31
5562	GAGACATACCCAGACACAAACGG	28.03	29.67	7.69	35.17	18.53	10.52	33.25	20.41
5560	AGACATACCCAGACACAAACGGC	24.21	33.06	23.24	30.63	29.74	33.32	50.76	39.49
5561	GACATACCCAGACACAAACGGCC	2.47	35.11	2.89	26.90	26.29	25.67	46.66	32.30
5573	AGGCAGCTGGAAGAGACATACCCAG	47.19	57.85	15.52	30.16	2.07	3.30	13.45	13.12
5571	AGGCAGCTGGAAGAGACATACCC	37.80	13.72	1.51	9.33	2.32	3.41	22.31	14.52
5570	GGCAGCTGGAAGAGACATACCCA	39.83	25.50	19.20	21.74	7.01	5.73	25.13	28.23
5572	GCAGCTGGAAGAGACATACCCAG	43.08	23.32	4.48	7.87	5.11	6.91	32.17	23.76
5567	CAGCTGGAAGAGACATACCCAGA	-21.34	16.48	-144.30	28.86	7.59	6.87	21.20	16.74
5568	AGCTGGAAGAGACATACCCAGAC	-173.70	29.80	-75.73	8.72	4.20	7.60	165.20	96.22
5253	GCAGCTGSAAGAGACSTACCCAG	64.46	20.00	-11.79	20.17	2.34	1.77	17.01	6.37
5251	CAGCTGGSAGAGACASACCCAGA	87.01	8.70	28.35	13.19	5.72	3.41	22.86	10.45
5266	GTTCTTSCCAGGAAACCCSGGCAGC	-8.32	3.39	-10.50	8.45	29.49	14.34	51.95	12.36
5265	GTTCTTTCSAGGAAACCCSGGCAGC	6.29	22.23	6.58	3.64	8.10	5.42	28.87	7.85
5269	AGAGTTCSTTCCAGGSAACCCAG	61.99	21.81	-24.46	58.00	12.82	3.63	55.05	18.66
5267	GAGTTCTSTCCAGGASACCCAGG	38.47	29.10	-14.70	48.97	17.11	11.96	80.63	36.03
5268	AGTTCTTSCCAGGAASCCCAGGC	9.90	25.86	-7.31	26.47	26.33	9.18	92.35	32.38
5271	AGAGTTSTTTCCAGGAAASCCAGGC	44.52	32.61	57.40	14.54	9.44	4.83	22.79	6.99
5270	AGAGTTCTSTCCAGGAAASCCAGGC	44.46	8.40	48.23	22.36	3.31	2.76	14.18	10.22

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5243	GAGACATSCCCAGACSCAAACGG	84.50	29.82	47.59	10.35	31.74	13.09	79.61	17.53
5241	AGACATASCCAGACASAAACGGC	90.95	10.72	22.20	40.15	30.38	13.73	82.12	14.48
5242	GACATACSCAGACACSAACGGCC	73.81	41.97	36.23	29.75	22.06	9.58	70.87	9.37
5245	GAGACASACCCAGACACASACGGCC	80.40	19.16	23.13	19.81	31.05	15.73	88.26	28.47
5244	GAGACATASCCAGACACASACGGCC	126.50	25.60	88.00	43.30	17.80	10.45	77.70	25.98
5257	AGGCAGSTGGAAGAGACASACCCAG	96.50	22.07	44.00	25.12	10.88	6.15	35.95	13.92
5256	AGGCAGCTSGAAGAGACASACCCAG	103.10	12.62	66.18	15.49	4.04	2.80	27.84	10.66
5255	AGGCAGCSGGAAGAGSCATACCC	92.83	15.27	58.96	6.90	12.26	4.78	31.13	9.49
5254	GGCAGCTSGAAGAGASATACCCA	82.43	18.79	58.45	12.96	8.83	8.20	37.74	10.12
5252	AGCTGGASGAGACATSCCCAGAC	87.57	8.14	9.59	32.49	7.43	3.22	28.79	15.38
5250	GAAGAGSCATACCCAGACSCAAACG	102.70	14.83	54.28	31.30	29.53	14.04	75.86	28.78
5249	GAAGAGACSTACCCAGACSCAAACG	99.18	24.63	46.29	25.42	22.36	7.32	75.43	35.92
5248	GAAGAGASATACCCASACACAAA	49.24	20.69	21.53	23.44	89.72	39.56	135.70	43.02
5246	AAGAGACSTACCCAGSCACAAAC	28.09	21.14	22.72	15.94	52.17	11.17	112.70	38.44
5247	AGAGACASACCCAGASACAAACG	78.70	27.23	29.31	21.53	29.70	17.53	85.44	19.01
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	25.91	16.04	21.89	19.68	4.99	12.69	17.06	44.28
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	19.94	10.97	10.81	5.00	20.25	27.06	28.08	34.90
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	8.93	9.25	6.86	7.65	-1.28	1.43	7.60	13.16
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.18	4.96	12.23	11.77	-1.20	1.39	29.03	35.58
5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	14.39	10.91	10.40	7.95	6.29	12.97	21.83	31.86
5287	GCA[LNA-G]CTGGSAGAGACATASCC[LNA-A]GAC	-10.22	30.13	29.91	20.97	11.14	21.19	6.45	7.80
5286	GCA[LNA-G]CTGGSAGA[LNA-G]ACATASCC[LNA-A]GAC	10.40	16.54	5.17	18.78	12.36	10.45	32.23	21.90
5285	GCAGCTG[LNA-G]SAGAGACAT[LNA-A]SCCAGAC	0.57	12.49	-14.07	16.60	7.76	8.69	16.24	14.15
5284	GCAGCTG[LNA-G]SAGAGACATAS[LNA-C]CAGAC	-6.16	17.10	7.57	18.74	14.62	9.19	46.32	24.49
5283	GCAGCTGGS[LNA-A]GAGACATAS[LNA-C]CAGAC	18.14	16.98	9.28	26.20	8.90	6.17	40.24	12.47
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	4.16	16.50	4.89	11.13	15.39	21.60	19.66	21.58
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	-0.74	10.05	1.42	8.15	11.70	16.06	52.88	33.79
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	-3.14	10.20	0.93	12.63	11.03	12.72	21.48	26.72
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.43	5.96	0.99	9.62	6.88	15.65	39.99	36.29

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5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	-6.06	6.61	-11.46	10.35	6.58	11.97	20.12	30.75
5241	AGACATASCCAGACASAAACGGC	37.10	22.45	53.64	15.42	43.13	22.30	79.66	21.62
5242	GACATACSCAGACACSAACGGCC	50.01	21.60	21.58	15.74	67.02	35.41	83.55	61.27
5243	GAGACATSCCCAGACSCAAACGG	49.95	11.51	29.51	6.61	40.47	25.79	143.30	44.64
5237	AGACATA(S1)CCAGACA(S1)AAACGGC	41.00	21.58	27.91	8.85	51.69	49.87	103.79	37.66
5236	GACATAC(S1)CAGACAC(S1)AACGGCC	46.48	5.54	20.34	11.08	9.03	14.52	72.91	57.87
5235	GAGACAT(S1)CCCAGAC(S1)CAAACGG	45.33	8.89	33.99	13.59	23.89	18.73	133.34	42.50
5157	TTCTTTCSAGGAAACSCAGGCAG	11.16	8.04	9.91	7.60	5.90	10.52	94.03	74.88
5156	GTTCTTTSCAGGAAASCCAGGCA	5.10	4.93	-8.11	6.11	12.92	15.28	25.15	25.51
5155	TCTTTCCSGGAAACCSAGGCAGC	10.06	10.19	3.12	11.72	6.96	9.36	26.97	9.87
5261	TTCTTTC(S1)AGGAAAC(S1)CAGGCAG	11.38	11.69	7.69	15.12	11.99	14.32	54.16	41.27
5260	GTTCTTT(S1)CAGGAAA(S1)CCAGGCA	1.44	7.33	-4.17	4.75	9.79	9.57	27.69	15.98
5259	TCTTTCC(S1)GGAAACC(S1)AGGCAGC	7.18	11.81	-11.24	5.27	18.13	13.56	55.71	28.06
5182	ACATCCASCCATCCASCCATTCA	-37.97	26.85	-4.07	52.32	129.74	41.79	122.30	48.42
5181	ACACATCSATCCATCSATCCATT	5.77	35.61	-11.91	27.75	96.81	38.14	111.73	35.15
5180	CACATCCSTCCATCCSTCCATTC	-14.00	37.66	1.96	30.50	159.36	43.66	164.55	47.07
5274	ACATCCA(S1)CCATCCA(S1)CCATTCA	-16.66	14.80	-5.26	26.53	165.82	42.96	151.38	29.35
5273	ACACATC(S1)ATCCATC(S1)ATCCATT	-7.44	24.85	-21.89	16.44	162.48	39.49	116.38	15.71
5272	CACATCC(S1)TCCATCC(S1)TCCATTC	-9.65	36.42	-0.61	27.96	145.25	19.25	132.10	35.74
5209	TCTTTCCAGGAAACCCAGGCA	18.29	17.99	9.91	14.01	16.42	18.29	16.34	9.91
5220	CAGGAAACCCAGGCA	2.74	3.88	2.44	1.85	16.24	2.74	14.66	2.44
5221	TCTTTCCAGGAAACC	12.94	2.00	7.34	7.10	12.75	12.94	12.29	7.34
5218	CCAGGAAACCCAGGCA	0.00	0.00	0.74	1.05	13.49	0.00	16.04	0.74
5219	TCTTTCCAGGAAACCC	17.89	25.30	17.60	2.62	18.82	17.89	15.79	17.60
5216	TCCAGGAAACCCAGGCA	0.00	0.00	1.54	2.17	14.54	0.00	15.41	1.54
5217	TCTTTCCAGGAAACCCA	6.80	9.61	2.79	1.25	12.77	6.80	15.04	2.79
5214	TTCCAGGAAACCCAGGCA	0.70	0.98	0.00	0.00	16.31	0.70	11.42	0.00
5215	TCTTTCCAGGAAACCCAG	19.21	8.43	49.84	70.94	16.89	19.21	19.14	49.84
5212	TTTCCAGGAAACCCAGGCA	0.55	0.78	3.96	5.60	13.97	0.55	12.15	3.96

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5213	TCTTTCCAGGAAACCCAGG	11.47	8.56	2.24	3.17	16.52	11.47	15.47	2.24
5210	CTTTCCAGGAAACCCAGGCA	6.60	0.75	1.59	2.25	18.60	6.60	12.55	1.59
5211	TCTTTCCAGGAAACCCAGGC	15.08	15.12	11.29	4.48	15.92	15.08	12.81	11.29

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by any of **S, S1, or S#,** is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. S1 represents a spacer of Formula (IIIa'); S# represents a spacer of Formula (IIib'). [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a cytosine nucleobase).

AMENDED SHEET - IPEA/US

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INCORPORATION BY REFERENCE

[00473] The entire disclosure of each of the patent documents and scientific articles cited herein is incorporated by reference for all purposes.

EQUIVALENTS

[00474] The disclosure can be embodied in other specific forms without departing from the essential characteristics thereof. The foregoing embodiments therefore are to be considered illustrative rather than limiting on the disclosure described herein. The scope of the disclosure is indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No.
PCT/US2022/051713

Applicant's or agent's file reference
QRL-014WO

For International Preliminary Examining Authority use only

02 October 2023 (02.10.2023)
Date stamp of the IPEA

Applicant
QURALIS CORPORATION

CALCULATION OF PRESCRIBED FEES

(Applicants may be entitled to a reduction of the preliminary examination fee and the handling fee as indicated in the PCT Fee Tables (www.wipo.int/pct/en/fees.pdf))

1. PRELIMINARY EXAMINATION FEE	256 P	
2. HANDLING FEE	216 H	
3. TOTAL OF PRESCRIBED FEES Add the amounts entered at P and H and enter total in the TOTAL box	472 TOTAL	

MODE OF PAYMENT

(Not all modes of payment may be available at all IPEAs)

- ☒ credit card *(details should not be included on this sheet)*
- ☒ authorization to charge deposit or current account with the IPEA (see below)
- ☐ bank transfer
- ☐ cash
- ☐ postal money order
- ☐ check
- ☐ revenue stamps
- ☐ other *(specify)*: _____

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT OR CURRENT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ US

☐ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit or current accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit or Current Account No.: 07-1700

Date: October 2, 2023

Name: ZHANG, Clark

Signature: /Clark Zhang/

See Notes to the fee calculation sheet

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ UNITED STATES

PCT

DEMAND

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
IPEA/US	02 October 2023 (02.10.2023)

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference	International application No.
QRL-014WO	PCT/US2022/051713
International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
02/12/2022	03/12/2021

Title of invention
TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

QURALIS CORPORATION
100 Cambridgepark Drive
Suite 500
Cambridge, Massachusetts 02140
United States of America

E-mail address*

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

* **E-mail authorization**: Indicating an e-mail address above authorizes the International Bureau and the International Preliminary Examining Authority, if they provide such a service, to send notifications exclusively by e-mail to that address, unless the following box is marked:

☐ notifications are requested to be sent exclusively by postal mail.

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US2022/051713

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ZHANG, Clark
Goodwin Procter LLP
100 Northern Avenue
Boston, MA 02210

E-mail address: patentBOS@goodwinlaw.com

E-mail address*
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Telephone No.
(617) 570-1000

Facsimile No.
(617) 523-1231

Agent's registration No. with the Office
73804

* **E-mail authorization**: Indicating an e-mail address above authorizes the International Bureau and the International Preliminary Examining Authority, if they provide such a service, to send notifications exclusively by e-mail to that address, unless the following box is marked:

☐ notifications are requested to be sent exclusively by postal mail.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

the description	☐	as originally filed, or
	☒	as amended under Article 34
the sequence listing (if any)	☒	~~as originally filed, or~~ [DELETED IPEA/US]
	☐	as amended under Article 34
the claims	☐	as originally filed, or
	☐	as amended under Article 19, and/or
	☒	as amended under Article 34
the drawings (if any)	☒	as originally filed, or
	☐	as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA **to postpone** the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
4. ☐ The applicant expressly requests **to postpone** the start of the international preliminary examination until the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

[DELETED IPEA/US]

International application No.
PCT/US2022/051713

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only: received	not received
1.	translation of international application	:	sheets	☐	☐
2.	amendments under Article 34	:	294 sheets	☑	☐
3.	amended sequence listing under Article 34	:	☐	☐	☐
4.	letter accompanying the amendments under Article 34 (Rule 66.8)	:	5 sheets	☑	☐
5.	copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
6.	copy of the letter accompanying the amendments under Article 19 (Rules 46.5(b) and 53.9)	:	sheets	☐	☐
7.	copy (or, where applicable, translation) of any statement under Article 19 (Rule 62.1(ii))	:	sheets	☐	☐
8.	other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ sequence listing for the purposes of international preliminary examination (Rule 13*ter*)
6. ☐ a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed
7. ☐ other *(specify)*: _____

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

/Clark Zhang/
ZHANG, Clark
Reg. No. 73804
Agent for Applicant
Goodwin Procter LLP
100 Northern Avenue
Boston, MA 02210

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: 02 October 2023 (02.10.2023)

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rules 82 or 82*quater*.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rules 82 or 82*quater*.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

IN THE U.S. PATENT AND TRADEMARK OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
FOR THE PATENT COOPERATION TREATY

International Application No.:	PCT/US2022/051713
International Filing Date:	December 2, 2022
Applicant:	QurAlis Corporation
Title:	TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS
Attorney Reference No.:	QRL-014WO

REQUEST FOR INTERNATIONAL PRELIMINARY EXAMINATION UNDER PCT ARTICLE 31, AMENDMENTS UNDER PCT ARTICLE 34, AND LETTER COMPLYING WITH RULE 46.5(B)(I)-(III)

Dear Sir or Madam:

Applicant hereby requests International Preliminary Examination (Article 31). Before the preparation of the International Preliminary Examination Report, please consider the following remarks submitted under Article 31.2(a) of the Patent Cooperation Treaty and enter the attached amendments being submitted under Article 34(2)(b) of the PCT.

As a demand for international preliminary examination must be submitted by 22 months from the earliest priority date of the application (here December 3, 2021), Applicant submits that the present request is timely filed.

The amendments provided herein are fully supported by the application (including specification and claims) as originally filed. No new matter has been added.

Both marked-up and clean copies of the Substitute Specification and Amended Claims containing the amendments are submitted herewith.

A letter accompanying the Article 34 Amendments as required by Rule 46.5(b)(i)-(iii), detailing the requested changes and support in the specification as filed, is submitted herewith.

Amendments to the Specification begin on page 2.

Amendments to the claims begin on page 3.

Remarks begin on page 4.

AMENDMENTS TO THE SPECIFICATION

Please replace the specification as filed with the substitute specification enclosed herewith. No new matter has been added.

Attachments:

Substitute Specification (Clean)

Substitute Specification (Marked up)

AMENDMENTS TO THE CLAIMS

Please replace the claims as filed with the amended claims enclosed herewith. No new matter has been added.

Attachments:

Amended claims (Clean)

Amended claims (Marked up)

REMARKS

Amendments to the Specification

The specification has been amended to update the SEQ ID NOs to align with the sequences in the Sequence Listing filed on May 31st, 2023. Specifically, the amendments to the specification include:

(1) Paragraph [0001.1] including reference to the XML Sequence Listing filed on May 31, 2023 in response to the PCT/ISA/225 Invitation to Furnish Sequence Listing dated May 22, 2023.

(2) Tables 3A, 3B, 4, and 5 have been amended to eliminate SEQ ID NOs (e.g., originally SEQ ID NOs: 5066-5132) that referenced sequences that do not meet the requirements set forth in paragraph 7 of WIPO Standard ST.26.

(3) Tables 7, 8, and 9 have been amended to renumber SEQ ID NOs: 5293-5573. The sequences are found in the original application as filed on December 2, 2022.

(4) In view of the renumbering of SEQ ID NOs as described above in (2) and (3), the specification has been amended to reflect the updated SEQ ID NOs.

(A) Recitation of "SEQ ID NOs: 5066-5166" has been replaced with "SEQ ID NOs: 5133-5166" throughout the specification.

(B) Recitation of "SEQ ID NOs: 5235-5292" has been replaced with "SEQ ID NOs: 5235-5573".

(C) Prior reference to "SEQ ID NOs: 5066-5132" (which have now been eliminated) has been replaced with reference to their corresponding tables (e.g., "any of the sequences in Tables 3A, 3B, 4, and 5").

Altogether, the amendments to the specification update the SEQ ID NOs and no new matter has been added.

Amendments to the claims

Clean copies of the replacement sheets of the claims are attached to replace the originally filed claims. The changes to the claims are shown in the attached marked-up copy of the claims.

The amendments to the claims have been made in light of the updates to the SEQ ID NOs in the specification. Specifically, the amendments to the claims include:

(1) In view of the removal of SEQ ID NOs: 5066-5132 in the specification in Tables 3A, 3B, 4, and 5, the claims have been amended to replace recitation of "SEQ ID NOs: 5066-5166" with "SEQ ID NOs: 5133-5166". Furthermore, the claims have been amended to remove prior reference to "SEQ ID NOs: 5066-5132" and now reference the corresponding tables (e.g., "any of the sequences in Tables 3A, 3B, 4, and 5").

(2) In view of the renumbering of SEQ ID NOs: 5293-5573 in Tables 7, 8, and 9, the claims have been amended to replace recitation of "SEQ ID NOs: 5235-5292" with "SEQ ID NOs: 5235-5573".

Altogether, the amendments to the claims update the SEQ ID NOs and no new matter has been added.

Dated: October 2nd, 2023

Respectfully submitted,

By /Clark Zhang/

ZHANG, CLARK
GOODWIN PROCTER LLP
Patent Administrator
100 Northern Avenue
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Agent for the Applicant

TREATMENT OF NEUROLOGICAL DISEASES USING MODULATORS OF UNC13A GENE TRANSCRIPTS

CROSS-REFERENCE TO RELATED APPLICATIONS

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

REFERENCE TO A SEQUENCE LISTING XML

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

FIELD OF THE DISCLOSURE

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

BACKGROUND

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

[0004] Amyotrophic lateral sclerosis (ALS) is a group of motor neuron diseases affecting about 15,000 individuals in the United States of America. ALS is characterized by degeneration and death of upper and lower motor neurons, resulting in loss of voluntary muscle control. Motor neuron death is accompanied by muscle fasciculation and atrophy. Early symptoms of ALS include muscle cramps, muscle spasticity, muscle weakness (for example, affecting an arm, a leg,

neck, or diaphragm), slurred and nasal speech, and difficulty chewing or swallowing. Loss of strength and control over movements, including those necessary for speech, eating, and breathing, eventually occur. Disease progression may be accompanied by weight loss, malnourishment, anxiety, depression, increased risk of pneumonia, muscle cramps, neuropathy, and possibly dementia. Most individuals diagnosed with ALS die of respiratory failure within five years of the first appearance of symptoms. Currently, there is no effective treatment for ALS.

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

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

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

[0008] Thus, there is a pressing need to identify compounds and/or compositions capable of preventing, ameliorating, and treating neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant

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

SUMMARY

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

[0010] In one aspect the present disclosure provides a compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (i.e., one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage. In various embodiments, the oligonucleotide comprises a spacer.

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

[0012] In various embodiments, the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221,

or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.. In various embodiments, the oligonucleotide comprises a sequence that shares 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.. In various embodiments, the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~..

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

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

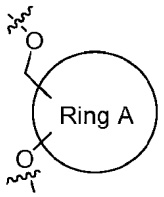
[0015] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 11 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a second spacer, wherein the second spacer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

least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide. In various embodiments, the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide. In various embodiments, the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

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

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

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

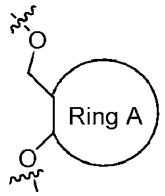


Formula (X)

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

the $-\!\!\lesssim\!\!-$ symbol represents the point of connection to an internucleoside linkage.

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



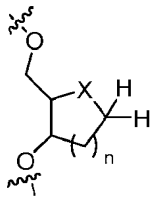
Formula (Xa).

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

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

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

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

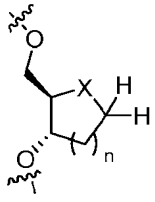


Formula (I)

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

n is 0, 1, 2 or 3.

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

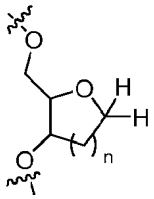


Formula (I')

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

n is 0, 1, 2 or 3.

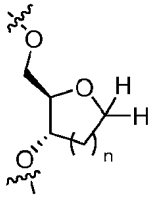
[0025] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

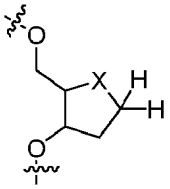
[0026] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

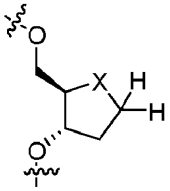
[0027] In certain embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

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

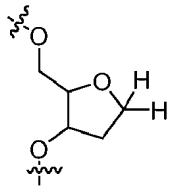
[0028] In further embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

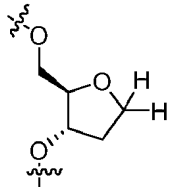
X is selected from -CH_2- and -O-.

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



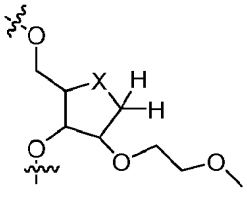
Formula (IIa).

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



Formula (IIa').

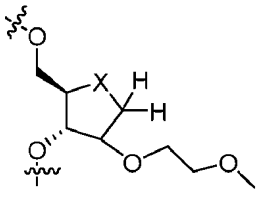
[0031] In some embodiments, the spacer is represented by Formula (III), wherein:



Formula (III)

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

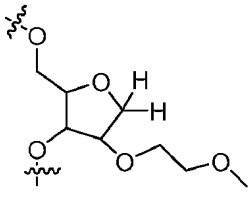
[0032] In some embodiments, the spacer is represented by Formula (III'), wherein:



Formula (III')

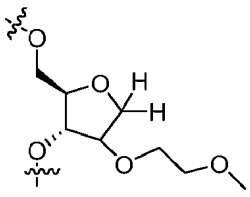
X is selected from $-CH_2-$and -O.

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

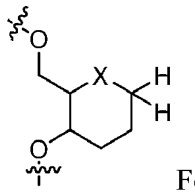


Formula (IIIb).

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

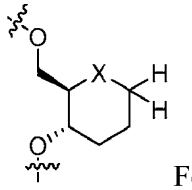

Formula (IIib').

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


Formula (III); and

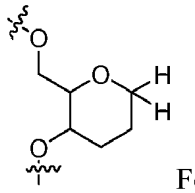
X is selected from -CH_2- and -O-.

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

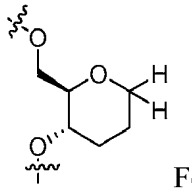

Formula (III'); and

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

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


Formula (IIIa).

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


Formula (IIIa').

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

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

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

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

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

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

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

[0044] Additionally disclosed herein is a compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. Additionally disclosed herein is an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the

sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

[0045] In various embodiments, an internucleoside linkage of the oligonucleotide is a modified internucleoside linkage. In various embodiments, the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. In various embodiments, the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration. In various embodiments, the oligonucleotide comprises at least one modified sugar moiety. In various embodiments, the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid (tcDNA) (e.g., tricyclic nucleic acid with ethyl (2'O-CH_2-CH_2-4'C) as the bridge or tricyclic nucleic acid with methyl substituted methyl (2'O-CH(CH_2)-4'C) bridge), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), tricyclic analog (*e.g.*, tcDNA), and unlocked nucleic acids.

[0046] In various embodiments, the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein. In various embodiments, increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. In various embodiments, the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In various embodiments, the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

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

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

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

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

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

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

[0051] Additionally disclosed herein is a method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition disclosed above. In various embodiments, the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, 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 embodiments, the neurological disease is ALS. In various embodiments, the neurological disease is FTD. In various embodiments, the neurological disease is ALS with FTD. In various embodiments, the neuropathy is chemotherapy induced neuropathy. In various embodiments, the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, intravenously, intramuscularly, transdermally, or intraduodenally. In various embodiments, wherein the pharmaceutical composition is administered intrathecally, intrathalamically intracerebroventricularly, or intracisternally. In various embodiments, a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally. In various embodiments, the patient is human.

[0052] Additionally disclosed herein is a method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[0053] Additionally disclosed herein is a method for treating ALS in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a

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

[0054] Additionally disclosed herein is a method for treating FTD in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[0055] Additionally disclosed herein is a method for treating ALS with FTD in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

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

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

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

[0058] In various embodiments, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In various embodiments, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

[0059] Additionally disclosed herein is an oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a

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

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

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

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

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

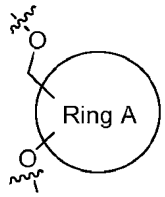
between positions 14 and 22 of the oligonucleotide. In various embodiments, the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide. In various embodiments, the spacer is located between positions 7 and 9 of the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

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

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

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

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



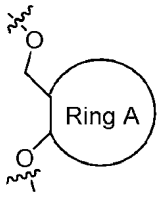
Formula (X)

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

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

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

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



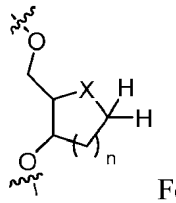
Formula (Xa).

[0069] In some embodiments, ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

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

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

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

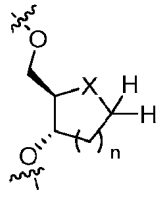


Formula (I)

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

n is 0, 1, 2 or 3.

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

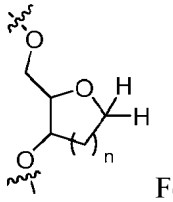


Formula (I')

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

n is 0, 1, 2 or 3.

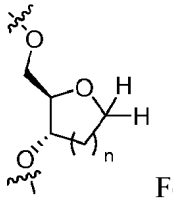
[0074] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

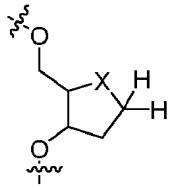
[0075] In various embodiments, each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

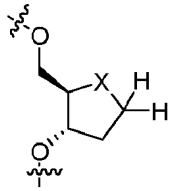
[0076] In certain embodiments, each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

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

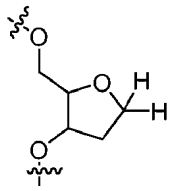
[0077] In further embodiments, each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

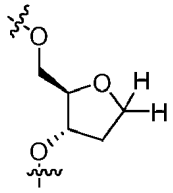
X is selected from -CH_2- and -O-.

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



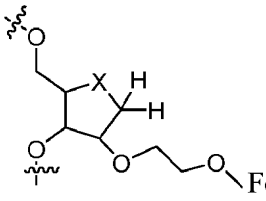
Formula (Iia).

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



Formula (Iia').

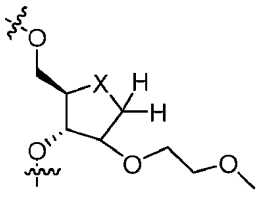
[0080] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

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

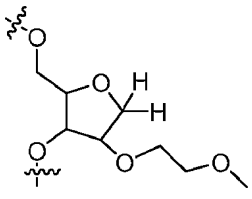
[0081] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

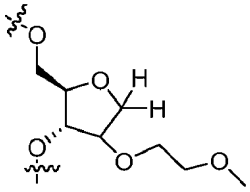
X is selected from -CH_2-and -O.

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



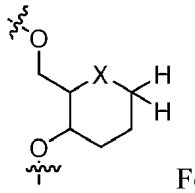
Formula (IIib).

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



Formula (IIib').

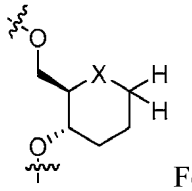
[0084] In various embodiments, each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

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

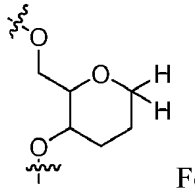
[0085] In further embodiments, each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

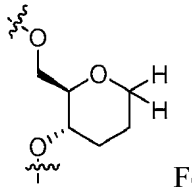
X is selected from -CH_2- and -O-.

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



Formula (IIIa).

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



Formula (IIIa').

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

DETAILED DESCRIPTION

[0090] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

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

Definitions

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

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

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

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

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

[0096] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or non-human primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, non-human primates, and the like). In some embodiments, the mammal treated in

the methods of the invention is desirably a mammal in whom modulation of UNC13A expression and/or activity is desired.

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

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

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

[00100] In various embodiments, UNC13A oligonucleotides are characterized by having one or more spacers, where each spacer divides up the UNC13A oligonucleotide into segments of linked nucleosides. In various embodiments, UNC13A oligonucleotides have two spacers. In one embodiment, UNC13A oligonucleotides have two segments of linked nucleosides separated by one spacer. In one embodiment, UNC13A oligonucleotides have three segments of linked nucleosides separated by two spacers. In such embodiments, UNC13A oligonucleotides have one segment with at most 7 linked nucleosides. For example, a UNC13A oligonucleotide may have, from the 5' to the 3' end, 5 linked nucleosides, followed by a spacer, 10 linked nucleosides, followed by a second spacer, and 8 linked nucleosides. Thus, the first segment of 5 linked nucleosides satisfies the one segment with at most 7 linked nucleosides. In various

embodiments, UNC13A oligonucleotides have three spacers that divide the UNC13A oligonucleotide into four segments. In various embodiments, each of the four segments of the UNC13A oligonucleotide have at most 7 linked nucleosides.

[00101] As used herein, the term "UNC13A oligonucleotide" encompasses a "UNC13A parent oligonucleotide," a "UNC13A oligonucleotide with one or more spacers" (e.g., UNC13A oligonucleotide with two spacers or a UNC13A oligonucleotide with three spacers), a "UNC13A oligonucleotide variant with one or more spacers." Examples of UNC13A oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

[00102] The term "UNC13A parent oligonucleotide" refers to an oligonucleotide that targets a UNC13A transcript and is capable of increasing, restoring, or stabilizing full-length UNC13A activity e.g., full length UNC13A expression, for example, full length UNC13A mRNA and/or full length UNC13A protein expression. UNC13A parent oligonucleotides do not include a spacer. Examples of UNC13A parent oligonucleotides include oligonucleotides comprising a sequence of any one of SEQ ID NO: 1-1264. As described hereafter, UNC13A oligonucleotide with spacers and UNC13A oligonucleotide variants are described in relation to a corresponding UNC13A parent oligonucleotide.

[00103] The term "UNC13A oligonucleotide variant" refers to a UNC13A oligonucleotide that represents a modified version of a corresponding UNC13A parent oligonucleotide. For example, a UNC13A oligonucleotide variant represents a shortened version of a UNC13A parent oligonucleotide. In various embodiments, a UNC13A oligonucleotide variant is any one of a 15mer, 16mer, 17mer, 18mer 19mer, 20mer, 21mer, 22mer 23mer, 24mer, 25mer, 26mer, or 27mer. Examples of UNC13A oligonucleotide variants include oligonucleotides comprising a sequence of any one of SEQ ID NO: 2529-3792. In various embodiments, UNC13A oligonucleotide variants comprise one or more spacers. Such UNC13A oligonucleotide variants comprise a sequence of any one of SEQ ID NO: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

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

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

[00105] Generally, UNC13A oligonucleotides comprising one or more spacers are described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A oligonucleotide variant. Example UNC13A oligonucleotides comprising one or more spacers include any of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

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

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

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

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

[00109] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in a UNC13A oligonucleotide used in the present compositions. A UNC13A oligonucleotide included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A UNC13A oligonucleotide included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, and lithium salts. Pharmaceutically acceptable salts of the disclosure include, for example, pharmaceutically acceptable salts of UNC13A oligonucleotides that include a sequence of any of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

[00110] A UNC13A oligonucleotide of the disclosure may contain one or more chiral centers, groups, linkages, and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all

geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S" (or "R*p*" or "S*p*") depending on the configuration of substituents around the stereogenic atom, for example, a stereogenic carbon, phosphorous, or sulfur atom. In some embodiments, one or more linkages of the compound may have a Rp or Sp configuration (*e.g.*, one or more phosphorothioate linkages have either a Rp or Sp configuration). The configuration of each phosphorothioate linkage may be independent of another phosphorothioate linkage (*e.g.*, one phosphorothioate linkage has a Rp configuration and a second phosphorothioate linkage has a Sp configuration). In various embodiments, the UNC13A oligonucleotide can have a mixed configuration of phosphorothioate linkages. For example, the UNC13A oligonucleotide may have five phosphorothioate linkages in a R*p* configuration, followed by fifteen phosphorothioate linkages in a S*p* configuration, followed by five phosphorothioate linkages in a R*p* configuration. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

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

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

[00113] The disclosure also embraces fluorescently labeled compounds of the invention. The disclosure also embraces isotopically labeled compounds of the invention (*i.e.*, isotopically labeled UNC13A oligonucleotide) which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number abundantly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{33}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

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

[00115] As used herein, "2'-*O*-(2-methoxyethyl)" (also 2'-MOE and 2'-$O(CH_2)_2OCH_3$ and MOE) refers to an *O*-methoxyethyl modification of the 2' position of a furanose ring. A 2'-O-(2-methoxyethyl) is used interchangeably as "2'-*O*-methoxyethyl" in the present disclosure. A sugar moiety in a nucleoside modified with 2'-MOE is a modified sugar.

[00116] As used herein, "2'-MOE nucleoside" (also 2'-*O*-(2-methoxyethyl) nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

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

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

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

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

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

[00122] As used herein, "cEt" or "constrained ethyl" means a bicyclic nucleoside having a sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-CH(CH_3)—*O*-2'.

[00123] As used herein, "constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH(CH_3)—*O*-2' bridge. In some embodiments, cEt can be modified. In some embodiments, the cEt can be *S*-cEt (in an *S*-constrained ethyl 2'-4'-bridged nucleic acid). In some other embodiments, the cEt can be *R*-cEt.

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

[00125] As used herein, "contiguous" in the context of an oligonucleotide refers to nucleosides, nucleobases, sugar moieties, or internucleoside linkages that are immediately adjacent to each other. For example, "contiguous nucleobases" means nucleobases that are immediately adjacent to each other in a sequence. As an example to the contrary, two nucleosides separated by a spacer are not contiguous.

[00126] As used herein, "locked nucleic acid" or "LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to (A) α-L-Methyleneoxy (4'-CH_2—O-2') LNA, (B) β-D-Methyleneoxy (4'-CH_2—O-2') LNA, (C) Ethyleneoxy (4'-$(CH_2)_2$—O-2') LNA, (D) Aminooxy (4'-CH_2—O—N(R)-2') LNA and (E) Oxyamino (4'-CH_2—N(R)—O-2') LNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00127] As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from —$[C(R_1)(R_2)]_n$ —, —$C(R_1)$=$C(R_2)$—, —$C(R_1)$=N—, —C(=NR_1)—, —C(=O)—, —C(=S)—, —O—, —$Si(R_1)_2$—, —$S(=O)_x$— and —$N(R_1)$ —; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, a heterocycle radical, a substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O) —H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl

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

[00128] Examples of 4'-2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: —$[C(R_1)(R_2)]_n$ —, — $[C(R_1)(R_2)]_n$—O—, — $C(R_1R_2)$—$N(R_1)$—O— or —$C(R_1R_2)$—O—$N(R_1)$—. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'- CH_2—O—$N(R_1)$-2' and 4'- CH_2—$N(R_1)$—O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

[00129] Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a bridge to form the bicyclic sugar moiety. The bridge can be a methylene (—CH_2—) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2—O-2') LNA is used. Furthermore, in the case of the bicyclic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2—O-2') LNA is used.

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

the nucleoside (A, C, G, or U) at the same corresponding position of the target UNC13A transcript)).

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

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

[00133] As used herein, "modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymine, or uracil. Examples of a modified nucleobase include 5-methyl cytosine, pseudouridine, or 5-methoxyuridine. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[00134] As used herein, a "modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases. Modified nucleosides include abasic nucleosides, which lack a nucleobase. However, modified nucleosides do not include spacers or other groups that are incapable of linking a nucleobase.

[00135] As used herein, "linked nucleosides" are nucleosides that are connected in a contiguous sequence (*i.e.*, no additional nucleosides are presented between those that are linked). In various embodiments, an oligonucleotide may have different segments of linked nucleosides connected through a spacer. Here, the spacer (*i.e.*, nucleoside replacement) is not considered a nucleoside and therefore, divides up the oligonucleotide into two segments of linked nucleosides. The oligonucleotide may have a first segment of Y linked nucleosides (*e.g.*, Y nucleosides that are connected in a contiguous sequence), followed by a spacer, and then a second segment of Z linked nucleosides. Here, the Y and Z linked nucleosides is described in either the 5' to 3' direction or the 3' to 5' direction. In various embodiments, the first segment consists of 7 or fewer linked nucleosides (e.g., Y = 7 or fewer) whereas the second segment comprises 8 or more linked nucleosides (*e.g.*, Z = 8 or more).

[00136] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one (*i.e.*, one or more) modified internucleoside linkage, modified sugar, and/or modified nucleobase.

[00137] As used herein, "modified sugar" or "modified sugar moiety" means a modified furanosyl sugar moiety or a modified sugar moiety having other than a furanosyl moiety that can

link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide.

[00138] As used herein, "monomer" means a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occurring or modified.

[00139] As used herein, "motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

[00140] As used herein, "natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

[00141] As used herein, "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

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

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

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

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

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

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

[00148] As used herein, "nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo, or tricyclo sugar mimetics, *e.g.*, non-furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by a phosphorodiamidate or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

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

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

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

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

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

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

Antisense Therapeutics

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

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

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

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

various embodiments, the oligonucleotide is at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 21 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 26 oligonucleotide units in length. In various embodiments, the oligonucleotide is at least 27 oligonucleotide units in length.

[00159] In certain embodiments, AONs may include chemically modified nucleosides (for example, 2'-O-methylated nucleosides or 2'-O-(2-methoxyethyl) nucleosides) as well as modified internucleoside linkages (for example, phosphorothioate linkages). In certain embodiments, AONs described herein include oligonucleotide sequences that are complementary to RNA sequences, such as UNC13A mRNA sequences. In certain embodiments, AONs described herein can include chemically modified nucleosides and modified internucleoside linkages (for example, phosphorothioate linkages). In particular embodiments, AONs described herein include one or more spacers.

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

[00161] In some embodiments, an antisense oligonucleotide can be, but is not limited to, inhibitors of a gene transcript (for example, shRNAs, siRNAs, PNAs, LNAs, 2'-*O*-methyl (2'OMe) antisense oligonucleotide (AON), 2'-*O*-(2-methoxyethyl) (MOE) AON, or morpholino oligomers (*e.g.*, phosphorodiamidate morpholino (PMO))), or compositions that include such compounds. In some embodiments an oligonucleotide is an antisense oligonucleotide (AON) comprising 2'OMe (*e.g.*, a AON comprising one or more 2'OMe modified sugar), MOE (*e.g.*, a AON comprising one or more MOE modified sugar), peptide nucleic acids (*e.g.*, a AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl

methylene linkage as repeating units in place of a sugar-phosphate backbone), locked nucleic acids (*e.g.*, a AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a AON comprising one or more cET sugar), constrained methoxyethyl (cMOE) (*e.g.*, a AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tricyclo-DNAs (tcDNA) (*e.g.*, a AON comprising one or more tcDNA modified sugar), 2'-O,4'-C-Ethylene-bridged nucleic acid (ENA) (*e.g.*, a AON comprising one or more ENA modified sugar), or hexitol nucleic acids (HNA) (*e.g.*, a AON comprising one or more HNA modified sugar). In some embodiments, a AON comprises one or more internucleoside linkage independently selected from a phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, thiophosphorodiamidate linkage, phosphorodiamidate morpholino (PMO) (morpholino) linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

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

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

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

UNC13A Oligonucleotides Complementary to UNC13A Transcript

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

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

[00166] In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

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

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

[00169] In some embodiments, a UNC13A AON can include a non-duplexed oligonucleotide. In some embodiments, a UNC13A AON can include a duplex of two oligonucleotides where the first oligonucleotide includes a nucleobase sequence that is completely or almost completely complementary to a UNC13A pre-mRNA sequence and the second oligonucleotide includes a nucleobase sequence that is complementary to the nucleobase sequence of the first oligonucleotide.

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

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

Table 1. Example UNC13A AON Sequences.

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
1	GGAGGGGCCGAGCAATGACCCTCAC	1265	GTGAGGGTCATTGCTCGGCCCCTCC
2	GGGAGGGGCCGAGCAATGACCCTCA	1266	TGAGGGTCATTGCTCGGCCCCTCCC
3	TGGGAGGGGCCGAGCAATGACCCTC	1267	GAGGGTCATTGCTCGGCCCCTCCCA
4	ATGGGAGGGGCCGAGCAATGACCCT	1268	AGGGTCATTGCTCGGCCCCTCCCAT
5	CATGGGAGGGGCCGAGCAATGACCC	1269	GGGTCATTGCTCGGCCCCTCCCATG
6	GCATGGGAGGGGCCGAGCAATGACC	1270	GGTCATTGCTCGGCCCCTCCCATGC
7	GGCATGGGAGGGGCCGAGCAATGAC	1271	GTCATTGCTCGGCCCCTCCCATGCC
8	TGGCATGGGAGGGGCCGAGCAATGA	1272	TCATTGCTCGGCCCCTCCCATGCCA
9	GTGGCATGGGAGGGGCCGAGCAATG	1273	CATTGCTCGGCCCCTCCCATGCCAC
10	AGTGGCATGGGAGGGGCCGAGCAAT	1274	ATTGCTCGGCCCCTCCCATGCCACT
11	AAGTGGCATGGGAGGGGCCGAGCAA	1275	TTGCTCGGCCCCTCCCATGCCACTT
12	GAAGTGGCATGGGAGGGGCCGAGCA	1276	TGCTCGGCCCCTCCCATGCCACTTC
13	GGAAGTGGCATGGGAGGGGCCGAGC	1277	GCTCGGCCCCTCCCATGCCACTTCC
14	TGGAAGTGGCATGGGAGGGGCCGAG	1278	CTCGGCCCCTCCCATGCCACTTCCA
15	GTGGAAGTGGCATGGGAGGGGCCGA	1279	TCGGCCCCTCCCATGCCACTTCCAC
16	AGTGGAAGTGGCATGGGAGGGGCCG	1280	CGGCCCCTCCCATGCCACTTCCACT
17	GAGTGGAAGTGGCATGGGAGGGGCC	1281	GGCCCCTCCCATGCCACTTCCACTC
18	TGAGTGGAAGTGGCATGGGAGGGGC	1282	GCCCCTCCCATGCCACTTCCACTCA
19	GTGAGTGGAAGTGGCATGGGAGGGG	1283	CCCCTCCCATGCCACTTCCACTCAC
20	GGTGAGTGGAAGTGGCATGGGAGGG	1284	CCCTCCCATGCCACTTCCACTCACC
21	TGGTGAGTGGAAGTGGCATGGGAGG	1285	CCTCCCATGCCACTTCCACTCACCA
22	ATGGTGAGTGGAAGTGGCATGGGAG	1286	CTCCCATGCCACTTCCACTCACCAT
23	AATGGTGAGTGGAAGTGGCATGGGA	1287	TCCCATGCCACTTCCACTCACCATT
24	GAATGGTGAGTGGAAGTGGCATGGG	1288	CCCATGCCACTTCCACTCACCATTC
25	GGAATGGTGAGTGGAAGTGGCATGG	1289	CCATGCCACTTCCACTCACCATTCC
26	AGGAATGGTGAGTGGAAGTGGCATG	1290	CATGCCACTTCCACTCACCATTCCT
27	CAGGAATGGTGAGTGGAAGTGGCAT	1291	ATGCCACTTCCACTCACCATTCCTG
28	GCAGGAATGGTGAGTGGAAGTGGCA	1292	TGCCACTTCCACTCACCATTCCTGC
29	GGCAGGAATGGTGAGTGGAAGTGGC	1293	GCCACTTCCACTCACCATTCCTGCC
30	AGGCAGGAATGGTGAGTGGAAGTGG	1294	CCACTTCCACTCACCATTCCTGCCT
31	CAGGCAGGAATGGTGAGTGGAAGTG	1295	CACTTCCACTCACCATTCCTGCCTG
32	GCAGGCAGGAATGGTGAGTGGAAGT	1296	ACTTCCACTCACCATTCCTGCCTGC
33	GGCAGGCAGGAATGGTGAGTGGAAG	1297	CTTCCACTCACCATTCCTGCCTGCC
34	GGGCAGGCAGGAATGGTGAGTGGAA	1298	TTCCACTCACCATTCCTGCCTGCCC
35	TGGGCAGGCAGGAATGGTGAGTGGA	1299	TCCACTCACCATTCCTGCCTGCCCA

36	CTGGGCAGGCAGGAATGGTGAGTGG	1300	CCACTCACCATTCCTGCCTGCCCAG
37	GCTGGGCAGGCAGGAATGGTGAGTG	1301	CACTCACCATTCCTGCCTGCCCAGC
38	AGCTGGGCAGGCAGGAATGGTGAGT	1302	ACTCACCATTCCTGCCTGCCCAGCT
39	GAGCTGGGCAGGCAGGAATGGTGAG	1303	CTCACCATTCCTGCCTGCCCAGCTC
40	AGAGCTGGGCAGGCAGGAATGGTGA	1304	TCACCATTCCTGCCTGCCCAGCTCT
41	AAGAGCTGGGCAGGCAGGAATGGTG	1305	CACCATTCCTGCCTGCCCAGCTCTT
42	GAAGAGCTGGGCAGGCAGGAATGGT	1306	ACCATTCCTGCCTGCCCAGCTCTTC
43	GGAAGAGCTGGGCAGGCAGGAATGG	1307	CCATTCCTGCCTGCCCAGCTCTTCC
44	AGGAAGAGCTGGGCAGGCAGGAATG	1308	CATTCCTGCCTGCCCAGCTCTTCCT
45	GAGGAAGAGCTGGGCAGGCAGGAAT	1309	ATTCCTGCCTGCCCAGCTCTTCCTC
46	AGAGGAAGAGCTGGGCAGGCAGGAA	1310	TTCCTGCCTGCCCAGCTCTTCCTCT
47	AAGAGGAAGAGCTGGGCAGGCAGGA	1311	TCCTGCCTGCCCAGCTCTTCCTCTT
48	AAAGAGGAAGAGCTGGGCAGGCAGG	1312	CCTGCCTGCCCAGCTCTTCCTCTTT
49	GAAAGAGGAAGAGCTGGGCAGGCAG	1313	CTGCCTGCCCAGCTCTTCCTCTTTC
50	AGAAAGAGGAAGAGCTGGGCAGGCA	1314	TGCCTGCCCAGCTCTTCCTCTTTCT
51	CAGAAAGAGGAAGAGCTGGGCAGGC	1315	GCCTGCCCAGCTCTTCCTCTTTCTG
52	CCAGAAAGAGGAAGAGCTGGGCAGG	1316	CCTGCCCAGCTCTTCCTCTTTCTGG
53	GCCAGAAAGAGGAAGAGCTGGGCAG	1317	CTGCCCAGCTCTTCCTCTTTCTGGC
54	GGCCAGAAAGAGGAAGAGCTGGGCA	1318	TGCCCAGCTCTTCCTCTTTCTGGCC
55	TGGCCAGAAAGAGGAAGAGCTGGGC	1319	GCCCAGCTCTTCCTCTTTCTGGCCA
56	GTGGCCAGAAAGAGGAAGAGCTGGG	1320	CCCAGCTCTTCCTCTTTCTGGCCAC
57	TGTGGCCAGAAAGAGGAAGAGCTGG	1321	CCAGCTCTTCCTCTTTCTGGCCACA
58	GTGTGGCCAGAAAGAGGAAGAGCTG	1322	CAGCTCTTCCTCTTTCTGGCCACAC
59	GGTGTGGCCAGAAAGAGGAAGAGCT	1323	AGCTCTTCCTCTTTCTGGCCACACC
60	TGGTGTGGCCAGAAAGAGGAAGAGC	1324	GCTCTTCCTCTTTCTGGCCACACCA
61	ATGGTGTGGCCAGAAAGAGGAAGAG	1325	CTCTTCCTCTTTCTGGCCACACCAT
62	GATGGTGTGGCCAGAAAGAGGAAGA	1326	TCTTCCTCTTTCTGGCCACACCATC
63	GGATGGTGTGGCCAGAAAGAGGAAG	1327	CTTCCTCTTTCTGGCCACACCATCC
64	TGGATGGTGTGGCCAGAAAGAGGAA	1328	TTCCTCTTTCTGGCCACACCATCCA
65	GTGGATGGTGTGGCCAGAAAGAGGA	1329	TCCTCTTTCTGGCCACACCATCCAC
66	TGTGGATGGTGTGGCCAGAAAGAGG	1330	CCTCTTTCTGGCCACACCATCCACA
67	GTGTGGATGGTGTGGCCAGAAAGAG	1331	CTCTTTCTGGCCACACCATCCACAC
68	AGTGTGGATGGTGTGGCCAGAAAGA	1332	TCTTTCTGGCCACACCATCCACACT
69	GAGTGTGGATGGTGTGGCCAGAAAG	1333	CTTTCTGGCCACACCATCCACACTC
70	AGAGTGTGGATGGTGTGGCCAGAAA	1334	TTTCTGGCCACACCATCCACACTCT
71	GAGAGTGTGGATGGTGTGGCCAGAA	1335	TTCTGGCCACACCATCCACACTCTC
72	GGAGAGTGTGGATGGTGTGGCCAGA	1336	TCTGGCCACACCATCCACACTCTCC
73	AGGAGAGTGTGGATGGTGTGGCCAG	1337	CTGGCCACACCATCCACACTCTCCT
74	CAGGAGAGTGTGGATGGTGTGGCCA	1338	TGGCCACACCATCCACACTCTCCTG
75	CCAGGAGAGTGTGGATGGTGTGGCC	1339	GGCCACACCATCCACACTCTCCTGG
76	GCCAGGAGAGTGTGGATGGTGTGGC	1340	GCCACACCATCCACACTCTCCTGGC
77	GGCCAGGAGAGTGTGGATGGTGTGG	1341	CCACACCATCCACACTCTCCTGGCC

78	GGGCCAGGAGAGTGTGGATGGTGTG	1342	CACACCATCCACACTCTCCTGGCCC
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81	AGAGGGCCAGGAGAGTGTGGATGGT	1345	ACCATCCACACTCTCCTGGCCCTCT
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84	CTCAGAGGGCCAGGAGAGTGTGGAT	1348	ATCCACACTCTCCTGGCCCTCTGAG
85	TCTCAGAGGGCCAGGAGAGTGTGGA	1349	TCCACACTCTCCTGGCCCTCTGAGA
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87	AGTCTCAGAGGGCCAGGAGAGTGTG	1351	CACACTCTCCTGGCCCTCTGAGACT
88	CAGTCTCAGAGGGCCAGGAGAGTGT	1352	ACACTCTCCTGGCCCTCTGAGACTG
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90	GGCAGTCTCAGAGGGCCAGGAGAGT	1354	ACTCTCCTGGCCCTCTGAGACTGCC
91	GGGCAGTCTCAGAGGGCCAGGAGAG	1355	CTCTCCTGGCCCTCTGAGACTGCCC
92	CGGGCAGTCTCAGAGGGCCAGGAGA	1356	TCTCCTGGCCCTCTGAGACTGCCCG
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95	TGGCGGGCAGTCTCAGAGGGCCAGG	1359	CCTGGCCCTCTGAGACTGCCCGCCA
96	ATGGCGGGCAGTCTCAGAGGGCCAG	1360	CTGGCCCTCTGAGACTGCCCGCCAT
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99	GGCATGGCGGGCAGTCTCAGAGGGC	1363	GCCCTCTGAGACTGCCCGCCATGCC
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108	AAAGGGAATGGCATGGCGGGCAGTC	1372	GACTGCCCGCCATGCCATTCCCTTT
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111	GGTAAAGGGAATGGCATGGCGGGCA	1375	TGCCCGCCATGCCATTCCCTTTACC
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113	CAGGTAAAGGGAATGGCATGGCGGG	1377	CCCGCCATGCCATTCCCTTTACCTG
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117	TTTCCAGGTAAAGGGAATGGCATGG	1381	CCATGCCATTCCCTTTACCTGGAAA
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122	GGAGTTTTCCAGGTAAAGGGAATGG	1386	CCATTCCCTTTACCTGGAAAACTCC
123	AGGAGTTTTCCAGGTAAAGGGAATG	1387	CATTCCCTTTACCTGGAAAACTCCT
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126	GGGAGGAGTTTTCCAGGTAAAGGGA	1390	TCCCTTTACCTGGAAAACTCCTCCC
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323	ACTAGTTCCTGGGGATAAGAGTTCT	1587	AGAACTCTTATCCCCAGGAACTAGT
324	AACTAGTTCCTGGGGATAAGAGTTC	1588	GAACTCTTATCCCCAGGAACTAGTT
325	AAACTAGTTCCTGGGGATAAGAGTT	1589	AACTCTTATCCCCAGGAACTAGTTT
326	CAAACTAGTTCCTGGGGATAAGAGT	1590	ACTCTTATCCCCAGGAACTAGTTTG
327	ACAAACTAGTTCCTGGGGATAAGAG	1591	CTCTTATCCCCAGGAACTAGTTTGT
328	AACAAACTAGTTCCTGGGGATAAGA	1592	TCTTATCCCCAGGAACTAGTTTGTT
329	CAACAAACTAGTTCCTGGGGATAAG	1593	CTTATCCCCAGGAACTAGTTTGTTG

330	TCAACAAACTAGTTCCTGGGGATAA	1594	TTATCCCCAGGAACTAGTTTGTTGA
331	TTCAACAAACTAGTTCCTGGGGATA	1595	TATCCCCAGGAACTAGTTTGTTGAA
332	ATTCAACAAACTAGTTCCTGGGGAT	1596	ATCCCCAGGAACTAGTTTGTTGAAT
333	TATTCAACAAACTAGTTCCTGGGGA	1597	TCCCCAGGAACTAGTTTGTTGAATA
334	TTATTCAACAAACTAGTTCCTGGGG	1598	CCCCAGGAACTAGTTTGTTGAATAA
335	TTTATTCAACAAACTAGTTCCTGGG	1599	CCCAGGAACTAGTTTGTTGAATAAA
336	ATTTATTCAACAAACTAGTTCCTGG	1600	CCAGGAACTAGTTTGTTGAATAAAT
337	CATTTATTCAACAAACTAGTTCCTG	1601	CAGGAACTAGTTTGTTGAATAAATG
338	GCATTTATTCAACAAACTAGTTCCT	1602	AGGAACTAGTTTGTTGAATAAATGC
339	AGCATTTATTCAACAAACTAGTTCC	1603	GGAACTAGTTTGTTGAATAAATGCT
340	CAGCATTTATTCAACAAACTAGTTC	1604	GAACTAGTTTGTTGAATAAATGCTG
341	CCAGCATTTATTCAACAAACTAGTT	1605	AACTAGTTTGTTGAATAAATGCTGG
342	ACCAGCATTTATTCAACAAACTAGT	1606	ACTAGTTTGTTGAATAAATGCTGGT
343	CACCAGCATTTATTCAACAAACTAG	1607	CTAGTTTGTTGAATAAATGCTGGTG
344	TCACCAGCATTTATTCAACAAACTA	1608	TAGTTTGTTGAATAAATGCTGGTGA
345	TTCACCAGCATTTATTCAACAAACT	1609	AGTTTGTTGAATAAATGCTGGTGAA
346	ATTCACCAGCATTTATTCAACAAAC	1610	GTTTGTTGAATAAATGCTGGTGAAT
347	CATTCACCAGCATTTATTCAACAAA	1611	TTTGTTGAATAAATGCTGGTGAATG
348	TCATTCACCAGCATTTATTCAACAA	1612	TTGTTGAATAAATGCTGGTGAATGA
349	TTCATTCACCAGCATTTATTCAACA	1613	TGTTGAATAAATGCTGGTGAATGAA
350	ATTCATTCACCAGCATTTATTCAAC	1614	GTTGAATAAATGCTGGTGAATGAAT
351	CATTCATTCACCAGCATTTATTCAA	1615	TTGAATAAATGCTGGTGAATGAATG
352	TCATTCATTCACCAGCATTTATTCA	1616	TGAATAAATGCTGGTGAATGAATGA
353	TTCATTCATTCACCAGCATTTATTC	1617	GAATAAATGCTGGTGAATGAATGAA
354	ATTCATTCATTCACCAGCATTTATT	1618	AATAAATGCTGGTGAATGAATGAAT
355	CATTCATTCATTCACCAGCATTTAT	1619	ATAAATGCTGGTGAATGAATGAATG
356	TCATTCATTCATTCACCAGCATTTA	1620	TAAATGCTGGTGAATGAATGAATGA
357	ATCATTCATTCATTCACCAGCATTT	1621	AAATGCTGGTGAATGAATGAATGAT
358	AATCATTCATTCATTCACCAGCATT	1622	AATGCTGGTGAATGAATGAATGATT
359	CAATCATTCATTCATTCACCAGCAT	1623	ATGCTGGTGAATGAATGAATGATTG
360	TCAATCATTCATTCATTCACCAGCA	1624	TGCTGGTGAATGAATGAATGATTGA
361	TTCAATCATTCATTCATTCACCAGC	1625	GCTGGTGAATGAATGAATGATTGAA
362	GTTCAATCATTCATTCATTCACCAG	1626	CTGGTGAATGAATGAATGATTGAAC
363	TGTTCAATCATTCATTCATTCACCA	1627	TGGTGAATGAATGAATGATTGAACA
364	CTGTTCAATCATTCATTCATTCACC	1628	GGTGAATGAATGAATGATTGAACAG
365	TCTGTTCAATCATTCATTCATTCAC	1629	GTGAATGAATGAATGATTGAACAGA
366	ATCTGTTCAATCATTCATTCATTCA	1630	TGAATGAATGAATGATTGAACAGAT
367	CATCTGTTCAATCATTCATTCATTC	1631	GAATGAATGAATGATTGAACAGATG
368	TCATCTGTTCAATCATTCATTCATT	1632	AATGAATGAATGATTGAACAGATGA
369	TTCATCTGTTCAATCATTCATTCAT	1633	ATGAATGAATGATTGAACAGATGAA
370	ATTCATCTGTTCAATCATTCATTCA	1634	TGAATGAATGATTGAACAGATGAAT
371	CATTCATCTGTTCAATCATTCATTC	1635	GAATGAATGATTGAACAGATGAATG

372	TCATTCATCTGTTCAATCATTCATT	1636	AATGAATGATTGAACAGATGAATGA
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374	ACTCATTCATCTGTTCAATCATTCA	1638	TGAATGATTGAACAGATGAATGAGT
375	CACTCATTCATCTGTTCAATCATTC	1639	GAATGATTGAACAGATGAATGAGTG
376	TCACTCATTCATCTGTTCAATCATT	1640	AATGATTGAACAGATGAATGAGTGA
377	ATCACTCATTCATCTGTTCAATCAT	1641	ATGATTGAACAGATGAATGAGTGAT
378	CATCACTCATTCATCTGTTCAATCA	1642	TGATTGAACAGATGAATGAGTGATG
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380	CTCATCACTCATTCATCTGTTCAAT	1644	ATTGAACAGATGAATGAGTGATGAG
381	ACTCATCACTCATTCATCTGTTCAA	1645	TTGAACAGATGAATGAGTGATGAGT
382	TACTCATCACTCATTCATCTGTTCA	1646	TGAACAGATGAATGAGTGATGAGTA
383	CTACTCATCACTCATTCATCTGTTC	1647	GAACAGATGAATGAGTGATGAGTAG
384	TCTACTCATCACTCATTCATCTGTT	1648	AACAGATGAATGAGTGATGAGTAGA
385	ATCTACTCATCACTCATTCATCTGT	1649	ACAGATGAATGAGTGATGAGTAGAT
386	TATCTACTCATCACTCATTCATCTG	1650	CAGATGAATGAGTGATGAGTAGATA
387	TTATCTACTCATCACTCATTCATCT	1651	AGATGAATGAGTGATGAGTAGATAA
388	TTTATCTACTCATCACTCATTCATC	1652	GATGAATGAGTGATGAGTAGATAAA
389	TTTTATCTACTCATCACTCATTCAT	1653	ATGAATGAGTGATGAGTAGATAAAA
390	CTTTTATCTACTCATCACTCATTCA	1654	TGAATGAGTGATGAGTAGATAAAAG
391	CCTTTTATCTACTCATCACTCATTC	1655	GAATGAGTGATGAGTAGATAAAAGG
392	TCCTTTTATCTACTCATCACTCATT	1656	AATGAGTGATGAGTAGATAAAAGGA
393	ATCCTTTTATCTACTCATCACTCAT	1657	ATGAGTGATGAGTAGATAAAAGGAT
394	CATCCTTTTATCTACTCATCACTCA	1658	TGAGTGATGAGTAGATAAAAGGATG
395	CCATCCTTTTATCTACTCATCACTC	1659	GAGTGATGAGTAGATAAAAGGATGG
396	TCCATCCTTTTATCTACTCATCACT	1660	AGTGATGAGTAGATAAAAGGATGGA
397	ATCCATCCTTTTATCTACTCATCAC	1661	GTGATGAGTAGATAAAAGGATGGAT
398	CATCCATCCTTTTATCTACTCATCA	1662	TGATGAGTAGATAAAAGGATGGATG
399	CCATCCATCCTTTTATCTACTCATC	1663	GATGAGTAGATAAAAGGATGGATGG
400	TCCATCCATCCTTTTATCTACTCAT	1664	ATGAGTAGATAAAAGGATGGATGGA
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402	TCTCCATCCATCCTTTTATCTACTC	1666	GAGTAGATAAAAGGATGGATGGAGA
403	CTCTCCATCCATCCTTTTATCTACT	1667	AGTAGATAAAAGGATGGATGGAGAG
404	TCTCTCCATCCATCCTTTTATCTAC	1668	GTAGATAAAAGGATGGATGGAGAGA
405	ATCTCTCCATCCATCCTTTTATCTA	1669	TAGATAAAAGGATGGATGGAGAGAT
406	CATCTCTCCATCCATCCTTTTATCT	1670	AGATAAAAGGATGGATGGAGAGATG
407	CCATCTCTCCATCCATCCTTTTATC	1671	GATAAAAGGATGGATGGAGAGATGG
408	CCCATCTCTCCATCCATCCTTTTAT	1672	ATAAAAGGATGGATGGAGAGATGGG
409	ACCCATCTCTCCATCCATCCTTTTA	1673	TAAAAGGATGGATGGAGAGATGGGT
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411	TCACCCATCTCTCCATCCATCCTTT	1675	AAAGGATGGATGGAGAGATGGGTGA
412	CTCACCCATCTCTCCATCCATCCTT	1676	AAGGATGGATGGAGAGATGGGTGAG
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414	TACTCACCCATCTCTCCATCCATCC	1678	GGATGGATGGAGAGATGGGTGAGTA
415	GTACTCACCCATCTCTCCATCCATC	1679	GATGGATGGAGAGATGGGTGAGTAC
416	TGTACTCACCCATCTCTCCATCCAT	1680	ATGGATGGAGAGATGGGTGAGTACA
417	ATGTACTCACCCATCTCTCCATCCA	1681	TGGATGGAGAGATGGGTGAGTACAT
418	CATGTACTCACCCATCTCTCCATCC	1682	GGATGGAGAGATGGGTGAGTACATG
419	CCATGTACTCACCCATCTCTCCATC	1683	GATGGAGAGATGGGTGAGTACATGG
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421	ATCCATGTACTCACCCATCTCTCCA	1685	TGGAGAGATGGGTGAGTACATGGAT
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423	CCATCCATGTACTCACCCATCTCTC	1687	GAGAGATGGGTGAGTACATGGATGG
424	TCCATCCATGTACTCACCCATCTCT	1688	AGAGATGGGTGAGTACATGGATGGA
425	ATCCATCCATGTACTCACCCATCTC	1689	GAGATGGGTGAGTACATGGATGGAT
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441	ACCAACTCATCCATCTATCCATCCA	1705	TGGATGGATAGATGGATGAGTTGGT
442	CACCAACTCATCCATCTATCCATCC	1706	GGATGGATAGATGGATGAGTTGGTG
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445	ACCCACCAACTCATCCATCTATCCA	1709	TGGATAGATGGATGAGTTGGTGGGT
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453	ACGAATCTACCCACCAACTCATCCA	1717	TGGATGAGTTGGTGGGTAGATTCGT
454	CACGAATCTACCCACCAACTCATCC	1718	GGATGAGTTGGTGGGTAGATTCGTG
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583	ATCCATCATTCATCTATACTCATCC	1847	GGATGAGTATAGATGAATGATGGAT
584	CATCCATCATTCATCTATACTCATC	1848	GATGAGTATAGATGAATGATGGATG
585	CCATCCATCATTCATCTATACTCAT	1849	ATGAGTATAGATGAATGATGGATGG
586	TCCATCCATCATTCATCTATACTCA	1850	TGAGTATAGATGAATGATGGATGGA
587	ATCCATCCATCATTCATCTATACTC	1851	GAGTATAGATGAATGATGGATGGAT
588	TATCCATCCATCATTCATCTATACT	1852	AGTATAGATGAATGATGGATGGATA
589	TTATCCATCCATCATTCATCTATAC	1853	GTATAGATGAATGATGGATGGATAA
590	GTTATCCATCCATCATTCATCTATA	1854	TATAGATGAATGATGGATGGATAAC
591	AGTTATCCATCCATCATTCATCTAT	1855	ATAGATGAATGATGGATGGATAACT
592	AAGTTATCCATCCATCATTCATCTA	1856	TAGATGAATGATGGATGGATAACTT
593	CAAGTTATCCATCCATCATTCATCT	1857	AGATGAATGATGGATGGATAACTTG
594	TCAAGTTATCCATCCATCATTCATC	1858	GATGAATGATGGATGGATAACTTGA
595	ATCAAGTTATCCATCCATCATTCAT	1859	ATGAATGATGGATGGATAACTTGAT
596	CATCAAGTTATCCATCCATCATTCA	1860	TGAATGATGGATGGATAACTTGATG
597	TCATCAAGTTATCCATCCATCATTC	1861	GAATGATGGATGGATAACTTGATGA
598	CTCATCAAGTTATCCATCCATCATT	1862	AATGATGGATGGATAACTTGATGAG
599	ACTCATCAAGTTATCCATCCATCAT	1863	ATGATGGATGGATAACTTGATGAGT
600	CACTCATCAAGTTATCCATCCATCA	1864	TGATGGATGGATAACTTGATGAGTG
601	CCACTCATCAAGTTATCCATCCATC	1865	GATGGATGGATAACTTGATGAGTGG
602	TCCACTCATCAAGTTATCCATCCAT	1866	ATGGATGGATAACTTGATGAGTGGA
603	ATCCACTCATCAAGTTATCCATCCA	1867	TGGATGGATAACTTGATGAGTGGAT
604	TATCCACTCATCAAGTTATCCATCC	1868	GGATGGATAACTTGATGAGTGGATA
605	CTATCCACTCATCAAGTTATCCATC	1869	GATGGATAACTTGATGAGTGGATAG
606	TCTATCCACTCATCAAGTTATCCAT	1870	ATGGATAACTTGATGAGTGGATAGA
607	ATCTATCCACTCATCAAGTTATCCA	1871	TGGATAACTTGATGAGTGGATAGAT
608	TATCTATCCACTCATCAAGTTATCC	1872	GGATAACTTGATGAGTGGATAGATA
609	CTATCTATCCACTCATCAAGTTATC	1873	GATAACTTGATGAGTGGATAGATAG
610	TCTATCTATCCACTCATCAAGTTAT	1874	ATAACTTGATGAGTGGATAGATAGA
611	ATCTATCTATCCACTCATCAAGTTA	1875	TAACTTGATGAGTGGATAGATAGAT
612	AATCTATCTATCCACTCATCAAGTT	1876	AACTTGATGAGTGGATAGATAGATT
613	CAATCTATCTATCCACTCATCAAGT	1877	ACTTGATGAGTGGATAGATAGATTG
614	GCAATCTATCTATCCACTCATCAAG	1878	CTTGATGAGTGGATAGATAGATTGC
615	AGCAATCTATCTATCCACTCATCAA	1879	TTGATGAGTGGATAGATAGATTGCT
616	CAGCAATCTATCTATCCACTCATCA	1880	TGATGAGTGGATAGATAGATTGCTG
617	CCAGCAATCTATCTATCCACTCATC	1881	GATGAGTGGATAGATAGATTGCTGG
618	TCCAGCAATCTATCTATCCACTCAT	1882	ATGAGTGGATAGATAGATTGCTGGA
619	ATCCAGCAATCTATCTATCCACTCA	1883	TGAGTGGATAGATAGATTGCTGGAT
620	TATCCAGCAATCTATCTATCCACTC	1884	GAGTGGATAGATAGATTGCTGGATA
621	CTATCCAGCAATCTATCTATCCACT	1885	AGTGGATAGATAGATTGCTGGATAG
622	TCTATCCAGCAATCTATCTATCCAC	1886	GTGGATAGATAGATTGCTGGATAGA
623	ATCTATCCAGCAATCTATCTATCCA	1887	TGGATAGATAGATTGCTGGATAGAT

624	CATCTATCCAGCAATCTATCTATCC	1888	GGATAGATAGATTGCTGGATAGATG
625	TCATCTATCCAGCAATCTATCTATC	1889	GATAGATAGATTGCTGGATAGATGA
626	ATCATCTATCCAGCAATCTATCTAT	1890	ATAGATAGATTGCTGGATAGATGAT
627	AATCATCTATCCAGCAATCTATCTA	1891	TAGATAGATTGCTGGATAGATGATT
628	CAATCATCTATCCAGCAATCTATCT	1892	AGATAGATTGCTGGATAGATGATTG
629	TCAATCATCTATCCAGCAATCTATC	1893	GATAGATTGCTGGATAGATGATTGA
630	GTCAATCATCTATCCAGCAATCTAT	1894	ATAGATTGCTGGATAGATGATTGAC
631	AGTCAATCATCTATCCAGCAATCTA	1895	TAGATTGCTGGATAGATGATTGACT
632	CAGTCAATCATCTATCCAGCAATCT	1896	AGATTGCTGGATAGATGATTGACTG
633	CCAGTCAATCATCTATCCAGCAATC	1897	GATTGCTGGATAGATGATTGACTGG
634	CCCAGTCAATCATCTATCCAGCAAT	1898	ATTGCTGGATAGATGATTGACTGGG
635	ACCCAGTCAATCATCTATCCAGCAA	1899	TTGCTGGATAGATGATTGACTGGGT
636	CACCCAGTCAATCATCTATCCAGCA	1900	TGCTGGATAGATGATTGACTGGGTG
637	CCACCCAGTCAATCATCTATCCAGC	1901	GCTGGATAGATGATTGACTGGGTGG
638	TCCACCCAGTCAATCATCTATCCAG	1902	CTGGATAGATGATTGACTGGGTGGA
639	ATCCACCCAGTCAATCATCTATCCA	1903	TGGATAGATGATTGACTGGGTGGAT
640	TATCCACCCAGTCAATCATCTATCC	1904	GGATAGATGATTGACTGGGTGGATA
641	CTATCCACCCAGTCAATCATCTATC	1905	GATAGATGATTGACTGGGTGGATAG
642	TCTATCCACCCAGTCAATCATCTAT	1906	ATAGATGATTGACTGGGTGGATAGA
643	ATCTATCCACCCAGTCAATCATCTA	1907	TAGATGATTGACTGGGTGGATAGAT
644	CATCTATCCACCCAGTCAATCATCT	1908	AGATGATTGACTGGGTGGATAGATG
645	TCATCTATCCACCCAGTCAATCATC	1909	GATGATTGACTGGGTGGATAGATGA
646	TTCATCTATCCACCCAGTCAATCAT	1910	ATGATTGACTGGGTGGATAGATGAA
647	TTTCATCTATCCACCCAGTCAATCA	1911	TGATTGACTGGGTGGATAGATGAAA
648	ATTTCATCTATCCACCCAGTCAATC	1912	GATTGACTGGGTGGATAGATGAAAT
649	CATTTCATCTATCCACCCAGTCAAT	1913	ATTGACTGGGTGGATAGATGAAATG
650	ACATTTCATCTATCCACCCAGTCAA	1914	TTGACTGGGTGGATAGATGAAATGT
651	AACATTTCATCTATCCACCCAGTCA	1915	TGACTGGGTGGATAGATGAAATGTT
652	CAACATTTCATCTATCCACCCAGTC	1916	GACTGGGTGGATAGATGAAATGTTG
653	CCAACATTTCATCTATCCACCCAGT	1917	ACTGGGTGGATAGATGAAATGTTGG
654	TCCAACATTTCATCTATCCACCCAG	1918	CTGGGTGGATAGATGAAATGTTGGA
655	ATCCAACATTTCATCTATCCACCCA	1919	TGGGTGGATAGATGAAATGTTGGAT
656	CATCCAACATTTCATCTATCCACCC	1920	GGGTGGATAGATGAAATGTTGGATG
657	TCATCCAACATTTCATCTATCCACC	1921	GGTGGATAGATGAAATGTTGGATGA
658	CTCATCCAACATTTCATCTATCCAC	1922	GTGGATAGATGAAATGTTGGATGAG
659	GCTCATCCAACATTTCATCTATCCA	1923	TGGATAGATGAAATGTTGGATGAGC
660	TGCTCATCCAACATTTCATCTATCC	1924	GGATAGATGAAATGTTGGATGAGCA
661	CTGCTCATCCAACATTTCATCTATC	1925	GATAGATGAAATGTTGGATGAGCAG
662	TCTGCTCATCCAACATTTCATCTAT	1926	ATAGATGAAATGTTGGATGAGCAGA
663	ATCTGCTCATCCAACATTTCATCTA	1927	TAGATGAAATGTTGGATGAGCAGAT
664	AATCTGCTCATCCAACATTTCATCT	1928	AGATGAAATGTTGGATGAGCAGATT
665	TAATCTGCTCATCCAACATTTCATC	1929	GATGAAATGTTGGATGAGCAGATTA

666	TTAATCTGCTCATCCAACATTTCAT	1930	ATGAAATGTTGGATGAGCAGATTAA
667	CTTAATCTGCTCATCCAACATTTCA	1931	TGAAATGTTGGATGAGCAGATTAAG
668	ACTTAATCTGCTCATCCAACATTTC	1932	GAAATGTTGGATGAGCAGATTAAGT
669	AACTTAATCTGCTCATCCAACATTT	1933	AAATGTTGGATGAGCAGATTAAGTT
670	CAACTTAATCTGCTCATCCAACATT	1934	AATGTTGGATGAGCAGATTAAGTTG
671	ACAACTTAATCTGCTCATCCAACAT	1935	ATGTTGGATGAGCAGATTAAGTTGT
672	TACAACTTAATCTGCTCATCCAACA	1936	TGTTGGATGAGCAGATTAAGTTGTA
673	ATACAACTTAATCTGCTCATCCAAC	1937	GTTGGATGAGCAGATTAAGTTGTAT
674	AATACAACTTAATCTGCTCATCCAA	1938	TTGGATGAGCAGATTAAGTTGTATT
675	CAATACAACTTAATCTGCTCATCCA	1939	TGGATGAGCAGATTAAGTTGTATTG
676	CCAATACAACTTAATCTGCTCATCC	1940	GGATGAGCAGATTAAGTTGTATTGG
677	TCCAATACAACTTAATCTGCTCATC	1941	GATGAGCAGATTAAGTTGTATTGGA
678	ATCCAATACAACTTAATCTGCTCAT	1942	ATGAGCAGATTAAGTTGTATTGGAT
679	CATCCAATACAACTTAATCTGCTCA	1943	TGAGCAGATTAAGTTGTATTGGATG
680	CCATCCAATACAACTTAATCTGCTC	1944	GAGCAGATTAAGTTGTATTGGATGG
681	CCCATCCAATACAACTTAATCTGCT	1945	AGCAGATTAAGTTGTATTGGATGGG
682	TCCCATCCAATACAACTTAATCTGC	1946	GCAGATTAAGTTGTATTGGATGGGA
683	ATCCCATCCAATACAACTTAATCTG	1947	CAGATTAAGTTGTATTGGATGGGAT
684	CATCCCATCCAATACAACTTAATCT	1948	AGATTAAGTTGTATTGGATGGGATG
685	CCATCCCATCCAATACAACTTAATC	1949	GATTAAGTTGTATTGGATGGGATGG
686	TCCATCCCATCCAATACAACTTAAT	1950	ATTAAGTTGTATTGGATGGGATGGA
687	ATCCATCCCATCCAATACAACTTAA	1951	TTAAGTTGTATTGGATGGGATGGAT
688	CATCCATCCCATCCAATACAACTTA	1952	TAAGTTGTATTGGATGGGATGGATG
689	CCATCCATCCCATCCAATACAACTT	1953	AAGTTGTATTGGATGGGATGGATGG
690	TCCATCCATCCCATCCAATACAACT	1954	AGTTGTATTGGATGGGATGGATGGA
691	TTCCATCCATCCCATCCAATACAAC	1955	GTTGTATTGGATGGGATGGATGGAA
692	CTTCCATCCATCCCATCCAATACAA	1956	TTGTATTGGATGGGATGGATGGAAG
693	ACTTCCATCCATCCCATCCAATACA	1957	TGTATTGGATGGGATGGATGGAAGT
694	CACTTCCATCCATCCCATCCAATAC	1958	GTATTGGATGGGATGGATGGAAGTG
695	ACACTTCCATCCATCCCATCCAATA	1959	TATTGGATGGGATGGATGGAAGTGT
696	CACACTTCCATCCATCCCATCCAAT	1960	ATTGGATGGGATGGATGGAAGTGTG
697	CCACACTTCCATCCATCCCATCCAA	1961	TTGGATGGGATGGATGGAAGTGTGG
698	ACCACACTTCCATCCATCCCATCCA	1962	TGGATGGGATGGATGGAAGTGTGGT
699	AACCACACTTCCATCCATCCCATCC	1963	GGATGGGATGGATGGAAGTGTGGTT
700	CAACCACACTTCCATCCATCCCATC	1964	GATGGGATGGATGGAAGTGTGGTTG
701	TCAACCACACTTCCATCCATCCCAT	1965	ATGGGATGGATGGAAGTGTGGTTGA
702	CTCAACCACACTTCCATCCATCCCA	1966	TGGGATGGATGGAAGTGTGGTTGAG
703	ACTCAACCACACTTCCATCCATCCC	1967	GGGATGGATGGAAGTGTGGTTGAGT
704	AACTCAACCACACTTCCATCCATCC	1968	GGATGGATGGAAGTGTGGTTGAGTT
705	TAACTCAACCACACTTCCATCCATC	1969	GATGGATGGAAGTGTGGTTGAGTTA
706	ATAACTCAACCACACTTCCATCCAT	1970	ATGGATGGAAGTGTGGTTGAGTTAT
707	AATAACTCAACCACACTTCCATCCA	1971	TGGATGGAAGTGTGGTTGAGTTATT

708	TAATAACTCAACCACACTTCCATCC	1972	GGATGGAAGTGTGGTTGAGTTATTA
709	CTAATAACTCAACCACACTTCCATC	1973	GATGGAAGTGTGGTTGAGTTATTAG
710	TCTAATAACTCAACCACACTTCCAT	1974	ATGGAAGTGTGGTTGAGTTATTAGA
711	TTCTAATAACTCAACCACACTTCCA	1975	TGGAAGTGTGGTTGAGTTATTAGAA
712	CTTCTAATAACTCAACCACACTTCC	1976	GGAAGTGTGGTTGAGTTATTAGAAG
713	CCTTCTAATAACTCAACCACACTTC	1977	GAAGTGTGGTTGAGTTATTAGAAGG
714	TCCTTCTAATAACTCAACCACACTT	1978	AAGTGTGGTTGAGTTATTAGAAGGA
715	TTCCTTCTAATAACTCAACCACACT	1979	AGTGTGGTTGAGTTATTAGAAGGAA
716	CTTCCTTCTAATAACTCAACCACAC	1980	GTGTGGTTGAGTTATTAGAAGGAAG
717	TCTTCCTTCTAATAACTCAACCACA	1981	TGTGGTTGAGTTATTAGAAGGAAGA
718	ATCTTCCTTCTAATAACTCAACCAC	1982	GTGGTTGAGTTATTAGAAGGAAGAT
719	AATCTTCCTTCTAATAACTCAACCA	1983	TGGTTGAGTTATTAGAAGGAAGATT
720	CAATCTTCCTTCTAATAACTCAACC	1984	GGTTGAGTTATTAGAAGGAAGATTG
721	TCAATCTTCCTTCTAATAACTCAAC	1985	GTTGAGTTATTAGAAGGAAGATTGA
722	CTCAATCTTCCTTCTAATAACTCAA	1986	TTGAGTTATTAGAAGGAAGATTGAG
723	ACTCAATCTTCCTTCTAATAACTCA	1987	TGAGTTATTAGAAGGAAGATTGAGT
724	TACTCAATCTTCCTTCTAATAACTC	1988	GAGTTATTAGAAGGAAGATTGAGTA
725	CTACTCAATCTTCCTTCTAATAACT	1989	AGTTATTAGAAGGAAGATTGAGTAG
726	TCTACTCAATCTTCCTTCTAATAAC	1990	GTTATTAGAAGGAAGATTGAGTAGA
727	ATCTACTCAATCTTCCTTCTAATAA	1991	TTATTAGAAGGAAGATTGAGTAGAT
728	TATCTACTCAATCTTCCTTCTAATA	1992	TATTAGAAGGAAGATTGAGTAGATA
729	CTATCTACTCAATCTTCCTTCTAAT	1993	ATTAGAAGGAAGATTGAGTAGATAG
730	CCTATCTACTCAATCTTCCTTCTAA	1994	TTAGAAGGAAGATTGAGTAGATAGG
731	ACCTATCTACTCAATCTTCCTTCTA	1995	TAGAAGGAAGATTGAGTAGATAGGT
732	CACCTATCTACTCAATCTTCCTTCT	1996	AGAAGGAAGATTGAGTAGATAGGTG
733	TCACCTATCTACTCAATCTTCCTTC	1997	GAAGGAAGATTGAGTAGATAGGTGA
734	TTCACCTATCTACTCAATCTTCCTT	1998	AAGGAAGATTGAGTAGATAGGTGAA
735	ATTCACCTATCTACTCAATCTTCCT	1999	AGGAAGATTGAGTAGATAGGTGAAT
736	AATTCACCTATCTACTCAATCTTCC	2000	GGAAGATTGAGTAGATAGGTGAATT
737	AAATTCACCTATCTACTCAATCTTC	2001	GAAGATTGAGTAGATAGGTGAATTT
738	CAAATTCACCTATCTACTCAATCTT	2002	AAGATTGAGTAGATAGGTGAATTTG
739	ACAAATTCACCTATCTACTCAATCT	2003	AGATTGAGTAGATAGGTGAATTTGT
740	AACAAATTCACCTATCTACTCAATC	2004	GATTGAGTAGATAGGTGAATTTGTT
741	CAACAAATTCACCTATCTACTCAAT	2005	ATTGAGTAGATAGGTGAATTTGTTG
742	TCAACAAATTCACCTATCTACTCAA	2006	TTGAGTAGATAGGTGAATTTGTTGA
743	ATCAACAAATTCACCTATCTACTCA	2007	TGAGTAGATAGGTGAATTTGTTGAT
744	TATCAACAAATTCACCTATCTACTC	2008	GAGTAGATAGGTGAATTTGTTGATA
745	CTATCAACAAATTCACCTATCTACT	2009	AGTAGATAGGTGAATTTGTTGATAG
746	ACTATCAACAAATTCACCTATCTAC	2010	GTAGATAGGTGAATTTGTTGATAGT
747	GACTATCAACAAATTCACCTATCTA	2011	TAGATAGGTGAATTTGTTGATAGTC
748	TGACTATCAACAAATTCACCTATCT	2012	AGATAGGTGAATTTGTTGATAGTCA
749	CTGACTATCAACAAATTCACCTATC	2013	GATAGGTGAATTTGTTGATAGTCAG

750	TCTGACTATCAACAAATTCACCTAT	2014	ATAGGTGAATTTGTTGATAGTCAGA
751	ATCTGACTATCAACAAATTCACCTA	2015	TAGGTGAATTTGTTGATAGTCAGAT
752	CATCTGACTATCAACAAATTCACCT	2016	AGGTGAATTTGTTGATAGTCAGATG
753	CCATCTGACTATCAACAAATTCACC	2017	GGTGAATTTGTTGATAGTCAGATGG
754	CCCATCTGACTATCAACAAATTCAC	2018	GTGAATTTGTTGATAGTCAGATGGG
755	ACCCATCTGACTATCAACAAATTCA	2019	TGAATTTGTTGATAGTCAGATGGGT
756	TACCCATCTGACTATCAACAAATTC	2020	GAATTTGTTGATAGTCAGATGGGTA
757	CTACCCATCTGACTATCAACAAATT	2021	AATTTGTTGATAGTCAGATGGGTAG
758	TCTACCCATCTGACTATCAACAAAT	2022	ATTTGTTGATAGTCAGATGGGTAGA
759	ATCTACCCATCTGACTATCAACAAA	2023	TTTGTTGATAGTCAGATGGGTAGAT
760	TATCTACCCATCTGACTATCAACAA	2024	TTGTTGATAGTCAGATGGGTAGATA
761	CTATCTACCCATCTGACTATCAACA	2025	TGTTGATAGTCAGATGGGTAGATAG
762	CCTATCTACCCATCTGACTATCAAC	2026	GTTGATAGTCAGATGGGTAGATAGG
763	ACCTATCTACCCATCTGACTATCAA	2027	TTGATAGTCAGATGGGTAGATAGGT
764	TACCTATCTACCCATCTGACTATCA	2028	TGATAGTCAGATGGGTAGATAGGTA
765	CTACCTATCTACCCATCTGACTATC	2029	GATAGTCAGATGGGTAGATAGGTAG
766	TCTACCTATCTACCCATCTGACTAT	2030	ATAGTCAGATGGGTAGATAGGTAGA
767	ATCTACCTATCTACCCATCTGACTA	2031	TAGTCAGATGGGTAGATAGGTAGAT
768	CATCTACCTATCTACCCATCTGACT	2032	AGTCAGATGGGTAGATAGGTAGATG
769	CCATCTACCTATCTACCCATCTGAC	2033	GTCAGATGGGTAGATAGGTAGATGG
770	TCCATCTACCTATCTACCCATCTGA	2034	TCAGATGGGTAGATAGGTAGATGGA
771	ATCCATCTACCTATCTACCCATCTG	2035	CAGATGGGTAGATAGGTAGATGGAT
772	CATCCATCTACCTATCTACCCATCT	2036	AGATGGGTAGATAGGTAGATGGATG
773	CCATCCATCTACCTATCTACCCATC	2037	GATGGGTAGATAGGTAGATGGATGG
774	TCCATCCATCTACCTATCTACCCAT	2038	ATGGGTAGATAGGTAGATGGATGGA
775	ATCCATCCATCTACCTATCTACCCA	2039	TGGGTAGATAGGTAGATGGATGGAT
776	CATCCATCCATCTACCTATCTACCC	2040	GGGTAGATAGGTAGATGGATGGATG
777	CCATCCATCCATCTACCTATCTACC	2041	GGTAGATAGGTAGATGGATGGATGG
778	TCCATCCATCCATCTACCTATCTAC	2042	GTAGATAGGTAGATGGATGGATGGA
779	ATCCATCCATCCATCTACCTATCTA	2043	TAGATAGGTAGATGGATGGATGGAT
780	CATCCATCCATCCATCTACCTATCT	2044	AGATAGGTAGATGGATGGATGGATG
781	CCATCCATCCATCCATCTACCTATC	2045	GATAGGTAGATGGATGGATGGATGG
782	TCCATCCATCCATCCATCTACCTAT	2046	ATAGGTAGATGGATGGATGGATGGA
783	ATCCATCCATCCATCCATCTACCTA	2047	TAGGTAGATGGATGGATGGATGGAT
784	CATCCATCCATCCATCCATCTACCT	2048	AGGTAGATGGATGGATGGATGGATG
785	CCATCCATCCATCCATCCATCTACC	2049	GGTAGATGGATGGATGGATGGATGG
786	TCCATCCATCCATCCATCCATCTAC	2050	GTAGATGGATGGATGGATGGATGGA
787	ATCCATCCATCCATCCATCCATCTA	2051	TAGATGGATGGATGGATGGATGGAT
788	CATCCATCCATCCATCCATCCATCT	2052	AGATGGATGGATGGATGGATGGATG
789	ACATCCATCCATCCATCCATCCATC	2053	GATGGATGGATGGATGGATGGATGT
790	TACATCCATCCATCCATCCATCCAT	2054	ATGGATGGATGGATGGATGGATGTA
791	ATACATCCATCCATCCATCCATCCA	2055	TGGATGGATGGATGGATGGATGTAT

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

834	TCCATTCATCCACCCACCCATTCAT	2098	ATGAATGGGTGGGTGGATGAATGGA
835	TTCCATTCATCCACCCACCCATTCA	2099	TGAATGGGTGGGTGGATGAATGGAA
836	CTTCCATTCATCCACCCACCCATTC	2100	GAATGGGTGGGTGGATGAATGGAAG
837	CCTTCCATTCATCCACCCACCCATT	2101	AATGGGTGGGTGGATGAATGGAAGG
838	TCCTTCCATTCATCCACCCACCCAT	2102	ATGGGTGGGTGGATGAATGGAAGGA
839	ATCCTTCCATTCATCCACCCACCCA	2103	TGGGTGGGTGGATGAATGGAAGGAT
840	CATCCTTCCATTCATCCACCCACCC	2104	GGGTGGGTGGATGAATGGAAGGATG
841	ACATCCTTCCATTCATCCACCCACC	2105	GGTGGGTGGATGAATGGAAGGATGT
842	CACATCCTTCCATTCATCCACCCAC	2106	GTGGGTGGATGAATGGAAGGATGTG
843	ACACATCCTTCCATTCATCCACCCA	2107	TGGGTGGATGAATGGAAGGATGTGT
844	CACACATCCTTCCATTCATCCACCC	2108	GGGTGGATGAATGGAAGGATGTGTG
845	CCACACATCCTTCCATTCATCCACC	2109	GGTGGATGAATGGAAGGATGTGTGG
846	ACCACACATCCTTCCATTCATCCAC	2110	GTGGATGAATGGAAGGATGTGTGGT
847	AACCACACATCCTTCCATTCATCCA	2111	TGGATGAATGGAAGGATGTGTGGTT
848	CAACCACACATCCTTCCATTCATCC	2112	GGATGAATGGAAGGATGTGTGGTTG
849	TCAACCACACATCCTTCCATTCATC	2113	GATGAATGGAAGGATGTGTGGTTGA
850	TTCAACCACACATCCTTCCATTCAT	2114	ATGAATGGAAGGATGTGTGGTTGAA
851	GTTCAACCACACATCCTTCCATTCA	2115	TGAATGGAAGGATGTGTGGTTGAAC
852	AGTTCAACCACACATCCTTCCATTC	2116	GAATGGAAGGATGTGTGGTTGAACT
853	TAGTTCAACCACACATCCTTCCATT	2117	AATGGAAGGATGTGTGGTTGAACTA
854	ATAGTTCAACCACACATCCTTCCAT	2118	ATGGAAGGATGTGTGGTTGAACTAT
855	AATAGTTCAACCACACATCCTTCCA	2119	TGGAAGGATGTGTGGTTGAACTATT
856	CAATAGTTCAACCACACATCCTTCC	2120	GGAAGGATGTGTGGTTGAACTATTG
857	GCAATAGTTCAACCACACATCCTTC	2121	GAAGGATGTGTGGTTGAACTATTGC
858	TGCAATAGTTCAACCACACATCCTT	2122	AAGGATGTGTGGTTGAACTATTGCA
859	TTGCAATAGTTCAACCACACATCCT	2123	AGGATGTGTGGTTGAACTATTGCAA
860	CTTGCAATAGTTCAACCACACATCC	2124	GGATGTGTGGTTGAACTATTGCAAG
861	ACTTGCAATAGTTCAACCACACATC	2125	GATGTGTGGTTGAACTATTGCAAGT
862	TACTTGCAATAGTTCAACCACACAT	2126	ATGTGTGGTTGAACTATTGCAAGTA
863	ATACTTGCAATAGTTCAACCACACA	2127	TGTGTGGTTGAACTATTGCAAGTAT
864	AATACTTGCAATAGTTCAACCACAC	2128	GTGTGGTTGAACTATTGCAAGTATT
865	CAATACTTGCAATAGTTCAACCACA	2129	TGTGGTTGAACTATTGCAAGTATTG
866	TCAATACTTGCAATAGTTCAACCAC	2130	GTGGTTGAACTATTGCAAGTATTGA
867	ATCAATACTTGCAATAGTTCAACCA	2131	TGGTTGAACTATTGCAAGTATTGAT
868	TATCAATACTTGCAATAGTTCAACC	2132	GGTTGAACTATTGCAAGTATTGATA
869	TTATCAATACTTGCAATAGTTCAAC	2133	GTTGAACTATTGCAAGTATTGATAA
870	ATTATCAATACTTGCAATAGTTCAA	2134	TTGAACTATTGCAAGTATTGATAAT
871	AATTATCAATACTTGCAATAGTTCA	2135	TGAACTATTGCAAGTATTGATAATT
872	CAATTATCAATACTTGCAATAGTTC	2136	GAACTATTGCAAGTATTGATAATTG
873	CCAATTATCAATACTTGCAATAGTT	2137	AACTATTGCAAGTATTGATAATTGG
874	CCCAATTATCAATACTTGCAATAGT	2138	ACTATTGCAAGTATTGATAATTGGG
875	ACCCAATTATCAATACTTGCAATAG	2139	CTATTGCAAGTATTGATAATTGGGT

876	AACCCAATTATCAATACTTGCAATA	2140	TATTGCAAGTATTGATAATTGGGTT
877	GAACCCAATTATCAATACTTGCAAT	2141	ATTGCAAGTATTGATAATTGGGTTC
878	TGAACCCAATTATCAATACTTGCAA	2142	TTGCAAGTATTGATAATTGGGTTCA
879	ATGAACCCAATTATCAATACTTGCA	2143	TGCAAGTATTGATAATTGGGTTCAT
880	TATGAACCCAATTATCAATACTTGC	2144	GCAAGTATTGATAATTGGGTTCATA
881	TTATGAACCCAATTATCAATACTTG	2145	CAAGTATTGATAATTGGGTTCATAA
882	ATTATGAACCCAATTATCAATACTT	2146	AAGTATTGATAATTGGGTTCATAAT
883	AATTATGAACCCAATTATCAATACT	2147	AGTATTGATAATTGGGTTCATAATT
884	AAATTATGAACCCAATTATCAATAC	2148	GTATTGATAATTGGGTTCATAATTT
885	GAAATTATGAACCCAATTATCAATA	2149	TATTGATAATTGGGTTCATAATTTC
886	AGAAATTATGAACCCAATTATCAAT	2150	ATTGATAATTGGGTTCATAATTTCT
887	CAGAAATTATGAACCCAATTATCAA	2151	TTGATAATTGGGTTCATAATTTCTG
888	TCAGAAATTATGAACCCAATTATCA	2152	TGATAATTGGGTTCATAATTTCTGA
889	TTCAGAAATTATGAACCCAATTATC	2153	GATAATTGGGTTCATAATTTCTGAA
890	ATTCAGAAATTATGAACCCAATTAT	2154	ATAATTGGGTTCATAATTTCTGAAT
891	TATTCAGAAATTATGAACCCAATTA	2155	TAATTGGGTTCATAATTTCTGAATA
892	ATATTCAGAAATTATGAACCCAATT	2156	AATTGGGTTCATAATTTCTGAATAT
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894	AAATATTCAGAAATTATGAACCCAA	2158	TTGGGTTCATAATTTCTGAATATTT
895	TAAATATTCAGAAATTATGAACCCA	2159	TGGGTTCATAATTTCTGAATATTTA
896	CTAAATATTCAGAAATTATGAACCC	2160	GGGTTCATAATTTCTGAATATTTAG
897	TCTAAATATTCAGAAATTATGAACC	2161	GGTTCATAATTTCTGAATATTTAGA
898	ATCTAAATATTCAGAAATTATGAAC	2162	GTTCATAATTTCTGAATATTTAGAT
899	CATCTAAATATTCAGAAATTATGAA	2163	TTCATAATTTCTGAATATTTAGATG
900	CCATCTAAATATTCAGAAATTATGA	2164	TCATAATTTCTGAATATTTAGATGG
901	TCCATCTAAATATTCAGAAATTATG	2165	CATAATTTCTGAATATTTAGATGGA
902	ATCCATCTAAATATTCAGAAATTAT	2166	ATAATTTCTGAATATTTAGATGGAT
903	CATCCATCTAAATATTCAGAAATTA	2167	TAATTTCTGAATATTTAGATGGATG
904	CCATCCATCTAAATATTCAGAAATT	2168	AATTTCTGAATATTTAGATGGATGG
905	ACCATCCATCTAAATATTCAGAAAT	2169	ATTTCTGAATATTTAGATGGATGGT
906	AACCATCCATCTAAATATTCAGAAA	2170	TTTCTGAATATTTAGATGGATGGTT
907	CAACCATCCATCTAAATATTCAGAA	2171	TTCTGAATATTTAGATGGATGGTTG
908	ACAACCATCCATCTAAATATTCAGA	2172	TCTGAATATTTAGATGGATGGTTGT
909	CACAACCATCCATCTAAATATTCAG	2173	CTGAATATTTAGATGGATGGTTGTG
910	TCACAACCATCCATCTAAATATTCA	2174	TGAATATTTAGATGGATGGTTGTGA
911	CTCACAACCATCCATCTAAATATTC	2175	GAATATTTAGATGGATGGTTGTGAG
912	ACTCACAACCATCCATCTAAATATT	2176	AATATTTAGATGGATGGTTGTGAGT
913	CACTCACAACCATCCATCTAAATAT	2177	ATATTTAGATGGATGGTTGTGAGTG
914	CCACTCACAACCATCCATCTAAATA	2178	TATTTAGATGGATGGTTGTGAGTGG
915	GCCACTCACAACCATCCATCTAAAT	2179	ATTTAGATGGATGGTTGTGAGTGGC
916	AGCCACTCACAACCATCCATCTAAA	2180	TTTAGATGGATGGTTGTGAGTGGCT
917	CAGCCACTCACAACCATCCATCTAA	2181	TTAGATGGATGGTTGTGAGTGGCTG

918	CCAGCCACTCACAACCATCCATCTA	2182	TAGATGGATGGTTGTGAGTGGCTGG
919	ACCAGCCACTCACAACCATCCATCT	2183	AGATGGATGGTTGTGAGTGGCTGGT
920	CACCAGCCACTCACAACCATCCATC	2184	GATGGATGGTTGTGAGTGGCTGGTG
921	CCACCAGCCACTCACAACCATCCAT	2185	ATGGATGGTTGTGAGTGGCTGGTGG
922	TCCACCAGCCACTCACAACCATCCA	2186	TGGATGGTTGTGAGTGGCTGGTGGA
923	GTCCACCAGCCACTCACAACCATCC	2187	GGATGGTTGTGAGTGGCTGGTGGAC
924	TGTCCACCAGCCACTCACAACCATC	2188	GATGGTTGTGAGTGGCTGGTGGACA
925	CTGTCCACCAGCCACTCACAACCAT	2189	ATGGTTGTGAGTGGCTGGTGGACAG
926	TCTGTCCACCAGCCACTCACAACCA	2190	TGGTTGTGAGTGGCTGGTGGACAGA
927	GTCTGTCCACCAGCCACTCACAACC	2191	GGTTGTGAGTGGCTGGTGGACAGAC
928	CGTCTGTCCACCAGCCACTCACAAC	2192	GTTGTGAGTGGCTGGTGGACAGACG
929	TCGTCTGTCCACCAGCCACTCACAA	2193	TTGTGAGTGGCTGGTGGACAGACGA
930	TTCGTCTGTCCACCAGCCACTCACA	2194	TGTGAGTGGCTGGTGGACAGACGAA
931	TTTCGTCTGTCCACCAGCCACTCAC	2195	GTGAGTGGCTGGTGGACAGACGAAA
932	TTTTCGTCTGTCCACCAGCCACTCA	2196	TGAGTGGCTGGTGGACAGACGAAAA
933	TTTTTCGTCTGTCCACCAGCCACTC	2197	GAGTGGCTGGTGGACAGACGAAAAA
934	ATTTTTCGTCTGTCCACCAGCCACT	2198	AGTGGCTGGTGGACAGACGAAAAAT
935	CATTTTTCGTCTGTCCACCAGCCAC	2199	GTGGCTGGTGGACAGACGAAAAATG
936	CCATTTTTCGTCTGTCCACCAGCCA	2200	TGGCTGGTGGACAGACGAAAAATGG
937	TCCATTTTTCGTCTGTCCACCAGCC	2201	GGCTGGTGGACAGACGAAAAATGGA
938	ATCCATTTTTCGTCTGTCCACCAGC	2202	GCTGGTGGACAGACGAAAAATGGAT
939	CATCCATTTTTCGTCTGTCCACCAG	2203	CTGGTGGACAGACGAAAAATGGATG
940	CCATCCATTTTTCGTCTGTCCACCA	2204	TGGTGGACAGACGAAAAATGGATGG
941	ACCATCCATTTTTCGTCTGTCCACC	2205	GGTGGACAGACGAAAAATGGATGGT
942	AACCATCCATTTTTCGTCTGTCCAC	2206	GTGGACAGACGAAAAATGGATGGTT
943	CAACCATCCATTTTTCGTCTGTCCA	2207	TGGACAGACGAAAAATGGATGGTTG
944	CCAACCATCCATTTTTCGTCTGTCC	2208	GGACAGACGAAAAATGGATGGTTGG
945	TCCAACCATCCATTTTTCGTCTGTC	2209	GACAGACGAAAAATGGATGGTTGGA
946	ATCCAACCATCCATTTTTCGTCTGT	2210	ACAGACGAAAAATGGATGGTTGGAT
947	TATCCAACCATCCATTTTTCGTCTG	2211	CAGACGAAAAATGGATGGTTGGATA
948	TTATCCAACCATCCATTTTTCGTCT	2212	AGACGAAAAATGGATGGTTGGATAA
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953	TCAATTTATCCAACCATCCATTTTT	2217	AAAAATGGATGGTTGGATAAATTGA
954	ATCAATTTATCCAACCATCCATTTT	2218	AAAATGGATGGTTGGATAAATTGAT
955	CATCAATTTATCCAACCATCCATTT	2219	AAATGGATGGTTGGATAAATTGATG
956	CCATCAATTTATCCAACCATCCATT	2220	AATGGATGGTTGGATAAATTGATGG
957	CCCATCAATTTATCCAACCATCCAT	2221	ATGGATGGTTGGATAAATTGATGGG
958	ACCCATCAATTTATCCAACCATCCA	2222	TGGATGGTTGGATAAATTGATGGGT
959	CACCCATCAATTTATCCAACCATCC	2223	GGATGGTTGGATAAATTGATGGGTG

960	CCACCCATCAATTTATCCAACCATC	2224	GATGGTTGGATAAATTGATGGGTGG
961	TCCACCCATCAATTTATCCAACCAT	2225	ATGGTTGGATAAATTGATGGGTGGA
962	ATCCACCCATCAATTTATCCAACCA	2226	TGGTTGGATAAATTGATGGGTGGAT
963	CATCCACCCATCAATTTATCCAACC	2227	GGTTGGATAAATTGATGGGTGGATG
964	CCATCCACCCATCAATTTATCCAAC	2228	GTTGGATAAATTGATGGGTGGATGG
965	TCCATCCACCCATCAATTTATCCAA	2229	TTGGATAAATTGATGGGTGGATGGA
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975	CAACCAACCATCCATCCACCCATCA	2239	TGATGGGTGGATGGATGGTTGGTTG
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978	ATACAACCAACCATCCATCCACCCA	2242	TGGGTGGATGGATGGTTGGTTGTAT
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980	TCATACAACCAACCATCCATCCACC	2244	GGTGGATGGATGGTTGGTTGTATGA
981	TTCATACAACCAACCATCCATCCAC	2245	GTGGATGGATGGTTGGTTGTATGAA
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983	CTTTCATACAACCAACCATCCATCC	2247	GGATGGATGGTTGGTTGTATGAAAG
984	TCTTTCATACAACCAACCATCCATC	2248	GATGGATGGTTGGTTGTATGAAAGA
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987	CATTCTTTCATACAACCAACCATCC	2251	GGATGGTTGGTTGTATGAAAGAATG
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999	TACCCAATCATTCATTCTTTCATAC	2263	GTATGAAAGAATGAATGATTGGGTA
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1004	CCACCTACCCAATCATTCATTCTTT	2268	AAAGAATGAATGATTGGGTAGGTGG
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1006	ATCCACCTACCCAATCATTCATTCT	2270	AGAATGAATGATTGGGTAGGTGGAT
1007	AATCCACCTACCCAATCATTCATTC	2271	GAATGAATGATTGGGTAGGTGGATT
1008	TAATCCACCTACCCAATCATTCATT	2272	AATGAATGATTGGGTAGGTGGATTA
1009	TTAATCCACCTACCCAATCATTCAT	2273	ATGAATGATTGGGTAGGTGGATTAA
1010	CTTAATCCACCTACCCAATCATTCA	2274	TGAATGATTGGGTAGGTGGATTAAG
1011	ACTTAATCCACCTACCCAATCATTC	2275	GAATGATTGGGTAGGTGGATTAAGT
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1013	CAACTTAATCCACCTACCCAATCAT	2277	ATGATTGGGTAGGTGGATTAAGTTG
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1105	CCCAAATTTCACCCATCCACTCTTC	2369	GAAGAGTGGATGGGTGAAATTTGGG
1106	CCCCAAATTTCACCCATCCACTCTT	2370	AAGAGTGGATGGGTGAAATTTGGGG
1107	ACCCCAAATTTCACCCATCCACTCT	2371	AGAGTGGATGGGTGAAATTTGGGGT
1108	TACCCCAAATTTCACCCATCCACTC	2372	GAGTGGATGGGTGAAATTTGGGGTA
1109	CTACCCCAAATTTCACCCATCCACT	2373	AGTGGATGGGTGAAATTTGGGGTAG
1110	ACTACCCCAAATTTCACCCATCCAC	2374	GTGGATGGGTGAAATTTGGGGTAGT
1111	AACTACCCCAAATTTCACCCATCCA	2375	TGGATGGGTGAAATTTGGGGTAGTT
1112	TAACTACCCCAAATTTCACCCATCC	2376	GGATGGGTGAAATTTGGGGTAGTTA
1113	CTAACTACCCCAAATTTCACCCATC	2377	GATGGGTGAAATTTGGGGTAGTTAG
1114	TCTAACTACCCCAAATTTCACCCAT	2378	ATGGGTGAAATTTGGGGTAGTTAGA
1115	ATCTAACTACCCCAAATTTCACCCA	2379	TGGGTGAAATTTGGGGTAGTTAGAT
1116	CATCTAACTACCCCAAATTTCACCC	2380	GGGTGAAATTTGGGGTAGTTAGATG
1117	CCATCTAACTACCCCAAATTTCACC	2381	GGTGAAATTTGGGGTAGTTAGATGG
1118	CCCATCTAACTACCCCAAATTTCAC	2382	GTGAAATTTGGGGTAGTTAGATGGG
1119	ACCCATCTAACTACCCCAAATTTCA	2383	TGAAATTTGGGGTAGTTAGATGGGT
1120	CACCCATCTAACTACCCCAAATTTC	2384	GAAATTTGGGGTAGTTAGATGGGTG
1121	CCACCCATCTAACTACCCCAAATTT	2385	AAATTTGGGGTAGTTAGATGGGTGG
1122	CCCACCCATCTAACTACCCCAAATT	2386	AATTTGGGGTAGTTAGATGGGTGGG
1123	ACCCACCCATCTAACTACCCCAAAT	2387	ATTTGGGGTAGTTAGATGGGTGGGT
1124	CACCCACCCATCTAACTACCCCAAA	2388	TTTGGGGTAGTTAGATGGGTGGGTG
1125	ACACCCACCCATCTAACTACCCCAA	2389	TTGGGGTAGTTAGATGGGTGGGTGT
1126	CACACCCACCCATCTAACTACCCCA	2390	TGGGGTAGTTAGATGGGTGGGTGTG
1127	ACACACCCACCCATCTAACTACCCC	2391	GGGGTAGTTAGATGGGTGGGTGTGT

1128	CACACACCCACCCATCTAACTACCC	2392	GGGTAGTTAGATGGGTGGGTGTGTG
1129	CCACACACCCACCCATCTAACTACC	2393	GGTAGTTAGATGGGTGGGTGTGTGG
1130	TCCACACACCCACCCATCTAACTAC	2394	GTAGTTAGATGGGTGGGTGTGTGGA
1131	ATCCACACACCCACCCATCTAACTA	2395	TAGTTAGATGGGTGGGTGTGTGGAT
1132	CATCCACACACCCACCCATCTAACT	2396	AGTTAGATGGGTGGGTGTGTGGATG
1133	CCATCCACACACCCACCCATCTAAC	2397	GTTAGATGGGTGGGTGTGTGGATGG
1134	TCCATCCACACACCCACCCATCTAA	2398	TTAGATGGGTGGGTGTGTGGATGGA
1135	ATCCATCCACACACCCACCCATCTA	2399	TAGATGGGTGGGTGTGTGGATGGAT
1136	TATCCATCCACACACCCACCCATCT	2400	AGATGGGTGGGTGTGTGGATGGATA
1137	TTATCCATCCACACACCCACCCATC	2401	GATGGGTGGGTGTGTGGATGGATAA
1138	TTTATCCATCCACACACCCACCCAT	2402	ATGGGTGGGTGTGTGGATGGATAAA
1139	TTTTATCCATCCACACACCCACCCA	2403	TGGGTGGGTGTGTGGATGGATAAAA
1140	CTTTTATCCATCCACACACCCACCC	2404	GGGTGGGTGTGTGGATGGATAAAAG
1141	TCTTTTATCCATCCACACACCCACC	2405	GGTGGGTGTGTGGATGGATAAAAGA
1142	CTCTTTTATCCATCCACACACCCAC	2406	GTGGGTGTGTGGATGGATAAAAGAG
1143	ACTCTTTTATCCATCCACACACCCA	2407	TGGGTGTGTGGATGGATAAAAGAGT
1144	TACTCTTTTATCCATCCACACACCC	2408	GGGTGTGTGGATGGATAAAAGAGTA
1145	CTACTCTTTTATCCATCCACACACC	2409	GGTGTGTGGATGGATAAAAGAGTAG
1146	TCTACTCTTTTATCCATCCACACAC	2410	GTGTGTGGATGGATAAAAGAGTAGA
1147	ATCTACTCTTTTATCCATCCACACA	2411	TGTGTGGATGGATAAAAGAGTAGAT
1148	CATCTACTCTTTTATCCATCCACAC	2412	GTGTGGATGGATAAAAGAGTAGATG
1149	TCATCTACTCTTTTATCCATCCACA	2413	TGTGGATGGATAAAAGAGTAGATGA
1150	TTCATCTACTCTTTTATCCATCCAC	2414	GTGGATGGATAAAAGAGTAGATGAA
1151	ATTCATCTACTCTTTTATCCATCCA	2415	TGGATGGATAAAAGAGTAGATGAAT
1152	CATTCATCTACTCTTTTATCCATCC	2416	GGATGGATAAAAGAGTAGATGAATG
1153	TCATTCATCTACTCTTTTATCCATC	2417	GATGGATAAAAGAGTAGATGAATGA
1154	TTCATTCATCTACTCTTTTATCCAT	2418	ATGGATAAAAGAGTAGATGAATGAA
1155	ATTCATTCATCTACTCTTTTATCCA	2419	TGGATAAAAGAGTAGATGAATGAAT
1156	AATTCATTCATCTACTCTTTTATCC	2420	GGATAAAAGAGTAGATGAATGAATT
1157	TAATTCATTCATCTACTCTTTTATC	2421	GATAAAAGAGTAGATGAATGAATTA
1158	TTAATTCATTCATCTACTCTTTTAT	2422	ATAAAAGAGTAGATGAATGAATTAA
1159	ATTAATTCATTCATCTACTCTTTTA	2423	TAAAAGAGTAGATGAATGAATTAAT
1160	CATTAATTCATTCATCTACTCTTTT	2424	AAAAGAGTAGATGAATGAATTAATG
1161	TCATTAATTCATTCATCTACTCTTT	2425	AAAGAGTAGATGAATGAATTAATGA
1162	TTCATTAATTCATTCATCTACTCTT	2426	AAGAGTAGATGAATGAATTAATGAA
1163	ATTCATTAATTCATTCATCTACTCT	2427	AGAGTAGATGAATGAATTAATGAAT
1164	TATTCATTAATTCATTCATCTACTC	2428	GAGTAGATGAATGAATTAATGAATA
1165	TTATTCATTAATTCATTCATCTACT	2429	AGTAGATGAATGAATTAATGAATAA
1166	TTTATTCATTAATTCATTCATCTAC	2430	GTAGATGAATGAATTAATGAATAAA
1167	GTTTATTCATTAATTCATTCATCTA	2431	TAGATGAATGAATTAATGAATAAAC
1168	TGTTTATTCATTAATTCATTCATCT	2432	AGATGAATGAATTAATGAATAAACA
1169	CTGTTTATTCATTAATTCATTCATC	2433	GATGAATGAATTAATGAATAAACAG

1170	CCTGTTTATTCATTAATTCATTCAT	2434	ATGAATGAATTAATGAATAAACAGG
1171	GCCTGTTTATTCATTAATTCATTCA	2435	TGAATGAATTAATGAATAAACAGGC
1172	TGCCTGTTTATTCATTAATTCATTC	2436	GAATGAATTAATGAATAAACAGGCA
1173	CTGCCTGTTTATTCATTAATTCATT	2437	AATGAATTAATGAATAAACAGGCAG
1174	TCTGCCTGTTTATTCATTAATTCAT	2438	ATGAATTAATGAATAAACAGGCAGA
1175	ATCTGCCTGTTTATTCATTAATTCA	2439	TGAATTAATGAATAAACAGGCAGAT
1176	CATCTGCCTGTTTATTCATTAATTC	2440	GAATTAATGAATAAACAGGCAGATG
1177	CCATCTGCCTGTTTATTCATTAATT	2441	AATTAATGAATAAACAGGCAGATGG
1178	TCCATCTGCCTGTTTATTCATTAAT	2442	ATTAATGAATAAACAGGCAGATGGA
1179	ATCCATCTGCCTGTTTATTCATTAA	2443	TTAATGAATAAACAGGCAGATGGAT
1180	CATCCATCTGCCTGTTTATTCATTA	2444	TAATGAATAAACAGGCAGATGGATG
1181	TCATCCATCTGCCTGTTTATTCATT	2445	AATGAATAAACAGGCAGATGGATGA
1182	ATCATCCATCTGCCTGTTTATTCAT	2446	ATGAATAAACAGGCAGATGGATGAT
1183	CATCATCCATCTGCCTGTTTATTCA	2447	TGAATAAACAGGCAGATGGATGATG
1184	ACATCATCCATCTGCCTGTTTATTC	2448	GAATAAACAGGCAGATGGATGATGT
1185	TACATCATCCATCTGCCTGTTTATT	2449	AATAAACAGGCAGATGGATGATGTA
1186	TTACATCATCCATCTGCCTGTTTAT	2450	ATAAACAGGCAGATGGATGATGTAA
1187	CTTACATCATCCATCTGCCTGTTTA	2451	TAAACAGGCAGATGGATGATGTAAG
1188	GCTTACATCATCCATCTGCCTGTTT	2452	AAACAGGCAGATGGATGATGTAAGC
1189	AGCTTACATCATCCATCTGCCTGTT	2453	AACAGGCAGATGGATGATGTAAGCT
1190	CAGCTTACATCATCCATCTGCCTGT	2454	ACAGGCAGATGGATGATGTAAGCTG
1191	GCAGCTTACATCATCCATCTGCCTG	2455	CAGGCAGATGGATGATGTAAGCTGC
1192	GGCAGCTTACATCATCCATCTGCCT	2456	AGGCAGATGGATGATGTAAGCTGCC
1193	GGGCAGCTTACATCATCCATCTGCC	2457	GGCAGATGGATGATGTAAGCTGCCC
1194	GGGGCAGCTTACATCATCCATCTGC	2458	GCAGATGGATGATGTAAGCTGCCCC
1195	TGGGGCAGCTTACATCATCCATCTG	2459	CAGATGGATGATGTAAGCTGCCCCA
1196	CTGGGGCAGCTTACATCATCCATCT	2460	AGATGGATGATGTAAGCTGCCCCAG
1197	TCTGGGGCAGCTTACATCATCCATC	2461	GATGGATGATGTAAGCTGCCCCAGA
1198	GTCTGGGGCAGCTTACATCATCCAT	2462	ATGGATGATGTAAGCTGCCCCAGAC
1199	GGTCTGGGGCAGCTTACATCATCCA	2463	TGGATGATGTAAGCTGCCCCAGACC
1200	GGGTCTGGGGCAGCTTACATCATCC	2464	GGATGATGTAAGCTGCCCCAGACCC
1201	AGGGTCTGGGGCAGCTTACATCATC	2465	GATGATGTAAGCTGCCCCAGACCCT
1202	CAGGGTCTGGGGCAGCTTACATCAT	2466	ATGATGTAAGCTGCCCCAGACCCTG
1203	CCAGGGTCTGGGGCAGCTTACATCA	2467	TGATGTAAGCTGCCCCAGACCCTGG
1204	CCCAGGGTCTGGGGCAGCTTACATC	2468	GATGTAAGCTGCCCCAGACCCTGGG
1205	TCCCAGGGTCTGGGGCAGCTTACAT	2469	ATGTAAGCTGCCCCAGACCCTGGGA
1206	GTCCCAGGGTCTGGGGCAGCTTACA	2470	TGTAAGCTGCCCCAGACCCTGGGAC
1207	GGTCCCAGGGTCTGGGGCAGCTTAC	2471	GTAAGCTGCCCCAGACCCTGGGACC
1208	AGGTCCCAGGGTCTGGGGCAGCTTA	2472	TAAGCTGCCCCAGACCCTGGGACCT
1209	GAGGTCCCAGGGTCTGGGGCAGCTT	2473	AAGCTGCCCCAGACCCTGGGACCTC
1210	AGAGGTCCCAGGGTCTGGGGCAGCT	2474	AGCTGCCCCAGACCCTGGGACCTCT
1211	CAGAGGTCCCAGGGTCTGGGGCAGC	2475	GCTGCCCCAGACCCTGGGACCTCTG

1212	TCAGAGGTCCCAGGGTCTGGGGCAG	2476	CTGCCCCAGACCCTGGGACCTCTGA
1213	GTCAGAGGTCCCAGGGTCTGGGGCA	2477	TGCCCCAGACCCTGGGACCTCTGAC
1214	GGTCAGAGGTCCCAGGGTCTGGGGC	2478	GCCCCAGACCCTGGGACCTCTGACC
1215	GGGTCAGAGGTCCCAGGGTCTGGGG	2479	CCCCAGACCCTGGGACCTCTGACCC
1216	GGGGTCAGAGGTCCCAGGGTCTGGG	2480	CCCAGACCCTGGGACCTCTGACCCC
1217	GGGGGTCAGAGGTCCCAGGGTCTGG	2481	CCAGACCCTGGGACCTCTGACCCCC
1218	CGGGGGTCAGAGGTCCCAGGGTCTG	2482	CAGACCCTGGGACCTCTGACCCCCG
1219	CCGGGGGTCAGAGGTCCCAGGGTCT	2483	AGACCCTGGGACCTCTGACCCCCGG
1220	GCCGGGGGTCAGAGGTCCCAGGGTC	2484	GACCCTGGGACCTCTGACCCCCGGC
1221	CGCCGGGGGTCAGAGGTCCCAGGGT	2485	ACCCTGGGACCTCTGACCCCCGGCG
1222	TCGCCGGGGGTCAGAGGTCCCAGGG	2486	CCCTGGGACCTCTGACCCCCGGCGA
1223	GTCGCCGGGGGTCAGAGGTCCCAGG	2487	CCTGGGACCTCTGACCCCCGGCGAC
1224	GGTCGCCGGGGGTCAGAGGTCCCAG	2488	CTGGGACCTCTGACCCCCGGCGACC
1225	GGGTCGCCGGGGGTCAGAGGTCCCA	2489	TGGGACCTCTGACCCCCGGCGACCC
1226	GGGGTCGCCGGGGGTCAGAGGTCCC	2490	GGGACCTCTGACCCCCGGCGACCCC
1227	AGGGGTCGCCGGGGGTCAGAGGTCC	2491	GGACCTCTGACCCCCGGCGACCCCT
1228	AAGGGGTCGCCGGGGGTCAGAGGTC	2492	GACCTCTGACCCCCGGCGACCCCTT
1229	CAAGGGGTCGCCGGGGGTCAGAGGT	2493	ACCTCTGACCCCCGGCGACCCCTTG
1230	GCAAGGGGTCGCCGGGGGTCAGAGG	2494	CCTCTGACCCCCGGCGACCCCTTGC
1231	TGCAAGGGGTCGCCGGGGGTCAGAG	2495	CTCTGACCCCCGGCGACCCCTTGCA
1232	GTGCAAGGGGTCGCCGGGGGTCAGA	2496	TCTGACCCCCGGCGACCCCTTGCAC
1233	AGTGCAAGGGGTCGCCGGGGGTCAG	2497	CTGACCCCCGGCGACCCCTTGCACT
1234	GAGTGCAAGGGGTCGCCGGGGGTCA	2498	TGACCCCCGGCGACCCCTTGCACTC
1235	AGAGTGCAAGGGGTCGCCGGGGGTC	2499	GACCCCCGGCGACCCCTTGCACTCT
1236	GAGAGTGCAAGGGGTCGCCGGGGGT	2500	ACCCCCGGCGACCCCTTGCACTCTC
1237	GGAGAGTGCAAGGGGTCGCCGGGGG	2501	CCCCCGGCGACCCCTTGCACTCTCC
1238	TGGAGAGTGCAAGGGGTCGCCGGGG	2502	CCCCGGCGACCCCTTGCACTCTCCA
1239	ATGGAGAGTGCAAGGGGTCGCCGGG	2503	CCCGGCGACCCCTTGCACTCTCCAT
1240	CATGGAGAGTGCAAGGGGTCGCCGG	2504	CCGGCGACCCCTTGCACTCTCCATG
1241	TCATGGAGAGTGCAAGGGGTCGCCG	2505	CGGCGACCCCTTGCACTCTCCATGA
1242	GTCATGGAGAGTGCAAGGGGTCGCC	2506	GGCGACCCCTTGCACTCTCCATGAC
1243	TGTCATGGAGAGTGCAAGGGGTCGC	2507	GCGACCCCTTGCACTCTCCATGACA
1244	GTGTCATGGAGAGTGCAAGGGGTCG	2508	CGACCCCTTGCACTCTCCATGACAC
1245	AGTGTCATGGAGAGTGCAAGGGGTC	2509	GACCCCTTGCACTCTCCATGACACT
1246	AAGTGTCATGGAGAGTGCAAGGGGT	2510	ACCCCTTGCACTCTCCATGACACTT
1247	AAAGTGTCATGGAGAGTGCAAGGGG	2511	CCCCTTGCACTCTCCATGACACTTT
1248	GAAAGTGTCATGGAGAGTGCAAGGG	2512	CCCTTGCACTCTCCATGACACTTTC
1249	AGAAAGTGTCATGGAGAGTGCAAGG	2513	CCTTGCACTCTCCATGACACTTTCT
1250	GAGAAAGTGTCATGGAGAGTGCAAG	2514	CTTGCACTCTCCATGACACTTTCTC
1251	AGAGAAAGTGTCATGGAGAGTGCAA	2515	TTGCACTCTCCATGACACTTTCTCT
1252	GAGAGAAAGTGTCATGGAGAGTGCA	2516	TGCACTCTCCATGACACTTTCTCTC
1253	GGAGAGAAAGTGTCATGGAGAGTGC	2517	GCACTCTCCATGACACTTTCTCTCC

1254	GGGAGAGAAAGTGTCATGGAGAGTG	2518	CACTCTCCATGACACTTTCTCTCCC
1255	TGGGAGAGAAAGTGTCATGGAGAGT	2519	ACTCTCCATGACACTTTCTCTCCCA
1256	ATGGGAGAGAAAGTGTCATGGAGAG	2520	CTCTCCATGACACTTTCTCTCCCAT
1257	CATGGGAGAGAAAGTGTCATGGAGA	2521	TCTCCATGACACTTTCTCTCCCATG
1258	CCATGGGAGAGAAAGTGTCATGGAG	2522	CTCCATGACACTTTCTCTCCCATGG
1259	ACCATGGGAGAGAAAGTGTCATGGA	2523	TCCATGACACTTTCTCTCCCATGGT
1260	CACCATGGGAGAGAAAGTGTCATGG	2524	CCATGACACTTTCTCTCCCATGGTG
1261	CCACCATGGGAGAGAAAGTGTCATG	2525	CATGACACTTTCTCTCCCATGGTGG
1262	GCCACCATGGGAGAGAAAGTGTCAT	2526	ATGACACTTTCTCTCCCATGGTGGC
1263	TGCCACCATGGGAGAGAAAGTGTCA	2527	TGACACTTTCTCTCCCATGGTGGCA
1264	CTGCCACCATGGGAGAGAAAGTGTC	2528	GACACTTTCTCTCCCATGGTGGCAG

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

UNC13A Transcript

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

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
TGCGAGCTCGGAGACATGTCTCTGCTTTGCGTTGGAGTCAAAAAAGCCAAGTTTGATGGTGCCCAAGAGA
AATTCAACACGTACGTGACCCTGAAAGTGCAGAATGTCAAGAGCACGACCATCGCGGTGCGGGGCAGCCA
GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
AATAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGTGGATCCCACTGAGGACCATCCGCCAGTCCA
ATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCAGGTCATCATGGCAGACAGTGAGATCTGTGG
CACCAAGGACCCCACCTTCCACCGCATCCTCCTGGACACGCGCTTTGAGCTACCCTTAGACATTCCTGAA
GAGGAGGCTCGCTACTGGGCCAAGAAGCTGGAGCAGCTCAATGCTATGCGGGACCAGGATGAATATTCGT
TCCAAGATGAGCAAGACAAGCCTCTGCCTGTCCCCAGCAACCAGTGCTGCAACTGGAATTATTTTGGCTG
GGGTGAGCAGCACAACGATGACCCCGACAGTGCAGTGGATGATCGTGACAGTGACTACCGCAGTGAAACG
AGCAACAGCATCCCGCCGCCCTATTATACTACGTCACAACCCAACGCCTCAGTCCACCAATATTCTGTTC
GCCCACCACCCCTGGGCTCCCGGGAGTCCTACAGTGACTCCATGCACAGTTACGAGGAGTTCTCTGAGCC
ACAAGCCCTCAGCCCCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAGGGAAGCTCTCAG
CTGAGCGAGGACTTCGACCCTGACGAGCACAGCCTGCAGGGCTCCGACATGGAGGATGAGCGGGACCGGG
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GAGGAGGAGGAGGAGGTGCCTGACGATTTGGGCAGCTATGCCCAGCGTGAAGACGTAGCTGTGGCTGAGC
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CACCGAGGCCCCCGACATGGCCAAGGTGGCCCCCAAGCCAGCCACGCCCGACAAGGTGCCTGCAGCTGAG
CAGATCCCTGAGGCTGAGCCACCCAAGGACGAGGAGAGTTTCAGGCCGAGAGAGGATGAGGAAGGCCAGG
AGGGGCAGGACTCCATGTCCAGGGCCAAGGCCAACTGGCTGCGTGCCTTCAACAAGGTGCGGATGCAGCT
GCAGGAGGCCCGGGGAGAAGGAGAGATGTCTAAATCCCTATGGTTCAAAGGCGGCCCAGGGGGCGGTCTC
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CCCTGGTCCAGTCCAGGAAAGCGGGCATCACCTCGGCCTTGGCCTCCAGCACGTTGAACAACGAGGAGCT
GAAAAACCACGTTTACAAGAAGACCCTGCAAGCCTTAATCTACCCCATCTCGTGCACGACGCCACACAAC
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GGCAGGGCATGCGCTGCACCGAGTGCGGTGTCAAGTGCCACGAGAAGTGCCAGGACCTGCTCAACGCCGA
CTGCCTGCAGCGGGCTGCGGAGAAGAGCTCCAAGCACGGGGCGGAGGACCGGACACAGAACATCATCATG
GTGCTCAAGGACCGCATGAAGATCCGGGAGCGCAACAAGCCCGAGATCTTCGAGCTCATCCAGGAGATCT
TCGCGGTGACCAAGACGGCGCACACGCAGCAGATGAAGGCGGTCAAGCAGAGCGTGCTGGACGGCACGTC
CAAGTGGTCCGCCAAGATCAGCATCACCGTGGTCTGCGCCCAGGGCTTGCAGGCAAAGGACAAGACAGGA
TCCAGTGACCCCTATGTCACCGTCCAGGTCGGGAAGACCAAGAAACGGACAAAAACCATCTATGGGAACC
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CTGACAAATCTGCCGTGTCGGGTGCCATCCGGCTCCACATCAGTGTGGAGATCAAAGGCGAGGAGAAGGT
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AATGGGGTCGTGAAGATCCCAGATGCCAAGGGTGACGATGCCTGGAAGGTTTACTACGATGAGACAGCCC
AGGAGATTGTGGACGAGTTTGCCATGCGCTACGGCGTCGAGTCCATCTACCAAGCCATGACCCACTTTGC
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GCCTACTACGCACACACCACCGCCTCCACCAACGTGTCTGCCTCCGACCGCTTCGCCGCCTCCAACTTTG
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GTGTGAAAGCCTGCCTTAATTCTACCTACGAGTACATCTTCAATAACTGCCATGAACTGTACAGCCGGGA
GTACCAGACAGACCCGGCCAAGAAGGGGGAAGTTCTCCCAGAGGAACAGGGGCCCAGCATCAAGAACCTC
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GCCTCAACCAGTTTCCCCAGGAGCTGAATGTGGGTAAAATCAGCGCTGAAGTGATGTGGAATCTGTTTGC
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CTCCACTTCAAGGTGAAATGGCTCTACAATGAGTATGTGACGGAACTTCCCGCCTTCAAGGACCGCGTGC
CTGAGTACCCTGCATGGTTTGAACCCTTCGTCATCCAGTGGCTGGATGAGAATGAGGAGGTGTCCCGGGA
TTTCCTGCACGGTGCCCTGGAGCGAGACAAGAAGGATGGGTTCCAGCAGACCTCAGAGCATGCCCTATTC
TCCTGCTCCGTGGTGGATGTTTTCTCCCAACTCAACCAGAGCTTTGAAATCATCAAGAAACTCGAGTGTC
CCGACCCTCAGATCGTGGGGCACTACATGAGGCGCTTTGCCAAGACCATCAGTAATGTGCTCCTCCAGTA
TGCAGACATCATCTCCAAGGACTTTGCCTCCTACTGCTCCAAGGAGAAGGAGAAAGTGCCCTGCATTCTC
ATGAATAACACTCAACAGCTACGAGTTCAGCTGGAGAAGATGTTCGAAGCCATGGGAGGAAAGGAGCTGG
ATGCTGAAGCCAGTGACATCCTGAAGGAGCTTCAGGTGAAACTCAATAACGTCTTGGATGAGCTCAGCCG
GGTGTTTGCTACCAGCTTCCAGCCGCACATTGAAGAGTGTGTCAAACAGATGGGTGACATCCTTAGCCAG
GTTAAGGGCACAGGCAATGTGCCAGCCAGTGCCTGCAGCAGCGTGGCCCAGGACGCGGACAATGTGTTGC
AGCCCATCATGGACCTGCTGGACAGCAACCTGACCCTCTTTGCCAAAATCTGTGAGAAGACTGTGCTGAA
GCGAGTGCTGAAGGAGCTGTGGAAGCTGGTTATGAACACCATGGAGAAAACCATCGTCCTGCCGCCCCTC
ACTGACCAGACGATGATCGGGAACCTCTTGAGAAAACATGGCAAGGGATTAGAAAAGGGCAGGGTGAAAT
TGCCAAGCCACTCAGACGGAACCCAGATGATCTTCAATGCAGCCAAGGAGCTGGGTCAGCTGTCCAAACT
CAAGGATCACATGGTACGAGAAGAAGCCAAGAGCTTGACCCCAAAGCAGTGCGCGGTTGTTGAGTTGGCC
CTGGACACCATCAAGCAATATTTCCACGCGGGTGGCGTGGGCCTCAAGAAGACCTTCCTGGAGAAGAGCC
CGGACCTGCAATCCTTGCGCTATGCCCTGTCGCTCTACACGCAGGCCACCGACCTGCTAATCAAGACCTT
TGTACAGACGCAATCGGCCCAGGGCTTGGGTGTAGAAGACCCTGTGGGTGAAGTCTCTGTCCATGTTGAG
CTGTTCACTCATCCAGGAACTGGGGAACACAAGGTCACAGTGAAAGTGGTGGCTGCCAATGACCTCAAGT
GGCAGACTTCTGGCATCTTCCGGCCGTTCATCGAGGTCAACATCATTGGGCCCCAGCTCAGCGACAAGAA
ACGCAAGTTTGCGACCAAATCCAAGAACAATAGCTGGGCTCCCAAGTACAATGAGAGCTTCCAGTTCACG
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AGGACCGCACGGTGGGGCTGGCCGTGCTGCAGCTGCGTGAGCTGGCCCAGCGCGGGAGCGCCGCCTGCTG
GCTGCCGCTCGGCCGCCGCATCCACATGGACGACACGGGCCTCACGGTGCTGCGAATCCTCTCGCAGCGC
AGCAACGACGAGGTGGCCAAGGAGTTCGTGAAGCTCAAGTCGGACACGCGCTCCGCCGAGGAGGGCGGTG
CCGCGCCTGCGCCTTAGCGCGGGCGGTCGGCCGAGCGGCACTGCGCCTGCGCGGAGGGCGCTGGGCGGGG
AGGGACGGGGCTTGCGCCTTGGTGGGACCTCCCCAGGGGCGGGGCTCGGGGGGCTCCACGCCAAGGGTGG

GCTGCGCCTACGCCCTTGACTCAGCTTTCCCTTTTGGGGAATTAGGAATGGAGGATGCCCCGCCCTCTCG
GGAGGCCACGCCCAAGGGCGCGACGAAGGAAGGAGCCACATCCCCAACTTGAGGCCACGCCCCCAGCACC
TAGGGGGCATTTTGAGCTGGGATGGGGGAAACCTCGTCCCTATGGAGGAGGCCACATCCCGGGGCTCTGG
TACCGGGAGGCACCACCTCATGTCCCCTGGAAAAGCCATAAGATGGGACCCAGACCCCTGGGACCCCAGA
CCAATTGCCAAGTATGGAAATCTCAGCTCCCTCGAGGGGGGGCCCTGGGCAAGGGGTAGGGCTCTCTGGA
GCGCCCCTCTAGGTGGCCTGGGGACTGGAGGGACCAGGATGCTGGTTGGAGGGCCCCGGAATACCGGAGT
CCCTTTAGATATTTGTGCAAAAAATAAATGGGGGGAGGGGGGAGGATGGGATTTCAAAAGCACATGCGCC
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GATGGCAAAACTGAGGCTTAAAGAGCTGCTTGAGACTTGGCCAAGGTTCCAGGTGCCATACCCTCTGTGC
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CTTCTCCGGCTGCCAAGCAGGACCTTTGCCCTCAGCCCTTTCTCCTGGGATCTCCATGGGGGATGCCATG
AGGGCCTCCCACCACAAAAGAGAATTTGGGATCCCCTGGTCCCAGGTTTCTCCATCCCTTCTTCCTTTTC
CAGAATTTTCCAAATAGGAAAGAACAGAAGGAGACCAGAAACTCTAGGGGGGAGAAAGAGAATGAGAGAA
AGAGAATGAGAGAGAGAGAAACACAAACACAGTGACACAGTGAGAGCTTAGTCTCCAAGAGCCTATTCAT
TGATTCAAACACCCAAGCCACAGGATACCTCAGATGGCCCTCTTGCCAGCTGGAAGCTCTTTCTCCAATG
AGCAAAGTTACAGTGACCTGGCTGGAGTTACCTGGTGCACATAGGACCTTAGGGGAAAGTTCAGCGTGGA
CTACACTTGCTCTGGGATCTGCTTTTCCACATGTGTGTATGGCACGCCTTTTTCTGCTGGATTGGGAAGG
ACAAGATTTTGCTGTGCTAGGGAGAAATGAAAACGGGGTGAGCTGAGTAGCTGGGTTTCTGGAGGATAGA
ACATCAGATGGGGAGGCTTTCCGAGGTGAAGAATGAGAGGGAACCACTTACTAGAGAGAAAAGAGCTCCA
GGCCTGGGGAACAGCACGTGCGAAGGCCAGGAGAGAAGAACTGTTGAAACAACGAGAAGGGTGGCACGGC
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GGCAGGGCCTCGTACGCAGTCCTGAGGAGTTTTACTTTTATTCTAAGACAGTTGGGGAGCTCCAGGAGCT
GTTTTAAGTTGGGGAGAGACTGGATTCCAGCCTGCAAAAGCTGTTTTGTGAAGACTAAAACCAGTGAGGA
GAGGTGGAGGTGCTTTGGGGACACTGAAATGGATTCTTGGAAAGATTCTGAAGGCTGTGTTGAAAAGACA
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GTGCAGTGGTGCATGCCTGTAGTCCCAGCTACTCAGGAGACTGAGGCGGGAGAATTGTTTGAACCCTGGA
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CCTCCCCTCTACCCCACCAAAAAAAAAAAAAAATCCTGCCCTTAGATGAGCTCTAGGGCTGCTGAGTACA
GTTGTCCCAGTTGCACAGTGCCCAAGGGTTTGGCATTGCTAAGAAGGCCACGTGCAAATCCTAGATATTG
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ACCAAAGGTTAAAATGCAAATTCTCATACAGGGTTGGGAAGTTGTAGCCAGGGATAAGCTTATGTGACTG
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CTGTCTCGTGCTCCCTCAGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAACT
CTTAGCATGTGATTGCAGATGTGAAATCAAAACGTTGTTTGTTTTTTGTTTTGTTTTGATTCTACCCCGT
CGGTCCAGTGTCTGCACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAA
ACGAGAAGTGGTCATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAA
ATATTTTATTAACAGCAGACATTAAAAAAAGAAAAACCACACACA

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

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

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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GCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGTCTGGATTTGGGACTGACGGTGGAGGTGTGG
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ACAAGCCCTCAGCCCCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAGGGAAGCTCTCAG
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AGCACGTGCGAAGGCCAGGAGAGAAGAACTGTTGAAACAACGAGAAGGGTGGCACGGCTGGAGCTGAGCC
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CCTCTTGGAGAAAACCCTCCTTCCTTCCCCTCAGGACTTTCCCAGCCACCGTCTCTCCTCCAGTCCAGCC
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CATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAA
CAGCAGACATTAAAAAAAGAAAAACCACACACA

(**SEQ ID NO: 5058** (SOURCE NCBI Reference Sequence NM_001387021.1)).

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

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACC
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(**SEQ ID NO: 5059** (SOURCE NCBI Reference Sequence NM_001387022.1)).

[00175] In various embodiments, an UNC13A mRNA transcript comprises the sequence provided as SEQ ID NO: 5060.

GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCC
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GGAGGGTCCCCTGATCATCCCCAACCACACAGCCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTGC
TCCCTCAGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAACTCTTAGCATGTG
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CTGCACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGG
TCATGAATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTA
ACAGCAGACATTAAAAAAAGAAAAACCACACACA

(SEQ ID NO: 5060 (SOURCE NCBI Reference Sequence NM_001387023.1)).

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

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
CCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGGCCGCCTCCGGCCCACCTGCGAGCTCG
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GAGCACGACCATCGCGGTGCGGGGCAGCCAGCCCAGCTGGGAGCAGGATTTCATGTTCGAGATTAACCGT
CTGGATTTGGGACTGACGGTGGAGGTGTGGAATAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGT
GGATCCCACTGAGGACCATCCGCCAGTCCAATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCA
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TCCGGGGAGCTGAGCCAGGGAAGCTCTCAGCTGAGCGAGGACTTCGACCCTGACGAGCACAGCCTGCAGG
GCTCCGACATGGAGGATGAGCGGGACCGGGACTCCTACCACTCCTGCCACAGCTCGGTCAGCTACCACAA
AGACTCGCCTCGCTGGGACCAGGATGAGGAAGAGCTGGAGGAGGACCTGGAGGACTTCCTGGAGGAGGAG
GAGCTGCCTGAAGATGAGGAGGAGCTGGAGGAGGAGGAGGAGGAGGTGCCTGACGATTTGGGCAGCTATG
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AGGGAAGGAGGACAAGGCCCCAGTGGCACCCACCGAGGCCCCCGACATGGCCAAGGTGGCCCCCAAGCCA
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CTATCCCACTCGTGAGCGACTTGGCCATGTCCCTGGTCCAGTCCAGGAAAGCGGGCATCACCTCGGCCTT
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CGTCCAGCCATAGTGGCTCTCTGGAGACACAGGTCACAGGCGGAGGGTCCCCTGATCATCCCCAACCACA
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AGTCCGGGGAGGCTTCCCCTCCACACAACTCTTAGCATGTGATTGCAGATGTGAAATCAAAACGTTGTTT
GTTTTTTGTTTTGTTTTGATTCTACCCCGTCGGTCCAGTGTCTGCACAGACGCCTTCATTTCTCTGTAAA
TATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGGTCATGAATGCATGGTGTTGAGATGTTTTG
CACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAACAGCAGACATTAAAAAAAGAAAAACCAC
ACACAGCCTTGGA

(SEQ ID NO: 5061 (SOURCE NCBI Reference Sequence XM_011527810.2)).

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

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

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

CTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCGGCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCC
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TAACAGCAGACATTAAAAAAAGAAAAACCACACACAGCCTTGGA

(SEQ ID NO: 5063 (SOURCE NCBI Reference Sequence XM_011527811.2)).

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

CAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCGAGGTGGGTGGATCACTTGAGGTCAGGAGTT
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GCAAAAAATAAATGGGGGGAGGGGGGAGGATGGGATTTCAAAAGCACATGCGCCCTTGGGCGCCCAAACC
CTGGGGGCCGAGGGGACGGCTCTGGTTCCCCACGCTGCCCCTACTTCCCTTTGGGAGTTTGCCTCTCCCT
CTCCCCCAACAAACCCAGTCCTCATATCATAGAGTTCAACACACCCATTTGACAGATGGCAAAACTGAGG
CTTAAAGAGCTGCTTGAGACTTGGCCAAGGTTCCAGGTGCCATACCCTCTGTGCCCCTCCCTTAGGCCTG
TGTGCCCCATGGAAGGGTGGGCTGAGATCGGGATGACCTGACACAGCTCCCTATTGCTGCTAATTCCCCC

TCGGCCTCCTCCAAGGGGTGGGAATTCCAGGCCAAGACCCCTACTTCGCCTTTCCTTCTCCGGCTGCCAA
GCAGGACCTTTGCCCTCAGCCCTTTCTCCTGGGATCTCCATGGGGGATGCCATGAGGGCCTCCCACCACA
AAAGAGAATTTGGGATCCCCTGGTCCCAGGTTTCTCCATCCCTTCTTCCTTTTCCAGAATTTTCCAAATA
GGAAAGAACAGAAGGAGACCAGAAACTCTAGGGGGGAGAAAGAGAATGAGAGAAAGAGAATGAGAGAGAG
AGAAACACAAACACAGTGACACAGTGAGAGCTTAGTCTCCAAGAGCCTATTCATTGATTCAAACACCCAA
GCCACAGGATACCTCAGATGGCCCTCTTGCCAGCTGGAAGCTCTTTCTCCAATGAGCAAAGTTACAGTGA
CCTGGCTGGAGTTACCTGGTGCACATAGGACCTTAGGGGAAAGTTCAGCGTGGACTACACTTGCTCTGGG
ATCTGCTTTTCCACATGTGTGTATGGCACGCCTTTTTCTGCTGGATTGGGAAGGACAAGATTTTGCTGTG
CTAGGGAGAAATGAAAACGGGGTGAGCTGAGTAGCTGGGTTTCTGGAGGATAGAACATCAGATGGGGAGG
CTTTCCGAGGTGAAGAATGAGAGGGAACCACTTACTAGAGAGAAAAGAGCTCCAGGCCTGGGGAACAGCA
CGTGCGAAGGCCAGGAGAGAAGAACTGTTGAAACAACGAGAAGGGTGGCACGGCTGGAGCTGAGCCAGCA
AGGGGGATCGTGAGGAGCCTTGGGGTTGGGGAGATCTGCAGAAGCATCAGACCAGGCAGGGCCTCGTACG
CAGTCCTGAGGAGTTTTACTTTTATTCTAAGACAGTTGGGGAGCTCCAGGAGCTGTTTTAAGTTGGGGAG
AGACTGGATTCCAGCCTGCAAAAGCTGTTTTGTGAAGACTAAAACCAGTGAGGAGAGGTGGAGGTGCTTT
GGGGACACTGAAATGGATTCTTGGAAAGATTCTGAAGGCTGTGTTGAAAAGACACCTATAGCTGTGGGGA
CATGACTATAATCCCAGCATTTGGGGAGACCGAGGCTGGCAGATCACTTAAGGTCAGGAGTTTGAGACCA
GCCTGGCCAACATGGCGAAACCCCATCTCTGCTAAAAATACAAAAATTAGCTGGGTGCAGTGGTGCATGC
CTGTAGTCCCAGCTACTCAGGAGACTGAGGCGGGAGAATTGTTTGAACCCTGGAGGCAGAGGTTGTAGTG
AGTCGTGATCACACAACTGCACTCCAGCCTGGGCAACAGAACAATACTCCATTCCCTCCCCTCTACCCCA
CCAAAAAAAAAAAAAAAATCCTGCCCTTAGATGAGCTCTAGGGCTGCTGAGTACAGTTGTCCCAGTTGCAC
AGTGCCCAAGGGTTTGGCATTGCTAAGAAGGCCACGTGCAAATCCTAGATATTGAGTGTTGTATGTTTGT
GACGTTGGTTTCCCGACATGTGAATGGCCCAAGTGTCTGGAAGAAGTGGCGCCACTTTCTAATTTGCTTG
GAGATGTTGCATGTCCCTTAAATTCAGACAGGTGCAGGTAACTGGAGGTTCTGAACCAAAGGTTAAAATG
CAAATTCTCATACAGGGTTGGGAAGTTGTAGCCAGGGATAAGCTTATGTGACTGTTATATGGACTGAGGA
GCAGATGTGAATTTCGAACCATGACATGGCTGAGGGTAGGGGTCGGGTGGATGGATGATTCAGGGTTGTA
ACCCATAGAGCCCAAAGGGGAAGTGATCTGTGACCTGGGGTGAGGGTGATCTGGAAGATTTTTGGATGGC
TGGAAAGAAATGGGGAAGTCGAGCTGCCTGAGAGAGCCAAGTTATTTCCCAAAAGATTCCTTAGGAGTCT
TTCTGTTCAAGACCTCCGTGTGTGTGTGTGTGTTTAGGGTTCCCCAGCAATGGCCCAGGCATGTGAAG
GAAACAAGCTTCTTCAGGGAATATTTGTTGAATGAGTTTTCCTGACTCCCAGGCTAGAACTGTTTTTGCA
ATTTCCACCCTCTTTTCTTTCCCCCAGAGAACTCCTATTCGTCCTTCAAAACCCATCACGGAAACCCCTC
TTGGAGAAAACCCTCCTTCCTTCCCCTCAGGACTTTCCCAGCCACCGTCTCTCCTCCAGTCCAGCCTGAT
GCCATGGGACTGGGGGTTTCTCTGTCCAGCTCTGTTTCTCCCAGACTGGGGTCTGAGGACTCTCAGGACC
CCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGGTGACAGGGAGTCTACGCCTAGTGGAATTATGTAT
TGGGGCAGGGTCAGTGTGAGAATACACATCCGCATGCATGTCTGTCCATGTCTGTCCGTACCAACCTTCC
CCTTCCACACGGACCTGGGCACATAGGAGGTGTCTGAGCCTGACACATGGGACAGAGAGTGGACATGGCT
GAGACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCTGAAAGCCTTTTGAAATCAGGAAGTTCCTGTA
TTGGCAGAACAAAGCCCAGAGAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAAGTGGACACAGAGCCCG
GCCTTGGATGACACCTCCAGGGTTCTGAACCCTGGACCTCGCTTTATGCAAGGAGCTGGCCCCACATTTC
CATGAATCGGGGAAACAGCACAAGAAGGTTGGCCTGTGGCAGGGCAAGGGTTAAAGGGGTGACATTGAGG
GATGCCTCAGAGTCAAAGTCCCCTGACCAAGAGGAATAGAGTAGAAAACACAGAGACAGAGGGTGAGATC
ACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAGGTGGAAATATACAGAGAAAGAT
AAATGCAGAGACCAAGGCAGGGAGTGTCGGGGGAAGTAAAGAGGGTGTCCTGAAGAAAGAAGGATCTGTT
CACTCTTACCAGTCTGTCCTCGAATGATTTGCATAAAATGAGGAGGTGCCTGTCCACACCCCCAATTCCT
CTCTCAGGCCCCAGAGCCTGAGACCTCACCATGCCCCCATCAGAGATGCAAAAAACTAAACACCCAACTA
GAAATCCTTGGGACCTCTCTCGGCTGGGATCTCAGAGCCTTTCTGTCCCCTACCCCTACCCCATGTGCTG
TCGATTTTGCAGATGGGGACAACCTGGGGCCTCCCGGAACTCTGCCACCCTGGGGAAGTTGGGGGAGGGC
CTTAGTCCCGGATCACAACCCCGTCTGCTCCCCAGAATCCTTTCCTAAGAATCGTTGAGGACCAAAGTTG
TCTTTGCTGACACGTGTTGCTTTTCTCTTTGCCTTTTATTGTTTCAGAGAAAAATCAAGTTGACTGTGTC
AAGTAACACCCCACCCCTTACCCCCGTCCAGCCATAGTGGCTCTCTGGAGACACAGGTCACAGGCGGAGG
GTCCCCTGATCATCCCCAACCACACAGCCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTGCTCCCT
CAGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAACTCTTAGCATGTGATTGC
AGATGTGAAATCAAAACGTTGTTTGTTTTTTGTTTTGTTTTGATTCTACCCCGTCGGTCCAGTGTCTGCA
CAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAACAAATGTTTAACACAAACGAGAAGTGGTCATG
AATGCATGGTGTTGAGATGTTTTGCACTATTCTGACTTTTTGGTCTCTGTAAAAATATTTTATTAACAGC
AGACATTAAAAAAAGAAAAACCACACACAGCCTTGGACACGTGGTTGCCTCCTCCTTGCATTCCTTTATC
AGCAAAAAAACAAAAACAAAAACCTCACGTACGATTAGCACCTACTAGGTAGGCGCAGACTCAGTAGAAC
ACACTGCTTGCCCATGAACGCGGCTCATCCGCAACTGGAGTCATCCCCATTTTACAGAGAAGGAAACTGA
AGTACAGAGAGACAAGATCTTGCTCAGATCACATAGCCAGGAAGAGATGGAGCTGGGACTTGAACTCAGA
ACATTTGCAACCATTGCTTTTTTTTTTTTTTTTTGAGATGAAGTCTCTGTTGCCCAGGCTGGAATGCAGT
GGTGCAATCTCAGCTCACTGCAATCTCCACCTCCCAGATTCAAGCGATTCTCCTGCCTTAGCCTCCTGAG

TAGCTGGGATTACAGGCGCCCGCCACCTTGCCTGGCTAATTTTTGTATTTTTAGTAGAGATAGGATTTCA
CCATGTTGGCCAGGCTGGTCGCGAACCCCTGACCTCAGGTGATCCACTCCCTCGGCCTCCCAAAGTGCTG
GGATTACAGGCGTGAGCCACCGCACCCGGCCATCTGTTGCCCTTAAGGAAGTTAAGATACAAACACTAGG
AATACATGCCCTTAATTCAACCCACACCCCCATGCTTGTTTGGTTTTGTTGGGTTTTTTGGGATCTTCTT
GTTTGTTTGTTTTTGAGACAGGGTCTTGCTCTGTCACCCAGGATGGAGTTCAGTGTCACAATCTCAACTC
ACTGCATCCTCAACCTCCCAGGCTCAGGTGATCCTCCCACCTCAGCCTCCTGAGTAGTGTGCACCACCAC
ACCTGGCTAATTTGTGTATTTTTTGTAGTGATAGGATGTCGCCATGTTGCCCAGACTGCTCTCGAACTCC
TCACTTTGGGCAATCCTCTCTCCTCAGCCCTCCAAAGTGTTGGGATTACAGGCGTGAGCCACTGTGCCTG
GCCATGTCTGTTTTAAATGTAGCAGCTGGGGCCAGGCGCAGTGGCTCACGCCTGTAATCCCAGCACTTTA
GGAGGCCGAGGCGGGTGGATCACGAGGTCAGGAGATCGAGACCATCCTGGCTAACACGGTGAAACCCCGT
CTCTACTAAAAGTACCAAAAATTAGCCGGGCACGGTGGCAGGCACCTGTAGTTCCAGCTACTCGGGAGGC
TGAGGCAGGAGAATGGTGTGAACTGGGGAGGCGGAGCTTGCAGTGAGCCAAGATCACGCCACTGCATTCC
AGCCTGGGTGACGGAGCGAGACTCCATCTCAAAAAAAAAAAAAGAAAAAAAAGTAGCAGCTGGGAATCTC
ATTTCATAAACTCAGATGTGTGAGGAATGAAACTCCATTTTCCAACAGCTGAATTTAATTTCTGTTTTGA
GTCTCCATCCCACGAGGAAGCAGAAATGGAATCTCATTCAGCCCAGTTTCCTCGGTAAATTCCGAAATTC
CCCTCCTTATGTCTGGGGTTATTTCTACATTTGAGCGGACAGGACGGGAGCTGCGGGATCCACCACCAGG
AGTGGGTTCAGTGAGTGCTTTTGGTTGCAAGTAACAGACAGCAGGACTAAAAGTGGGGCCAGAAAGTGGC
TTACACCAGGAGTTATCCAGCACGCAGCAATCCCGCTCCTGGGGGACTTTTCTCCTTTGAGAAACTTGCA
CGTGGGGGTGTGGTATCTTCTCAAAGAATAGCATATAGCTGGGAAAAGGGGACAAACCGCAGCTGTCTGC
ATGATGTCTGCAGAGGCAGCCTGCAGGTCCTTGAGTGCCCCTGCTCATTAGCTGTTTCTGTACCCAAGTG
CATAGGCTACGCACTGTGACTGATGTGGATCTATTTGCCCCTCGCTACAAAAGGGTCTCAAGTCTTGTCC
TTCAGTGTGTGGGACCCATCGTGTTACCAATGGGGCTTGGGGACTGAGGCTCAAGACTGCTTGCTGGGAA
ATGTAACCCCTTTGTTCTGGACAGGTAGAAGGAGAGGAGAATGGTCATCCAGGCCTAATGTAAAGTTTCT
GCAACCC

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

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

UNC13A Transcript with a Cryptic Exon

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

TTCTGCCACCATGGGAGAGAAAGTGTCATGGAGAGTGCAAGGGGTCGCCG
GGGGTCAGAGGTCCCAGGGTCTGGGGCAGCTTACATCATCCATCTGCCTG
TTTATTCATTAATTCATTCATCTACTCTTTTATCCATCCACACACCCACC
CATCTAACTACCCCAAATTTCACCCATCCACTCTTCCAACCTTTCAGTAA
TTCAACCACACATCCATCCATCCATCCATTCATCCATCCCATACATTGAT
CCGCAACTTAATCCACCTACCCAATCATTCATTCTTTCATACAACCAACC
ATCCATCCACCCATCAATTTATCCAACCATCCATTTTTCGTCTGTCCACC
AGCCACTCACAACCATCCATCTAAATATTCAGAAATTATGAACCCAATTA
TCAATACTTGCAATAGTTCAACCACACATCCTTCCATTCATCCACCCACC
CATTCATCCATTTGTCCATCTGCCTATCATCCATCCATCCATCCATCCA
TCTACCTATCTACCCATCTGACTATCAACAAATTCACCTATCTACTCAAT
CTTCCTTCTAATAACTCAACCACACTTCCATCCATCCCATCCAATACAAC
TTAATCTGCTCATCCAACATTTCATCTATCCACCCAGTCAATCATCTATC
CAGCAATCTATCTATCCACTCATCAAGTTATCCATCCATCATTCATCTAT
ACTCATCCATCATCTAACAATTACCCCCAAATTCACCCATCCATACATCT
ATACTTTCAATAGTTCAATCATATATCCATCCATCTGTCCATCCATCCAT
CATCCATCTAGCCACGAATCTACCCACCAACTCATCCATCTATCCATCCA
TGTACTCACCCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTC
ATCTGTTCAATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTT
CCTGGGGATAAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACAT

ACCCAGACACAAACGGCCCAATCCTGAGTGGTTAGGGCTGGAATAGAAGG
AAGAACCTGATGATGAGTAGTGAGAGTCAACCTGGAGGCCAAGGTGGGCT
TCCCAGAGGAGGTGACCCTGAATCTGGACTTTGATGGATAGGGAGGAGTT
TTCCAGGTAAAGGGAATGGCATGGCGGGCAGTCTCAGAGGGCCAGGAGAG
TGTGGATGGTGTGGCCAGAAAGAGGAAGAGCTGGGCAGGCAGGAATGGTG
AGTGGAAGTGGCATGGGAGGGGCCGAGCAATGACCCTCAC
(SEQ ID NO: 5206) where underlined = TDP-43 binding site.

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

CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCATCTGTTCA
ATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTTCCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAGCTGGAAGAGACATACCCAGACA
CAAACGGCCCAATCCTGAGTGGTTAGGG
(SEQ ID NO: 5207).

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

CCATCTCTCCATCCATCCTTTTATCTACTCATCACTCATTCATCTGTTCA
ATCATTCATTCATTCACCAGCATTTATTCAACAAACTAGTTCCTGGGGAT
AAGAGTTCTTTCCAGGAAACCCAGGCAG
(SEQ ID NO: 5208).

UNC13A Oligonucleotides Targeting Regions of the UNC13A Transcript

[00184] In various embodiments, UNC13A AON disclosed herein are complementary to specific regions of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is complementary to a specific region of the UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. In some embodiments, a UNC13A AON comprises a sequence that is at least 85% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 99% complementary to a specific region of the UNC13A transcript. In some embodiments, a UNC13A AON comprises a sequence that is 90 to 95% complementary to a specific region of the UNC13A transcript. In some embodiments, a

UNC13A AON comprises a sequence that is 95 to 99% complementary to a specific region of the UNC13A transcript.

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

UNC13A Oligonucleotide Variants

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

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

parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where two oligonucleotide units were removed from one of the 3' or 5' end of a 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 23mer where one nucleotide base is removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where two oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 21mer where four oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and three oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where three oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 20mer where five oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where three oligonucleotide units are removed from each of the 3' and 5' ends of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and four oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where four oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 19mer where six oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00188] In one embodiment, the corresponding UNC13A AON variant may include a 18mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the

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

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

[00190] In one embodiment, the corresponding UNC13A AON variant may include a 16mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and seven oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 16mer where seven oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may

include a 16mer where nine oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide.

[00191] In one embodiment, the corresponding UNC13A AON variant may include a 15mer where two oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and eight oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where eight oligonucleotide units are removed from the 3' end of the 25mer included in the UNC13A parent oligonucleotide and two oligonucleotide units are removed from the 5' end of the 25mer included in the UNC13A parent oligonucleotide. In one embodiment, the corresponding UNC13A AON variant may include a 15mer where ten oligonucleotide units are removed from either the 3' or 5' end of the 25mer included in the UNC13A parent oligonucleotide. Example sequences of UNC13A AON variants are shown below in Table 2A and Table 2B.

Table 2A. Example UNC13A Oligonucleotide Variant Sequences

SEQ ID NO:	AON Sequence* (5' → 3')	SEQ ID NO:	Target Sequence (5' → 3')
2529	GGAGGGGCCGAGCAATGACCCTC	3793	GAGGGTCATTGCTCGGCCCCTCC
2530	GGGAGGGGCCGAGCAATGACCCT	3794	AGGGTCATTGCTCGGCCCCTCCC
2531	TGGGAGGGGCCGAGCAATGACCC	3795	GGGTCATTGCTCGGCCCCTCCCA
2532	ATGGGAGGGGCCGAGCAATGACC	3796	GGTCATTGCTCGGCCCCTCCCAT
2533	CATGGGAGGGGCCGAGCAATGAC	3797	GTCATTGCTCGGCCCCTCCCATG
2534	GCATGGGAGGGGCCGAGCAATGA	3798	TCATTGCTCGGCCCCTCCCATGC
2535	GGCATGGGAGGGGCCGAGCAATG	3799	CATTGCTCGGCCCCTCCCATGCC
2536	TGGCATGGGAGGGGCCGAGCAAT	3800	ATTGCTCGGCCCCTCCCATGCCA
2537	GTGGCATGGGAGGGGCCGAGCAA	3801	TTGCTCGGCCCCTCCCATGCCAC
2538	AGTGGCATGGGAGGGGCCGAGCA	3802	TGCTCGGCCCCTCCCATGCCACT
2539	AAGTGGCATGGGAGGGGCCGAGC	3803	GCTCGGCCCCTCCCATGCCACTT
2540	GAAGTGGCATGGGAGGGGCCGAG	3804	CTCGGCCCCTCCCATGCCACTTC
2541	GGAAGTGGCATGGGAGGGGCCGA	3805	TCGGCCCCTCCCATGCCACTTCC
2542	TGGAAGTGGCATGGGAGGGGCCG	3806	CGGCCCCTCCCATGCCACTTCCA
2543	GTGGAAGTGGCATGGGAGGGGCC	3807	GGCCCCTCCCATGCCACTTCCAC
2544	AGTGGAAGTGGCATGGGAGGGGC	3808	GCCCCTCCCATGCCACTTCCACT
2545	GAGTGGAAGTGGCATGGGAGGGG	3809	CCCCTCCCATGCCACTTCCACTC
2546	TGAGTGGAAGTGGCATGGGAGGG	3810	CCCTCCCATGCCACTTCCACTCA
2547	GTGAGTGGAAGTGGCATGGGAGG	3811	CCTCCCATGCCACTTCCACTCAC
2548	GGTGAGTGGAAGTGGCATGGGAG	3812	CTCCCATGCCACTTCCACTCACC

2549	TGGTGAGTGGAAGTGGCATGGGA	3813	TCCCATGCCACTTCCACTCACCA
2550	ATGGTGAGTGGAAGTGGCATGGG	3814	CCCATGCCACTTCCACTCACCAT
2551	AATGGTGAGTGGAAGTGGCATGG	3815	CCATGCCACTTCCACTCACCATT
2552	GAATGGTGAGTGGAAGTGGCATG	3816	CATGCCACTTCCACTCACCATTC
2553	GGAATGGTGAGTGGAAGTGGCAT	3817	ATGCCACTTCCACTCACCATTCC
2554	AGGAATGGTGAGTGGAAGTGGCA	3818	TGCCACTTCCACTCACCATTCCT
2555	CAGGAATGGTGAGTGGAAGTGGC	3819	GCCACTTCCACTCACCATTCCTG
2556	GCAGGAATGGTGAGTGGAAGTGG	3820	CCACTTCCACTCACCATTCCTGC
2557	GGCAGGAATGGTGAGTGGAAGTG	3821	CACTTCCACTCACCATTCCTGCC
2558	AGGCAGGAATGGTGAGTGGAAGT	3822	ACTTCCACTCACCATTCCTGCCT
2559	CAGGCAGGAATGGTGAGTGGAAG	3823	CTTCCACTCACCATTCCTGCCTG
2560	GCAGGCAGGAATGGTGAGTGGAA	3824	TTCCACTCACCATTCCTGCCTGC
2561	GGCAGGCAGGAATGGTGAGTGGA	3825	TCCACTCACCATTCCTGCCTGCC
2562	GGGCAGGCAGGAATGGTGAGTGG	3826	CCACTCACCATTCCTGCCTGCCC
2563	TGGGCAGGCAGGAATGGTGAGTG	3827	CACTCACCATTCCTGCCTGCCCA
2564	CTGGGCAGGCAGGAATGGTGAGT	3828	ACTCACCATTCCTGCCTGCCCAG
2565	GCTGGGCAGGCAGGAATGGTGAG	3829	CTCACCATTCCTGCCTGCCCAGC
2566	AGCTGGGCAGGCAGGAATGGTGA	3830	TCACCATTCCTGCCTGCCCAGCT
2567	GAGCTGGGCAGGCAGGAATGGTG	3831	CACCATTCCTGCCTGCCCAGCTC
2568	AGAGCTGGGCAGGCAGGAATGGT	3832	ACCATTCCTGCCTGCCCAGCTCT
2569	AAGAGCTGGGCAGGCAGGAATGG	3833	CCATTCCTGCCTGCCCAGCTCTT
2570	GAAGAGCTGGGCAGGCAGGAATG	3834	CATTCCTGCCTGCCCAGCTCTTC
2571	GGAAGAGCTGGGCAGGCAGGAAT	3835	ATTCCTGCCTGCCCAGCTCTTCC
2572	AGGAAGAGCTGGGCAGGCAGGAA	3836	TTCCTGCCTGCCCAGCTCTTCCT
2573	GAGGAAGAGCTGGGCAGGCAGGA	3837	TCCTGCCTGCCCAGCTCTTCCTC
2574	AGAGGAAGAGCTGGGCAGGCAGG	3838	CCTGCCTGCCCAGCTCTTCCTCT
2575	AAGAGGAAGAGCTGGGCAGGCAG	3839	CTGCCTGCCCAGCTCTTCCTCTT
2576	AAAGAGGAAGAGCTGGGCAGGCA	3840	TGCCTGCCCAGCTCTTCCTCTTT
2577	GAAAGAGGAAGAGCTGGGCAGGC	3841	GCCTGCCCAGCTCTTCCTCTTTC
2578	AGAAAGAGGAAGAGCTGGGCAGG	3842	CCTGCCCAGCTCTTCCTCTTTCT
2579	CAGAAAGAGGAAGAGCTGGGCAG	3843	CTGCCCAGCTCTTCCTCTTTCTG
2580	CCAGAAAGAGGAAGAGCTGGGCA	3844	TGCCCAGCTCTTCCTCTTTCTGG
2581	GCCAGAAAGAGGAAGAGCTGGGC	3845	GCCCAGCTCTTCCTCTTTCTGGC
2582	GGCCAGAAAGAGGAAGAGCTGGG	3846	CCCAGCTCTTCCTCTTTCTGGCC
2583	TGGCCAGAAAGAGGAAGAGCTGG	3847	CCAGCTCTTCCTCTTTCTGGCCA
2584	GTGGCCAGAAAGAGGAAGAGCTG	3848	CAGCTCTTCCTCTTTCTGGCCAC
2585	TGTGGCCAGAAAGAGGAAGAGCT	3849	AGCTCTTCCTCTTTCTGGCCACA
2586	GTGTGGCCAGAAAGAGGAAGAGC	3850	GCTCTTCCTCTTTCTGGCCACAC
2587	GGTGTGGCCAGAAAGAGGAAGAG	3851	CTCTTCCTCTTTCTGGCCACACC
2588	TGGTGTGGCCAGAAAGAGGAAGA	3852	TCTTCCTCTTTCTGGCCACACCA
2589	ATGGTGTGGCCAGAAAGAGGAAG	3853	CTTCCTCTTTCTGGCCACACCAT
2590	GATGGTGTGGCCAGAAAGAGGAA	3854	TTCCTCTTTCTGGCCACACCATC

2591	GGATGGTGTGGCCAGAAAGAGGA	3855	TCCTCTTTCTGGCCACACCATCC
2592	TGGATGGTGTGGCCAGAAAGAGG	3856	CCTCTTTCTGGCCACACCATCCA
2593	GTGGATGGTGTGGCCAGAAAGAG	3857	CTCTTTCTGGCCACACCATCCAC
2594	TGTGGATGGTGTGGCCAGAAAGA	3858	TCTTTCTGGCCACACCATCCACA
2595	GTGTGGATGGTGTGGCCAGAAAG	3859	CTTTCTGGCCACACCATCCACAC
2596	AGTGTGGATGGTGTGGCCAGAAA	3860	TTTCTGGCCACACCATCCACACT
2597	GAGTGTGGATGGTGTGGCCAGAA	3861	TTCTGGCCACACCATCCACACTC
2598	AGAGTGTGGATGGTGTGGCCAGA	3862	TCTGGCCACACCATCCACACTCT
2599	GAGAGTGTGGATGGTGTGGCCAG	3863	CTGGCCACACCATCCACACTCTC
2600	GGAGAGTGTGGATGGTGTGGCCA	3864	TGGCCACACCATCCACACTCTCC
2601	AGGAGAGTGTGGATGGTGTGGCC	3865	GGCCACACCATCCACACTCTCCT
2602	CAGGAGAGTGTGGATGGTGTGGC	3866	GCCACACCATCCACACTCTCCTG
2603	CCAGGAGAGTGTGGATGGTGTGG	3867	CCACACCATCCACACTCTCCTGG
2604	GCCAGGAGAGTGTGGATGGTGTG	3868	CACACCATCCACACTCTCCTGGC
2605	GGCCAGGAGAGTGTGGATGGTGT	3869	ACACCATCCACACTCTCCTGGCC
2606	GGGCCAGGAGAGTGTGGATGGTG	3870	CACCATCCACACTCTCCTGGCCC
2607	AGGGCCAGGAGAGTGTGGATGGT	3871	ACCATCCACACTCTCCTGGCCCT
2608	GAGGGCCAGGAGAGTGTGGATGG	3872	CCATCCACACTCTCCTGGCCCTC
2609	AGAGGGCCAGGAGAGTGTGGATG	3873	CATCCACACTCTCCTGGCCCTCT
2610	CAGAGGGCCAGGAGAGTGTGGAT	3874	ATCCACACTCTCCTGGCCCTCTG
2611	TCAGAGGGCCAGGAGAGTGTGGA	3875	TCCACACTCTCCTGGCCCTCTGA
2612	CTCAGAGGGCCAGGAGAGTGTGG	3876	CCACACTCTCCTGGCCCTCTGAG
2613	TCTCAGAGGGCCAGGAGAGTGTG	3877	CACACTCTCCTGGCCCTCTGAGA
2614	GTCTCAGAGGGCCAGGAGAGTGT	3878	ACACTCTCCTGGCCCTCTGAGAC
2615	AGTCTCAGAGGGCCAGGAGAGTG	3879	CACTCTCCTGGCCCTCTGAGACT
2616	CAGTCTCAGAGGGCCAGGAGAGT	3880	ACTCTCCTGGCCCTCTGAGACTG
2617	GCAGTCTCAGAGGGCCAGGAGAG	3881	CTCTCCTGGCCCTCTGAGACTGC
2618	GGCAGTCTCAGAGGGCCAGGAGA	3882	TCTCCTGGCCCTCTGAGACTGCC
2619	GGGCAGTCTCAGAGGGCCAGGAG	3883	CTCCTGGCCCTCTGAGACTGCCC
2620	CGGGCAGTCTCAGAGGGCCAGGA	3884	TCCTGGCCCTCTGAGACTGCCCG
2621	GCGGGCAGTCTCAGAGGGCCAGG	3885	CCTGGCCCTCTGAGACTGCCCGC
2622	GGCGGGCAGTCTCAGAGGGCCAG	3886	CTGGCCCTCTGAGACTGCCCGCC
2623	TGGCGGGCAGTCTCAGAGGGCCA	3887	TGGCCCTCTGAGACTGCCCGCCA
2624	ATGGCGGGCAGTCTCAGAGGGCC	3888	GGCCCTCTGAGACTGCCCGCCAT
2625	CATGGCGGGCAGTCTCAGAGGGC	3889	GCCCTCTGAGACTGCCCGCCATG
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2627	GGCATGGCGGGCAGTCTCAGAGG	3891	CCTCTGAGACTGCCCGCCATGCC
2628	TGGCATGGCGGGCAGTCTCAGAG	3892	CTCTGAGACTGCCCGCCATGCCA
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2630	AATGGCATGGCGGGCAGTCTCAG	3894	CTGAGACTGCCCGCCATGCCATT
2631	GAATGGCATGGCGGGCAGTCTCA	3895	TGAGACTGCCCGCCATGCCATTC
2632	GGAATGGCATGGCGGGCAGTCTC	3896	GAGACTGCCCGCCATGCCATTCC

2633	GGGAATGGCATGGCGGGCAGTCT	3897	AGACTGCCCGCCATGCCATTCCC
2634	AGGGAATGGCATGGCGGGCAGTC	3898	GACTGCCCGCCATGCCATTCCCT
2635	AAGGGAATGGCATGGCGGGCAGT	3899	ACTGCCCGCCATGCCATTCCCTT
2636	AAAGGGAATGGCATGGCGGGCAG	3900	CTGCCCGCCATGCCATTCCCTTT
2637	TAAAGGGAATGGCATGGCGGGCA	3901	TGCCCGCCATGCCATTCCCTTTA
2638	GTAAAGGGAATGGCATGGCGGGC	3902	GCCCGCCATGCCATTCCCTTTAC
2639	GGTAAAGGGAATGGCATGGCGGG	3903	CCCGCCATGCCATTCCCTTTACC
2640	AGGTAAAGGGAATGGCATGGCGG	3904	CCGCCATGCCATTCCCTTTACCT
2641	CAGGTAAAGGGAATGGCATGGCG	3905	CGCCATGCCATTCCCTTTACCTG
2642	CCAGGTAAAGGGAATGGCATGGC	3906	GCCATGCCATTCCCTTTACCTGG
2643	TCCAGGTAAAGGGAATGGCATGG	3907	CCATGCCATTCCCTTTACCTGGA
2644	TTCCAGGTAAAGGGAATGGCATG	3908	CATGCCATTCCCTTTACCTGGAA
2645	TTTCCAGGTAAAGGGAATGGCAT	3909	ATGCCATTCCCTTTACCTGGAAA
2646	TTTTCCAGGTAAAGGGAATGGCA	3910	TGCCATTCCCTTTACCTGGAAAA
2647	GTTTTCCAGGTAAAGGGAATGGC	3911	GCCATTCCCTTTACCTGGAAAAC
2648	AGTTTTCCAGGTAAAGGGAATGG	3912	CCATTCCCTTTACCTGGAAAACT
2649	GAGTTTTCCAGGTAAAGGGAATG	3913	CATTCCCTTTACCTGGAAAACTC
2650	GGAGTTTTCCAGGTAAAGGGAAT	3914	ATTCCCTTTACCTGGAAAACTCC
2651	AGGAGTTTTCCAGGTAAAGGGAA	3915	TTCCCTTTACCTGGAAAACTCCT
2652	GAGGAGTTTTCCAGGTAAAGGGA	3916	TCCCTTTACCTGGAAAACTCCTC
2653	GGAGGAGTTTTCCAGGTAAAGGG	3917	CCCTTTACCTGGAAAACTCCTCC
2654	GGGAGGAGTTTTCCAGGTAAAGG	3918	CCTTTACCTGGAAAACTCCTCCC
2655	AGGGAGGAGTTTTCCAGGTAAAG	3919	CTTTACCTGGAAAACTCCTCCCT
2656	TAGGGAGGAGTTTTCCAGGTAAA	3920	TTTACCTGGAAAACTCCTCCCTA
2657	ATAGGGAGGAGTTTTCCAGGTAA	3921	TTACCTGGAAAACTCCTCCCTAT
2658	GATAGGGAGGAGTTTTCCAGGTA	3922	TACCTGGAAAACTCCTCCCTATC
2659	GGATAGGGAGGAGTTTTCCAGGT	3923	ACCTGGAAAACTCCTCCCTATCC
2660	TGGATAGGGAGGAGTTTTCCAGG	3924	CCTGGAAAACTCCTCCCTATCCA
2661	ATGGATAGGGAGGAGTTTTCCAG	3925	CTGGAAAACTCCTCCCTATCCAT
2662	GATGGATAGGGAGGAGTTTTCCA	3926	TGGAAAACTCCTCCCTATCCATC
2663	TGATGGATAGGGAGGAGTTTTCC	3927	GGAAAACTCCTCCCTATCCATCA
2664	TTGATGGATAGGGAGGAGTTTTC	3928	GAAAACTCCTCCCTATCCATCAA
2665	TTTGATGGATAGGGAGGAGTTTT	3929	AAAACTCCTCCCTATCCATCAAA
2666	CTTTGATGGATAGGGAGGAGTTT	3930	AAACTCCTCCCTATCCATCAAAG
2667	ACTTTGATGGATAGGGAGGAGTT	3931	AACTCCTCCCTATCCATCAAAGT
2668	GACTTTGATGGATAGGGAGGAGT	3932	ACTCCTCCCTATCCATCAAAGTC
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2670	TGGACTTTGATGGATAGGGAGGA	3934	TCCTCCCTATCCATCAAAGTCCA
2671	CTGGACTTTGATGGATAGGGAGG	3935	CCTCCCTATCCATCAAAGTCCAG
2672	TCTGGACTTTGATGGATAGGGAG	3936	CTCCCTATCCATCAAAGTCCAGA
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2674	AATCTGGACTTTGATGGATAGGG	3938	CCCTATCCATCAAAGTCCAGATT

2675	GAATCTGGACTTTGATGGATAGG	3939	CCTATCCATCAAAGTCCAGATTC
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2677	CTGAATCTGGACTTTGATGGATA	3941	TATCCATCAAAGTCCAGATTCAG
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2680	ACCCTGAATCTGGACTTTGATGG	3944	CCATCAAAGTCCAGATTCAGGGT
2681	GACCCTGAATCTGGACTTTGATG	3945	CATCAAAGTCCAGATTCAGGGTC
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2684	GGTGACCCTGAATCTGGACTTTG	3948	CAAAGTCCAGATTCAGGGTCACC
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2686	GAGGTGACCCTGAATCTGGACTT	3950	AAGTCCAGATTCAGGGTCACCTC
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2818	AACCCAGGCAGCTGGAAGAGACA	4082	TGTCTCTTCCAGCTGCCTGGGTT
2819	AAACCCAGGCAGCTGGAAGAGAC	4083	GTCTCTTCCAGCTGCCTGGGTTT
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2842	TGGGGATAAGAGTTCTTTCCAGG	4106	CCTGGAAAGAACTCTTATCCCCA

2843	CTGGGGATAAGAGTTCTTTCCAG	4107	CTGGAAAGAACTCTTATCCCCAG
2844	CCTGGGGATAAGAGTTCTTTCCA	4108	TGGAAAGAACTCTTATCCCCAGG
2845	TCCTGGGGATAAGAGTTCTTTCC	4109	GGAAAGAACTCTTATCCCCAGGA
2846	TTCCTGGGGATAAGAGTTCTTTC	4110	GAAAGAACTCTTATCCCCAGGAA
2847	GTTCCTGGGGATAAGAGTTCTTT	4111	AAAGAACTCTTATCCCCAGGAAC
2848	AGTTCCTGGGGATAAGAGTTCTT	4112	AAGAACTCTTATCCCCAGGAACT
2849	TAGTTCCTGGGGATAAGAGTTCT	4113	AGAACTCTTATCCCCAGGAACTA
2850	CTAGTTCCTGGGGATAAGAGTTC	4114	GAACTCTTATCCCCAGGAACTAG
2851	ACTAGTTCCTGGGGATAAGAGTT	4115	AACTCTTATCCCCAGGAACTAGT
2852	AACTAGTTCCTGGGGATAAGAGT	4116	ACTCTTATCCCCAGGAACTAGTT
2853	AAACTAGTTCCTGGGGATAAGAG	4117	CTCTTATCCCCAGGAACTAGTTT
2854	CAAACTAGTTCCTGGGGATAAGA	4118	TCTTATCCCCAGGAACTAGTTTG
2855	ACAAACTAGTTCCTGGGGATAAG	4119	CTTATCCCCAGGAACTAGTTTGT
2856	AACAAACTAGTTCCTGGGGATAA	4120	TTATCCCCAGGAACTAGTTTGTT
2857	CAACAAACTAGTTCCTGGGGATA	4121	TATCCCCAGGAACTAGTTTGTTG
2858	TCAACAAACTAGTTCCTGGGGAT	4122	ATCCCCAGGAACTAGTTTGTTGA
2859	TTCAACAAACTAGTTCCTGGGGA	4123	TCCCCAGGAACTAGTTTGTTGAA
2860	ATTCAACAAACTAGTTCCTGGGG	4124	CCCCAGGAACTAGTTTGTTGAAT
2861	TATTCAACAAACTAGTTCCTGGG	4125	CCCAGGAACTAGTTTGTTGAATA
2862	TTATTCAACAAACTAGTTCCTGG	4126	CCAGGAACTAGTTTGTTGAATAA
2863	TTTATTCAACAAACTAGTTCCTG	4127	CAGGAACTAGTTTGTTGAATAAA
2864	ATTTATTCAACAAACTAGTTCCT	4128	AGGAACTAGTTTGTTGAATAAAT
2865	CATTTATTCAACAAACTAGTTCC	4129	GGAACTAGTTTGTTGAATAAATG
2866	GCATTTATTCAACAAACTAGTTC	4130	GAACTAGTTTGTTGAATAAATGC
2867	AGCATTTATTCAACAAACTAGTT	4131	AACTAGTTTGTTGAATAAATGCT
2868	CAGCATTTATTCAACAAACTAGT	4132	ACTAGTTTGTTGAATAAATGCTG
2869	CCAGCATTTATTCAACAAACTAG	4133	CTAGTTTGTTGAATAAATGCTGG
2870	ACCAGCATTTATTCAACAAACTA	4134	TAGTTTGTTGAATAAATGCTGGT
2871	CACCAGCATTTATTCAACAAACT	4135	AGTTTGTTGAATAAATGCTGGTG
2872	TCACCAGCATTTATTCAACAAAC	4136	GTTTGTTGAATAAATGCTGGTGA
2873	TTCACCAGCATTTATTCAACAAA	4137	TTTGTTGAATAAATGCTGGTGAA
2874	ATTCACCAGCATTTATTCAACAA	4138	TTGTTGAATAAATGCTGGTGAAT
2875	CATTCACCAGCATTTATTCAACA	4139	TGTTGAATAAATGCTGGTGAATG
2876	TCATTCACCAGCATTTATTCAAC	4140	GTTGAATAAATGCTGGTGAATGA
2877	TTCATTCACCAGCATTTATTCAA	4141	TTGAATAAATGCTGGTGAATGAA
2878	ATTCATTCACCAGCATTTATTCA	4142	TGAATAAATGCTGGTGAATGAAT
2879	CATTCATTCACCAGCATTTATTC	4143	GAATAAATGCTGGTGAATGAATG
2880	TCATTCATTCACCAGCATTTATT	4144	AATAAATGCTGGTGAATGAATGA
2881	TTCATTCATTCACCAGCATTTAT	4145	ATAAATGCTGGTGAATGAATGAA
2882	ATTCATTCATTCACCAGCATTTA	4146	TAAATGCTGGTGAATGAATGAAT
2883	CATTCATTCATTCACCAGCATTT	4147	AAATGCTGGTGAATGAATGAATG
2884	TCATTCATTCATTCACCAGCATT	4148	AATGCTGGTGAATGAATGAATGA

2885	ATCATTCATTCATTCACCAGCAT	4149	ATGCTGGTGAATGAATGAATGAT
2886	AATCATTCATTCATTCACCAGCA	4150	TGCTGGTGAATGAATGAATGATT
2887	CAATCATTCATTCATTCACCAGC	4151	GCTGGTGAATGAATGAATGATTG
2888	TCAATCATTCATTCATTCACCAG	4152	CTGGTGAATGAATGAATGATTGA
2889	TTCAATCATTCATTCATTCACCA	4153	TGGTGAATGAATGAATGATTGAA
2890	GTTCAATCATTCATTCATTCACC	4154	GGTGAATGAATGAATGATTGAAC
2891	TGTTCAATCATTCATTCATTCAC	4155	GTGAATGAATGAATGATTGAACA
2892	CTGTTCAATCATTCATTCATTCA	4156	TGAATGAATGAATGATTGAACAG
2893	TCTGTTCAATCATTCATTCATTC	4157	GAATGAATGAATGATTGAACAGA
2894	ATCTGTTCAATCATTCATTCATT	4158	AATGAATGAATGATTGAACAGAT
2895	CATCTGTTCAATCATTCATTCAT	4159	ATGAATGAATGATTGAACAGATG
2896	TCATCTGTTCAATCATTCATTCA	4160	TGAATGAATGATTGAACAGATGA
2897	TTCATCTGTTCAATCATTCATTC	4161	GAATGAATGATTGAACAGATGAA
2898	ATTCATCTGTTCAATCATTCATT	4162	AATGAATGATTGAACAGATGAAT
2899	CATTCATCTGTTCAATCATTCAT	4163	ATGAATGATTGAACAGATGAATG
2900	TCATTCATCTGTTCAATCATTCA	4164	TGAATGATTGAACAGATGAATGA
2901	CTCATTCATCTGTTCAATCATTC	4165	GAATGATTGAACAGATGAATGAG
2902	ACTCATTCATCTGTTCAATCATT	4166	AATGATTGAACAGATGAATGAGT
2903	CACTCATTCATCTGTTCAATCAT	4167	ATGATTGAACAGATGAATGAGTG
2904	TCACTCATTCATCTGTTCAATCA	4168	TGATTGAACAGATGAATGAGTGA
2905	ATCACTCATTCATCTGTTCAATC	4169	GATTGAACAGATGAATGAGTGAT
2906	CATCACTCATTCATCTGTTCAAT	4170	ATTGAACAGATGAATGAGTGATG
2907	TCATCACTCATTCATCTGTTCAA	4171	TTGAACAGATGAATGAGTGATGA
2908	CTCATCACTCATTCATCTGTTCA	4172	TGAACAGATGAATGAGTGATGAG
2909	ACTCATCACTCATTCATCTGTTC	4173	GAACAGATGAATGAGTGATGAGT
2910	TACTCATCACTCATTCATCTGTT	4174	AACAGATGAATGAGTGATGAGTA
2911	CTACTCATCACTCATTCATCTGT	4175	ACAGATGAATGAGTGATGAGTAG
2912	TCTACTCATCACTCATTCATCTG	4176	CAGATGAATGAGTGATGAGTAGA
2913	ATCTACTCATCACTCATTCATCT	4177	AGATGAATGAGTGATGAGTAGAT
2914	TATCTACTCATCACTCATTCATC	4178	GATGAATGAGTGATGAGTAGATA
2915	TTATCTACTCATCACTCATTCAT	4179	ATGAATGAGTGATGAGTAGATAA
2916	TTTATCTACTCATCACTCATTCA	4180	TGAATGAGTGATGAGTAGATAAA
2917	TTTTATCTACTCATCACTCATTC	4181	GAATGAGTGATGAGTAGATAAAA
2918	CTTTTATCTACTCATCACTCATT	4182	AATGAGTGATGAGTAGATAAAAG
2919	CCTTTTATCTACTCATCACTCAT	4183	ATGAGTGATGAGTAGATAAAAGG
2920	TCCTTTTATCTACTCATCACTCA	4184	TGAGTGATGAGTAGATAAAAGGA
2921	ATCCTTTTATCTACTCATCACTC	4185	GAGTGATGAGTAGATAAAAGGAT
2922	CATCCTTTTATCTACTCATCACT	4186	AGTGATGAGTAGATAAAAGGATG
2923	CCATCCTTTTATCTACTCATCAC	4187	GTGATGAGTAGATAAAAGGATGG
2924	TCCATCCTTTTATCTACTCATCA	4188	TGATGAGTAGATAAAAGGATGGA
2925	ATCCATCCTTTTATCTACTCATC	4189	GATGAGTAGATAAAAGGATGGAT
2926	CATCCATCCTTTTATCTACTCAT	4190	ATGAGTAGATAAAAGGATGGATG

2927	CCATCCATCCTTTTATCTACTCA	4191	TGAGTAGATAAAAGGATGGATGG
2928	TCCATCCATCCTTTTATCTACTC	4192	GAGTAGATAAAAGGATGGATGGA
2929	CTCCATCCATCCTTTTATCTACT	4193	AGTAGATAAAAGGATGGATGGAG
2930	TCTCCATCCATCCTTTTATCTAC	4194	GTAGATAAAAGGATGGATGGAGA
2931	CTCTCCATCCATCCTTTTATCTA	4195	TAGATAAAAGGATGGATGGAGAG
2932	TCTCTCCATCCATCCTTTTATCT	4196	AGATAAAAGGATGGATGGAGAGA
2933	ATCTCTCCATCCATCCTTTTATC	4197	GATAAAAGGATGGATGGAGAGAT
2934	CATCTCTCCATCCATCCTTTTAT	4198	ATAAAAGGATGGATGGAGAGATG
2935	CCATCTCTCCATCCATCCTTTTA	4199	TAAAAGGATGGATGGAGAGATGG
2936	CCCATCTCTCCATCCATCCTTTT	4200	AAAAGGATGGATGGAGAGATGGG
2937	ACCCATCTCTCCATCCATCCTTT	4201	AAAGGATGGATGGAGAGATGGGT
2938	CACCCATCTCTCCATCCATCCTT	4202	AAGGATGGATGGAGAGATGGGTG
2939	TCACCCATCTCTCCATCCATCCT	4203	AGGATGGATGGAGAGATGGGTGA
2940	CTCACCCATCTCTCCATCCATCC	4204	GGATGGATGGAGAGATGGGTGAG
2941	ACTCACCCATCTCTCCATCCATC	4205	GATGGATGGAGAGATGGGTGAGT
2942	TACTCACCCATCTCTCCATCCAT	4206	ATGGATGGAGAGATGGGTGAGTA
2943	GTACTCACCCATCTCTCCATCCA	4207	TGGATGGAGAGATGGGTGAGTAC
2944	TGTACTCACCCATCTCTCCATCC	4208	GGATGGAGAGATGGGTGAGTACA
2945	ATGTACTCACCCATCTCTCCATC	4209	GATGGAGAGATGGGTGAGTACAT
2946	CATGTACTCACCCATCTCTCCAT	4210	ATGGAGAGATGGGTGAGTACATG
2947	CCATGTACTCACCCATCTCTCCA	4211	TGGAGAGATGGGTGAGTACATGG
2948	TCCATGTACTCACCCATCTCTCC	4212	GGAGAGATGGGTGAGTACATGGA
2949	ATCCATGTACTCACCCATCTCTC	4213	GAGAGATGGGTGAGTACATGGAT
2950	CATCCATGTACTCACCCATCTCT	4214	AGAGATGGGTGAGTACATGGATG
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2952	TCCATCCATGTACTCACCCATCT	4216	AGATGGGTGAGTACATGGATGGA
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2954	TATCCATCCATGTACTCACCCAT	4218	ATGGGTGAGTACATGGATGGATA
2955	CTATCCATCCATGTACTCACCCA	4219	TGGGTGAGTACATGGATGGATAG
2956	TCTATCCATCCATGTACTCACCC	4220	GGGTGAGTACATGGATGGATAGA
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2958	CATCTATCCATCCATGTACTCAC	4222	GTGAGTACATGGATGGATAGATG
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2960	TCCATCTATCCATCCATGTACTC	4224	GAGTACATGGATGGATAGATGGA
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2962	CATCCATCTATCCATCCATGTAC	4226	GTACATGGATGGATAGATGGATG
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2966	AACTCATCCATCTATCCATCCAT	4230	ATGGATGGATAGATGGATGAGTT
2967	CAACTCATCCATCTATCCATCCA	4231	TGGATGGATAGATGGATGAGTTG
2968	CCAACTCATCCATCTATCCATCC	4232	GGATGGATAGATGGATGAGTTGG

2969	ACCAACTCATCCATCTATCCATC	4233	GATGGATAGATGGATGAGTTGGT
2970	CACCAACTCATCCATCTATCCAT	4234	ATGGATAGATGGATGAGTTGGTG
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2972	CCCACCAACTCATCCATCTATCC	4236	GGATAGATGGATGAGTTGGTGGG
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2978	AATCTACCCACCAACTCATCCAT	4242	ATGGATGAGTTGGTGGGTAGATT
2979	GAATCTACCCACCAACTCATCCA	4243	TGGATGAGTTGGTGGGTAGATTC
2980	CGAATCTACCCACCAACTCATCC	4244	GGATGAGTTGGTGGGTAGATTCG
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2982	CACGAATCTACCCACCAACTCAT	4246	ATGAGTTGGTGGGTAGATTCGTG
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2984	GCCACGAATCTACCCACCAACTC	4248	GAGTTGGTGGGTAGATTCGTGGC
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2986	TAGCCACGAATCTACCCACCAAC	4250	GTTGGTGGGTAGATTCGTGGCTA
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2988	TCTAGCCACGAATCTACCCACCA	4252	TGGTGGGTAGATTCGTGGCTAGA
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2992	TCCATCTAGCCACGAATCTACCC	4256	GGGTAGATTCGTGGCTAGATGGA
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2995	TCATCCATCTAGCCACGAATCTA	4259	TAGATTCGTGGCTAGATGGATGA
2996	ATCATCCATCTAGCCACGAATCT	4260	AGATTCGTGGCTAGATGGATGAT
2997	CATCATCCATCTAGCCACGAATC	4261	GATTCGTGGCTAGATGGATGATG
2998	CCATCATCCATCTAGCCACGAAT	4262	ATTCGTGGCTAGATGGATGATGG
2999	TCCATCATCCATCTAGCCACGAA	4263	TTCGTGGCTAGATGGATGATGGA
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3003	TCCATCCATCATCCATCTAGCCA	4267	TGGCTAGATGGATGATGGATGGA
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3009	TGTCCATCCATCCATCATCCATC	4273	GATGGATGATGGATGGATGGACA
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3013	CATCTGTCCATCCATCCATCATC	4277	GATGATGGATGGATGGACAGATG
3014	CCATCTGTCCATCCATCCATCAT	4278	ATGATGGATGGATGGACAGATGG
3015	TCCATCTGTCCATCCATCCATCA	4279	TGATGGATGGATGGACAGATGGA
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3033	AGTTCAATCATATATCCATCCAT	4297	ATGGATGGATATATGATTGAACT
3034	TAGTTCAATCATATATCCATCCA	4298	TGGATGGATATATGATTGAACTA
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3040	TTTCAATAGTTCAATCATATATC	4304	GATATATGATTGAACTATTGAAA
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3051	TACATCTATACTTTCAATAGTTC	4315	GAACTATTGAAAGTATAGATGTA
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3053	CATACATCTATACTTTCAATAGT	4317	ACTATTGAAAGTATAGATGTATG
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3056	ATCCATACATCTATACTTTCAAT	4320	ATTGAAAGTATAGATGTATGGAT
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3069	CCCAAATTCACCCATCCATACAT	4333	ATGTATGGATGGGTGAATTTGGG
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3095	TACTCATCCATCATCTAACAATT	4359	AATTGTTAGATGATGGATGAGTA
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3097	TATACTCATCCATCATCTAACAA	4361	TTGTTAGATGATGGATGAGTATA
3098	CTATACTCATCCATCATCTAACA	4362	TGTTAGATGATGGATGAGTATAG
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3100	ATCTATACTCATCCATCATCTAA	4364	TTAGATGATGGATGAGTATAGAT
3101	CATCTATACTCATCCATCATCTA	4365	TAGATGATGGATGAGTATAGATG
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3103	TTCATCTATACTCATCCATCATC	4367	GATGATGGATGAGTATAGATGAA
3104	ATTCATCTATACTCATCCATCAT	4368	ATGATGGATGAGTATAGATGAAT
3105	CATTCATCTATACTCATCCATCA	4369	TGATGGATGAGTATAGATGAATG
3106	TCATTCATCTATACTCATCCATC	4370	GATGGATGAGTATAGATGAATGA
3107	ATCATTCATCTATACTCATCCAT	4371	ATGGATGAGTATAGATGAATGAT
3108	CATCATTCATCTATACTCATCCA	4372	TGGATGAGTATAGATGAATGATG
3109	CCATCATTCATCTATACTCATCC	4373	GGATGAGTATAGATGAATGATGG
3110	TCCATCATTCATCTATACTCATC	4374	GATGAGTATAGATGAATGATGGA
3111	ATCCATCATTCATCTATACTCAT	4375	ATGAGTATAGATGAATGATGGAT
3112	CATCCATCATTCATCTATACTCA	4376	TGAGTATAGATGAATGATGGATG
3113	CCATCCATCATTCATCTATACTC	4377	GAGTATAGATGAATGATGGATGG
3114	TCCATCCATCATTCATCTATACT	4378	AGTATAGATGAATGATGGATGGA
3115	ATCCATCCATCATTCATCTATAC	4379	GTATAGATGAATGATGGATGGAT
3116	TATCCATCCATCATTCATCTATA	4380	TATAGATGAATGATGGATGGATA
3117	TTATCCATCCATCATTCATCTAT	4381	ATAGATGAATGATGGATGGATAA
3118	GTTATCCATCCATCATTCATCTA	4382	TAGATGAATGATGGATGGATAAC
3119	AGTTATCCATCCATCATTCATCT	4383	AGATGAATGATGGATGGATAACT
3120	AAGTTATCCATCCATCATTCATC	4384	GATGAATGATGGATGGATAACTT
3121	CAAGTTATCCATCCATCATTCAT	4385	ATGAATGATGGATGGATAACTTG
3122	TCAAGTTATCCATCCATCATTCA	4386	TGAATGATGGATGGATAACTTGA
3123	ATCAAGTTATCCATCCATCATTC	4387	GAATGATGGATGGATAACTTGAT
3124	CATCAAGTTATCCATCCATCATT	4388	AATGATGGATGGATAACTTGATG
3125	TCATCAAGTTATCCATCCATCAT	4389	ATGATGGATGGATAACTTGATGA
3126	CTCATCAAGTTATCCATCCATCA	4390	TGATGGATGGATAACTTGATGAG
3127	ACTCATCAAGTTATCCATCCATC	4391	GATGGATGGATAACTTGATGAGT
3128	CACTCATCAAGTTATCCATCCAT	4392	ATGGATGGATAACTTGATGAGTG
3129	CCACTCATCAAGTTATCCATCCA	4393	TGGATGGATAACTTGATGAGTGG
3130	TCCACTCATCAAGTTATCCATCC	4394	GGATGGATAACTTGATGAGTGGA
3131	ATCCACTCATCAAGTTATCCATC	4395	GATGGATAACTTGATGAGTGGAT
3132	TATCCACTCATCAAGTTATCCAT	4396	ATGGATAACTTGATGAGTGGATA
3133	CTATCCACTCATCAAGTTATCCA	4397	TGGATAACTTGATGAGTGGATAG
3134	TCTATCCACTCATCAAGTTATCC	4398	GGATAACTTGATGAGTGGATAGA
3135	ATCTATCCACTCATCAAGTTATC	4399	GATAACTTGATGAGTGGATAGAT
3136	TATCTATCCACTCATCAAGTTAT	4400	ATAACTTGATGAGTGGATAGATA

3137	CTATCTATCCACTCATCAAGTTA	4401	TAACTTGATGAGTGGATAGATAG
3138	TCTATCTATCCACTCATCAAGTT	4402	AACTTGATGAGTGGATAGATAGA
3139	ATCTATCTATCCACTCATCAAGT	4403	ACTTGATGAGTGGATAGATAGAT
3140	AATCTATCTATCCACTCATCAAG	4404	CTTGATGAGTGGATAGATAGATT
3141	CAATCTATCTATCCACTCATCAA	4405	TTGATGAGTGGATAGATAGATTG
3142	GCAATCTATCTATCCACTCATCA	4406	TGATGAGTGGATAGATAGATTGC
3143	AGCAATCTATCTATCCACTCATC	4407	GATGAGTGGATAGATAGATTGCT
3144	CAGCAATCTATCTATCCACTCAT	4408	ATGAGTGGATAGATAGATTGCTG
3145	CCAGCAATCTATCTATCCACTCA	4409	TGAGTGGATAGATAGATTGCTGG
3146	TCCAGCAATCTATCTATCCACTC	4410	GAGTGGATAGATAGATTGCTGGA
3147	ATCCAGCAATCTATCTATCCACT	4411	AGTGGATAGATAGATTGCTGGAT
3148	TATCCAGCAATCTATCTATCCAC	4412	GTGGATAGATAGATTGCTGGATA
3149	CTATCCAGCAATCTATCTATCCA	4413	TGGATAGATAGATTGCTGGATAG
3150	TCTATCCAGCAATCTATCTATCC	4414	GGATAGATAGATTGCTGGATAGA
3151	ATCTATCCAGCAATCTATCTATC	4415	GATAGATAGATTGCTGGATAGAT
3152	CATCTATCCAGCAATCTATCTAT	4416	ATAGATAGATTGCTGGATAGATG
3153	TCATCTATCCAGCAATCTATCTA	4417	TAGATAGATTGCTGGATAGATGA
3154	ATCATCTATCCAGCAATCTATCT	4418	AGATAGATTGCTGGATAGATGAT
3155	AATCATCTATCCAGCAATCTATC	4419	GATAGATTGCTGGATAGATGATT
3156	CAATCATCTATCCAGCAATCTAT	4420	ATAGATTGCTGGATAGATGATTG
3157	TCAATCATCTATCCAGCAATCTA	4421	TAGATTGCTGGATAGATGATTGA
3158	GTCAATCATCTATCCAGCAATCT	4422	AGATTGCTGGATAGATGATTGAC
3159	AGTCAATCATCTATCCAGCAATC	4423	GATTGCTGGATAGATGATTGACT
3160	CAGTCAATCATCTATCCAGCAAT	4424	ATTGCTGGATAGATGATTGACTG
3161	CCAGTCAATCATCTATCCAGCAA	4425	TTGCTGGATAGATGATTGACTGG
3162	CCCAGTCAATCATCTATCCAGCA	4426	TGCTGGATAGATGATTGACTGGG
3163	ACCCAGTCAATCATCTATCCAGC	4427	GCTGGATAGATGATTGACTGGGT
3164	CACCCAGTCAATCATCTATCCAG	4428	CTGGATAGATGATTGACTGGGTG
3165	CCACCCAGTCAATCATCTATCCA	4429	TGGATAGATGATTGACTGGGTGG
3166	TCCACCCAGTCAATCATCTATCC	4430	GGATAGATGATTGACTGGGTGGA
3167	ATCCACCCAGTCAATCATCTATC	4431	GATAGATGATTGACTGGGTGGAT
3168	TATCCACCCAGTCAATCATCTAT	4432	ATAGATGATTGACTGGGTGGATA
3169	CTATCCACCCAGTCAATCATCTA	4433	TAGATGATTGACTGGGTGGATAG
3170	TCTATCCACCCAGTCAATCATCT	4434	AGATGATTGACTGGGTGGATAGA
3171	ATCTATCCACCCAGTCAATCATC	4435	GATGATTGACTGGGTGGATAGAT
3172	CATCTATCCACCCAGTCAATCAT	4436	ATGATTGACTGGGTGGATAGATG
3173	TCATCTATCCACCCAGTCAATCA	4437	TGATTGACTGGGTGGATAGATGA
3174	TTCATCTATCCACCCAGTCAATC	4438	GATTGACTGGGTGGATAGATGAA
3175	TTTCATCTATCCACCCAGTCAAT	4439	ATTGACTGGGTGGATAGATGAAA
3176	ATTTCATCTATCCACCCAGTCAA	4440	TTGACTGGGTGGATAGATGAAAT
3177	CATTTCATCTATCCACCCAGTCA	4441	TGACTGGGTGGATAGATGAAATG
3178	ACATTTCATCTATCCACCCAGTC	4442	GACTGGGTGGATAGATGAAATGT

3179	AACATTTCATCTATCCACCCAGT	4443	ACTGGGTGGATAGATGAAATGTT
3180	CAACATTTCATCTATCCACCCAG	4444	CTGGGTGGATAGATGAAATGTTG
3181	CCAACATTTCATCTATCCACCCA	4445	TGGGTGGATAGATGAAATGTTGG
3182	TCCAACATTTCATCTATCCACCC	4446	GGGTGGATAGATGAAATGTTGGA
3183	ATCCAACATTTCATCTATCCACC	4447	GGTGGATAGATGAAATGTTGGAT
3184	CATCCAACATTTCATCTATCCAC	4448	GTGGATAGATGAAATGTTGGATG
3185	TCATCCAACATTTCATCTATCCA	4449	TGGATAGATGAAATGTTGGATGA
3186	CTCATCCAACATTTCATCTATCC	4450	GGATAGATGAAATGTTGGATGAG
3187	GCTCATCCAACATTTCATCTATC	4451	GATAGATGAAATGTTGGATGAGC
3188	TGCTCATCCAACATTTCATCTAT	4452	ATAGATGAAATGTTGGATGAGCA
3189	CTGCTCATCCAACATTTCATCTA	4453	TAGATGAAATGTTGGATGAGCAG
3190	TCTGCTCATCCAACATTTCATCT	4454	AGATGAAATGTTGGATGAGCAGA
3191	ATCTGCTCATCCAACATTTCATC	4455	GATGAAATGTTGGATGAGCAGAT
3192	AATCTGCTCATCCAACATTTCAT	4456	ATGAAATGTTGGATGAGCAGATT
3193	TAATCTGCTCATCCAACATTTCA	4457	TGAAATGTTGGATGAGCAGATTA
3194	TTAATCTGCTCATCCAACATTTC	4458	GAAATGTTGGATGAGCAGATTAA
3195	CTTAATCTGCTCATCCAACATTT	4459	AAATGTTGGATGAGCAGATTAAG
3196	ACTTAATCTGCTCATCCAACATT	4460	AATGTTGGATGAGCAGATTAAGT
3197	AACTTAATCTGCTCATCCAACAT	4461	ATGTTGGATGAGCAGATTAAGTT
3198	CAACTTAATCTGCTCATCCAACA	4462	TGTTGGATGAGCAGATTAAGTTG
3199	ACAACTTAATCTGCTCATCCAAC	4463	GTTGGATGAGCAGATTAAGTTGT
3200	TACAACTTAATCTGCTCATCCAA	4464	TTGGATGAGCAGATTAAGTTGTA
3201	ATACAACTTAATCTGCTCATCCA	4465	TGGATGAGCAGATTAAGTTGTAT
3202	AATACAACTTAATCTGCTCATCC	4466	GGATGAGCAGATTAAGTTGTATT
3203	CAATACAACTTAATCTGCTCATC	4467	GATGAGCAGATTAAGTTGTATTG
3204	CCAATACAACTTAATCTGCTCAT	4468	ATGAGCAGATTAAGTTGTATTGG
3205	TCCAATACAACTTAATCTGCTCA	4469	TGAGCAGATTAAGTTGTATTGGA
3206	ATCCAATACAACTTAATCTGCTC	4470	GAGCAGATTAAGTTGTATTGGAT
3207	CATCCAATACAACTTAATCTGCT	4471	AGCAGATTAAGTTGTATTGGATG
3208	CCATCCAATACAACTTAATCTGC	4472	GCAGATTAAGTTGTATTGGATGG
3209	CCCATCCAATACAACTTAATCTG	4473	CAGATTAAGTTGTATTGGATGGG
3210	TCCCATCCAATACAACTTAATCT	4474	AGATTAAGTTGTATTGGATGGGA
3211	ATCCCATCCAATACAACTTAATC	4475	GATTAAGTTGTATTGGATGGGAT
3212	CATCCCATCCAATACAACTTAAT	4476	ATTAAGTTGTATTGGATGGGATG
3213	CCATCCCATCCAATACAACTTAA	4477	TTAAGTTGTATTGGATGGGATGG
3214	TCCATCCCATCCAATACAACTTA	4478	TAAGTTGTATTGGATGGGATGGA
3215	ATCCATCCCATCCAATACAACTT	4479	AAGTTGTATTGGATGGGATGGAT
3216	CATCCATCCCATCCAATACAACT	4480	AGTTGTATTGGATGGGATGGATG
3217	CCATCCATCCCATCCAATACAAC	4481	GTTGTATTGGATGGGATGGATGG
3218	TCCATCCATCCCATCCAATACAA	4482	TTGTATTGGATGGGATGGATGGA
3219	TTCCATCCATCCCATCCAATACA	4483	TGTATTGGATGGGATGGATGGAA
3220	CTTCCATCCATCCCATCCAATAC	4484	GTATTGGATGGGATGGATGGAAG

3221	ACTTCCATCCATCCCATCCAATA	4485	TATTGGATGGGATGGATGGAAGT
3222	CACTTCCATCCATCCCATCCAAT	4486	ATTGGATGGGATGGATGGAAGTG
3223	ACACTTCCATCCATCCCATCCAA	4487	TTGGATGGGATGGATGGAAGTGT
3224	CACACTTCCATCCATCCCATCCA	4488	TGGATGGGATGGATGGAAGTGTG
3225	CCACACTTCCATCCATCCCATCC	4489	GGATGGGATGGATGGAAGTGTGG
3226	ACCACACTTCCATCCATCCCATC	4490	GATGGGATGGATGGAAGTGTGGT
3227	AACCACACTTCCATCCATCCCAT	4491	ATGGGATGGATGGAAGTGTGGTT
3228	CAACCACACTTCCATCCATCCCA	4492	TGGGATGGATGGAAGTGTGGTTG
3229	TCAACCACACTTCCATCCATCCC	4493	GGGATGGATGGAAGTGTGGTTGA
3230	CTCAACCACACTTCCATCCATCC	4494	GGATGGATGGAAGTGTGGTTGAG
3231	ACTCAACCACACTTCCATCCATC	4495	GATGGATGGAAGTGTGGTTGAGT
3232	AACTCAACCACACTTCCATCCAT	4496	ATGGATGGAAGTGTGGTTGAGTT
3233	TAACTCAACCACACTTCCATCCA	4497	TGGATGGAAGTGTGGTTGAGTTA
3234	ATAACTCAACCACACTTCCATCC	4498	GGATGGAAGTGTGGTTGAGTTAT
3235	AATAACTCAACCACACTTCCATC	4499	GATGGAAGTGTGGTTGAGTTATT
3236	TAATAACTCAACCACACTTCCAT	4500	ATGGAAGTGTGGTTGAGTTATTA
3237	CTAATAACTCAACCACACTTCCA	4501	TGGAAGTGTGGTTGAGTTATTAG
3238	TCTAATAACTCAACCACACTTCC	4502	GGAAGTGTGGTTGAGTTATTAGA
3239	TTCTAATAACTCAACCACACTTC	4503	GAAGTGTGGTTGAGTTATTAGAA
3240	CTTCTAATAACTCAACCACACTT	4504	AAGTGTGGTTGAGTTATTAGAAG
3241	CCTTCTAATAACTCAACCACACT	4505	AGTGTGGTTGAGTTATTAGAAGG
3242	TCCTTCTAATAACTCAACCACAC	4506	GTGTGGTTGAGTTATTAGAAGGA
3243	TTCCTTCTAATAACTCAACCACA	4507	TGTGGTTGAGTTATTAGAAGGAA
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3245	TCTTCCTTCTAATAACTCAACCA	4509	TGGTTGAGTTATTAGAAGGAAGA
3246	ATCTTCCTTCTAATAACTCAACC	4510	GGTTGAGTTATTAGAAGGAAGAT
3247	AATCTTCCTTCTAATAACTCAAC	4511	GTTGAGTTATTAGAAGGAAGATT
3248	CAATCTTCCTTCTAATAACTCAA	4512	TTGAGTTATTAGAAGGAAGATTG
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3250	CTCAATCTTCCTTCTAATAACTC	4514	GAGTTATTAGAAGGAAGATTGAG
3251	ACTCAATCTTCCTTCTAATAACT	4515	AGTTATTAGAAGGAAGATTGAGT
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3253	CTACTCAATCTTCCTTCTAATAA	4517	TTATTAGAAGGAAGATTGAGTAG
3254	TCTACTCAATCTTCCTTCTAATA	4518	TATTAGAAGGAAGATTGAGTAGA
3255	ATCTACTCAATCTTCCTTCTAAT	4519	ATTAGAAGGAAGATTGAGTAGAT
3256	TATCTACTCAATCTTCCTTCTAA	4520	TTAGAAGGAAGATTGAGTAGATA
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3258	CCTATCTACTCAATCTTCCTTCT	4522	AGAAGGAAGATTGAGTAGATAGG
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3260	CACCTATCTACTCAATCTTCCTT	4524	AAGGAAGATTGAGTAGATAGGTG
3261	TCACCTATCTACTCAATCTTCCT	4525	AGGAAGATTGAGTAGATAGGTGA
3262	TTCACCTATCTACTCAATCTTCC	4526	GGAAGATTGAGTAGATAGGTGAA

3263	ATTCACCTATCTACTCAATCTTC	4527	GAAGATTGAGTAGATAGGTGAAT
3264	AATTCACCTATCTACTCAATCTT	4528	AAGATTGAGTAGATAGGTGAATT
3265	AAATTCACCTATCTACTCAATCT	4529	AGATTGAGTAGATAGGTGAATTT
3266	CAAATTCACCTATCTACTCAATC	4530	GATTGAGTAGATAGGTGAATTTG
3267	ACAAATTCACCTATCTACTCAAT	4531	ATTGAGTAGATAGGTGAATTTGT
3268	AACAAATTCACCTATCTACTCAA	4532	TTGAGTAGATAGGTGAATTTGTT
3269	CAACAAATTCACCTATCTACTCA	4533	TGAGTAGATAGGTGAATTTGTTG
3270	TCAACAAATTCACCTATCTACTC	4534	GAGTAGATAGGTGAATTTGTTGA
3271	ATCAACAAATTCACCTATCTACT	4535	AGTAGATAGGTGAATTTGTTGAT
3272	TATCAACAAATTCACCTATCTAC	4536	GTAGATAGGTGAATTTGTTGATA
3273	CTATCAACAAATTCACCTATCTA	4537	TAGATAGGTGAATTTGTTGATAG
3274	ACTATCAACAAATTCACCTATCT	4538	AGATAGGTGAATTTGTTGATAGT
3275	GACTATCAACAAATTCACCTATC	4539	GATAGGTGAATTTGTTGATAGTC
3276	TGACTATCAACAAATTCACCTAT	4540	ATAGGTGAATTTGTTGATAGTCA
3277	CTGACTATCAACAAATTCACCTA	4541	TAGGTGAATTTGTTGATAGTCAG
3278	TCTGACTATCAACAAATTCACCT	4542	AGGTGAATTTGTTGATAGTCAGA
3279	ATCTGACTATCAACAAATTCACC	4543	GGTGAATTTGTTGATAGTCAGAT
3280	CATCTGACTATCAACAAATTCAC	4544	GTGAATTTGTTGATAGTCAGATG
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3285	CTACCCATCTGACTATCAACAAA	4549	TTTGTTGATAGTCAGATGGGTAG
3286	TCTACCCATCTGACTATCAACAA	4550	TTGTTGATAGTCAGATGGGTAGA
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3292	TACCTATCTACCCATCTGACTAT	4556	ATAGTCAGATGGGTAGATAGGTA
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3296	CATCTACCTATCTACCCATCTGA	4560	TCAGATGGGTAGATAGGTAGATG
3297	CCATCTACCTATCTACCCATCTG	4561	CAGATGGGTAGATAGGTAGATGG
3298	TCCATCTACCTATCTACCCATCT	4562	AGATGGGTAGATAGGTAGATGGA
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3300	CATCCATCTACCTATCTACCCAT	4564	ATGGGTAGATAGGTAGATGGATG
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3302	TCCATCCATCTACCTATCTACCC	4566	GGGTAGATAGGTAGATGGATGGA
3303	ATCCATCCATCTACCTATCTACC	4567	GGTAGATAGGTAGATGGATGGAT
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3308	CATCCATCCATCCATCTACCTAT	4572	ATAGGTAGATGGATGGATGGATG
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3344	CATTCATCCATTTGTCCATCTGC	4608	GCAGATGGACAAATGGATGAATG
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3346	CCCATTCATCCATTTGTCCATCT	4610	AGATGGACAAATGGATGAATGGG

3347	ACCCATTCATCCATTTGTCCATC	4611	GATGGACAAATGGATGAATGGGT
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3350	CCCACCCATTCATCCATTTGTCC	4614	GGACAAATGGATGAATGGGTGGG
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3354	TCCACCCACCCATTCATCCATTT	4618	AAATGGATGAATGGGTGGGTGGA
3355	ATCCACCCACCCATTCATCCATT	4619	AATGGATGAATGGGTGGGTGGAT
3356	CATCCACCCACCCATTCATCCAT	4620	ATGGATGAATGGGTGGGTGGATG
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3366	TCCTTCCATTCATCCACCCACCC	4630	GGGTGGGTGGATGAATGGAAGGA
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3368	CATCCTTCCATTCATCCACCCAC	4632	GTGGGTGGATGAATGGAAGGATG
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3371	ACACATCCTTCCATTCATCCACC	4635	GGTGGATGAATGGAAGGATGTGT
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3378	TTCAACCACACATCCTTCCATTC	4642	GAATGGAAGGATGTGTGGTTGAA
3379	GTTCAACCACACATCCTTCCATT	4643	AATGGAAGGATGTGTGGTTGAAC
3380	AGTTCAACCACACATCCTTCCAT	4644	ATGGAAGGATGTGTGGTTGAACT
3381	TAGTTCAACCACACATCCTTCCA	4645	TGGAAGGATGTGTGGTTGAACTA
3382	ATAGTTCAACCACACATCCTTCC	4646	GGAAGGATGTGTGGTTGAACTAT
3383	AATAGTTCAACCACACATCCTTC	4647	GAAGGATGTGTGGTTGAACTATT
3384	CAATAGTTCAACCACACATCCTT	4648	AAGGATGTGTGGTTGAACTATTG
3385	GCAATAGTTCAACCACACATCCT	4649	AGGATGTGTGGTTGAACTATTGC
3386	TGCAATAGTTCAACCACACATCC	4650	GGATGTGTGGTTGAACTATTGCA
3387	TTGCAATAGTTCAACCACACATC	4651	GATGTGTGGTTGAACTATTGCAA
3388	CTTGCAATAGTTCAACCACACAT	4652	ATGTGTGGTTGAACTATTGCAAG

3389	ACTTGCAATAGTTCAACCACACA	4653	TGTGTGGTTGAACTATTGCAAGT
3390	TACTTGCAATAGTTCAACCACAC	4654	GTGTGGTTGAACTATTGCAAGTA
3391	ATACTTGCAATAGTTCAACCACA	4655	TGTGGTTGAACTATTGCAAGTAT
3392	AATACTTGCAATAGTTCAACCAC	4656	GTGGTTGAACTATTGCAAGTATT
3393	CAATACTTGCAATAGTTCAACCA	4657	TGGTTGAACTATTGCAAGTATTG
3394	TCAATACTTGCAATAGTTCAACC	4658	GGTTGAACTATTGCAAGTATTGA
3395	ATCAATACTTGCAATAGTTCAAC	4659	GTTGAACTATTGCAAGTATTGAT
3396	TATCAATACTTGCAATAGTTCAA	4660	TTGAACTATTGCAAGTATTGATA
3397	TTATCAATACTTGCAATAGTTCA	4661	TGAACTATTGCAAGTATTGATAA
3398	ATTATCAATACTTGCAATAGTTC	4662	GAACTATTGCAAGTATTGATAAT
3399	AATTATCAATACTTGCAATAGTT	4663	AACTATTGCAAGTATTGATAATT
3400	CAATTATCAATACTTGCAATAGT	4664	ACTATTGCAAGTATTGATAATTG
3401	CCAATTATCAATACTTGCAATAG	4665	CTATTGCAAGTATTGATAATTGG
3402	CCCAATTATCAATACTTGCAATA	4666	TATTGCAAGTATTGATAATTGGG
3403	ACCCAATTATCAATACTTGCAAT	4667	ATTGCAAGTATTGATAATTGGGT
3404	AACCCAATTATCAATACTTGCAA	4668	TTGCAAGTATTGATAATTGGGTT
3405	GAACCCAATTATCAATACTTGCA	4669	TGCAAGTATTGATAATTGGGTTC
3406	TGAACCCAATTATCAATACTTGC	4670	GCAAGTATTGATAATTGGGTTCA
3407	ATGAACCCAATTATCAATACTTG	4671	CAAGTATTGATAATTGGGTTCAT
3408	TATGAACCCAATTATCAATACTT	4672	AAGTATTGATAATTGGGTTCATA
3409	TTATGAACCCAATTATCAATACT	4673	AGTATTGATAATTGGGTTCATAA
3410	ATTATGAACCCAATTATCAATAC	4674	GTATTGATAATTGGGTTCATAAT
3411	AATTATGAACCCAATTATCAATA	4675	TATTGATAATTGGGTTCATAATT
3412	AAATTATGAACCCAATTATCAAT	4676	ATTGATAATTGGGTTCATAATTT
3413	GAAATTATGAACCCAATTATCAA	4677	TTGATAATTGGGTTCATAATTTC
3414	AGAAATTATGAACCCAATTATCA	4678	TGATAATTGGGTTCATAATTTCT
3415	CAGAAATTATGAACCCAATTATC	4679	GATAATTGGGTTCATAATTTCTG
3416	TCAGAAATTATGAACCCAATTAT	4680	ATAATTGGGTTCATAATTTCTGA
3417	TTCAGAAATTATGAACCCAATTA	4681	TAATTGGGTTCATAATTTCTGAA
3418	ATTCAGAAATTATGAACCCAATT	4682	AATTGGGTTCATAATTTCTGAAT
3419	TATTCAGAAATTATGAACCCAAT	4683	ATTGGGTTCATAATTTCTGAATA
3420	ATATTCAGAAATTATGAACCCAA	4684	TTGGGTTCATAATTTCTGAATAT
3421	AATATTCAGAAATTATGAACCCA	4685	TGGGTTCATAATTTCTGAATATT
3422	AAATATTCAGAAATTATGAACCC	4686	GGGTTCATAATTTCTGAATATTT
3423	TAAATATTCAGAAATTATGAACC	4687	GGTTCATAATTTCTGAATATTTA
3424	CTAAATATTCAGAAATTATGAAC	4688	GTTCATAATTTCTGAATATTTAG
3425	TCTAAATATTCAGAAATTATGAA	4689	TTCATAATTTCTGAATATTTAGA
3426	ATCTAAATATTCAGAAATTATGA	4690	TCATAATTTCTGAATATTTAGAT
3427	CATCTAAATATTCAGAAATTATG	4691	CATAATTTCTGAATATTTAGATG
3428	CCATCTAAATATTCAGAAATTAT	4692	ATAATTTCTGAATATTTAGATGG
3429	TCCATCTAAATATTCAGAAATTA	4693	TAATTTCTGAATATTTAGATGGA
3430	ATCCATCTAAATATTCAGAAATT	4694	AATTTCTGAATATTTAGATGGAT

3431	CATCCATCTAAATATTCAGAAAT	4695	ATTTCTGAATATTTAGATGGATG
3432	CCATCCATCTAAATATTCAGAAA	4696	TTTCTGAATATTTAGATGGATGG
3433	ACCATCCATCTAAATATTCAGAA	4697	TTCTGAATATTTAGATGGATGGT
3434	AACCATCCATCTAAATATTCAGA	4698	TCTGAATATTTAGATGGATGGTT
3435	CAACCATCCATCTAAATATTCAG	4699	CTGAATATTTAGATGGATGGTTG
3436	ACAACCATCCATCTAAATATTCA	4700	TGAATATTTAGATGGATGGTTGT
3437	CACAACCATCCATCTAAATATTC	4701	GAATATTTAGATGGATGGTTGTG
3438	TCACAACCATCCATCTAAATATT	4702	AATATTTAGATGGATGGTTGTGA
3439	CTCACAACCATCCATCTAAATAT	4703	ATATTTAGATGGATGGTTGTGAG
3440	ACTCACAACCATCCATCTAAATA	4704	TATTTAGATGGATGGTTGTGAGT
3441	CACTCACAACCATCCATCTAAAT	4705	ATTTAGATGGATGGTTGTGAGTG
3442	CCACTCACAACCATCCATCTAAA	4706	TTTAGATGGATGGTTGTGAGTGG
3443	GCCACTCACAACCATCCATCTAA	4707	TTAGATGGATGGTTGTGAGTGGC
3444	AGCCACTCACAACCATCCATCTA	4708	TAGATGGATGGTTGTGAGTGGCT
3445	CAGCCACTCACAACCATCCATCT	4709	AGATGGATGGTTGTGAGTGGCTG
3446	CCAGCCACTCACAACCATCCATC	4710	GATGGATGGTTGTGAGTGGCTGG
3447	ACCAGCCACTCACAACCATCCAT	4711	ATGGATGGTTGTGAGTGGCTGGT
3448	CACCAGCCACTCACAACCATCCA	4712	TGGATGGTTGTGAGTGGCTGGTG
3449	CCACCAGCCACTCACAACCATCC	4713	GGATGGTTGTGAGTGGCTGGTGG
3450	TCCACCAGCCACTCACAACCATC	4714	GATGGTTGTGAGTGGCTGGTGGA
3451	GTCCACCAGCCACTCACAACCAT	4715	ATGGTTGTGAGTGGCTGGTGGAC
3452	TGTCCACCAGCCACTCACAACCA	4716	TGGTTGTGAGTGGCTGGTGGACA
3453	CTGTCCACCAGCCACTCACAACC	4717	GGTTGTGAGTGGCTGGTGGACAG
3454	TCTGTCCACCAGCCACTCACAAC	4718	GTTGTGAGTGGCTGGTGGACAGA
3455	GTCTGTCCACCAGCCACTCACAA	4719	TTGTGAGTGGCTGGTGGACAGAC
3456	CGTCTGTCCACCAGCCACTCACA	4720	TGTGAGTGGCTGGTGGACAGACG
3457	TCGTCTGTCCACCAGCCACTCAC	4721	GTGAGTGGCTGGTGGACAGACGA
3458	TTCGTCTGTCCACCAGCCACTCA	4722	TGAGTGGCTGGTGGACAGACGAA
3459	TTTCGTCTGTCCACCAGCCACTC	4723	GAGTGGCTGGTGGACAGACGAAA
3460	TTTTCGTCTGTCCACCAGCCACT	4724	AGTGGCTGGTGGACAGACGAAAA
3461	TTTTTCGTCTGTCCACCAGCCAC	4725	GTGGCTGGTGGACAGACGAAAAA
3462	ATTTTTCGTCTGTCCACCAGCCA	4726	TGGCTGGTGGACAGACGAAAAAT
3463	CATTTTTCGTCTGTCCACCAGCC	4727	GGCTGGTGGACAGACGAAAAATG
3464	CCATTTTTCGTCTGTCCACCAGC	4728	GCTGGTGGACAGACGAAAAATGG
3465	TCCATTTTTCGTCTGTCCACCAG	4729	CTGGTGGACAGACGAAAAATGGA
3466	ATCCATTTTTCGTCTGTCCACCA	4730	TGGTGGACAGACGAAAAATGGAT
3467	CATCCATTTTTCGTCTGTCCACC	4731	GGTGGACAGACGAAAAATGGATG
3468	CCATCCATTTTTCGTCTGTCCAC	4732	GTGGACAGACGAAAAATGGATGG
3469	ACCATCCATTTTTCGTCTGTCCA	4733	TGGACAGACGAAAAATGGATGGT
3470	AACCATCCATTTTTCGTCTGTCC	4734	GGACAGACGAAAAATGGATGGTT
3471	CAACCATCCATTTTTCGTCTGTC	4735	GACAGACGAAAAATGGATGGTTG
3472	CCAACCATCCATTTTTCGTCTGT	4736	ACAGACGAAAAATGGATGGTTGG

3473	TCCAACCATCCATTTTTCGTCTG	4737	CAGACGAAAAATGGATGGTTGGA
3474	ATCCAACCATCCATTTTTCGTCT	4738	AGACGAAAAATGGATGGTTGGAT
3475	TATCCAACCATCCATTTTTCGTC	4739	GACGAAAAATGGATGGTTGGATA
3476	TTATCCAACCATCCATTTTTCGT	4740	ACGAAAAATGGATGGTTGGATAA
3477	TTTATCCAACCATCCATTTTTCG	4741	CGAAAAATGGATGGTTGGATAAA
3478	ATTTATCCAACCATCCATTTTTC	4742	GAAAAATGGATGGTTGGATAAAT
3479	AATTTATCCAACCATCCATTTTT	4743	AAAAATGGATGGTTGGATAAATT
3480	CAATTTATCCAACCATCCATTTT	4744	AAAATGGATGGTTGGATAAATTG
3481	TCAATTTATCCAACCATCCATTT	4745	AAATGGATGGTTGGATAAATTGA
3482	ATCAATTTATCCAACCATCCATT	4746	AATGGATGGTTGGATAAATTGAT
3483	CATCAATTTATCCAACCATCCAT	4747	ATGGATGGTTGGATAAATTGATG
3484	CCATCAATTTATCCAACCATCCA	4748	TGGATGGTTGGATAAATTGATGG
3485	CCCATCAATTTATCCAACCATCC	4749	GGATGGTTGGATAAATTGATGGG
3486	ACCCATCAATTTATCCAACCATC	4750	GATGGTTGGATAAATTGATGGGT
3487	CACCCATCAATTTATCCAACCAT	4751	ATGGTTGGATAAATTGATGGGTG
3488	CCACCCATCAATTTATCCAACCA	4752	TGGTTGGATAAATTGATGGGTGG
3489	TCCACCCATCAATTTATCCAACC	4753	GGTTGGATAAATTGATGGGTGGA
3490	ATCCACCCATCAATTTATCCAAC	4754	GTTGGATAAATTGATGGGTGGAT
3491	CATCCACCCATCAATTTATCCAA	4755	TTGGATAAATTGATGGGTGGATG
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3493	TCCATCCACCCATCAATTTATCC	4757	GGATAAATTGATGGGTGGATGGA
3494	ATCCATCCACCCATCAATTTATC	4758	GATAAATTGATGGGTGGATGGAT
3495	CATCCATCCACCCATCAATTTAT	4759	ATAAATTGATGGGTGGATGGATG
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3498	AACCATCCATCCACCCATCAATT	4762	AATTGATGGGTGGATGGATGGTT
3499	CAACCATCCATCCACCCATCAAT	4763	ATTGATGGGTGGATGGATGGTTG
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3501	ACCAACCATCCATCCACCCATCA	4765	TGATGGGTGGATGGATGGTTGGT
3502	AACCAACCATCCATCCACCCATC	4766	GATGGGTGGATGGATGGTTGGTT
3503	CAACCAACCATCCATCCACCCAT	4767	ATGGGTGGATGGATGGTTGGTTG
3504	ACAACCAACCATCCATCCACCCA	4768	TGGGTGGATGGATGGTTGGTTGT
3505	TACAACCAACCATCCATCCACCC	4769	GGGTGGATGGATGGTTGGTTGTA
3506	ATACAACCAACCATCCATCCACC	4770	GGTGGATGGATGGTTGGTTGTAT
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3508	TCATACAACCAACCATCCATCCA	4772	TGGATGGATGGTTGGTTGTATGA
3509	TTCATACAACCAACCATCCATCC	4773	GGATGGATGGTTGGTTGTATGAA
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3511	CTTTCATACAACCAACCATCCAT	4775	ATGGATGGTTGGTTGTATGAAAG
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3513	TTCTTTCATACAACCAACCATCC	4777	GGATGGTTGGTTGTATGAAAGAA
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3515	CATTCTTTCATACAACCAACCAT	4779	ATGGTTGGTTGTATGAAAGAATG
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3517	TTCATTCTTTCATACAACCAACC	4781	GGTTGGTTGTATGAAAGAATGAA
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3527	TACCCAATCATTCATTCTTTCAT	4791	ATGAAAGAATGAATGATTGGGTA
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3535	AATCCACCTACCCAATCATTCAT	4799	ATGAATGATTGGGTAGGTGGATT
3536	TAATCCACCTACCCAATCATTCA	4800	TGAATGATTGGGTAGGTGGATTA
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3540	AACTTAATCCACCTACCCAATCA	4804	TGATTGGGTAGGTGGATTAAGTT
3541	CAACTTAATCCACCTACCCAATC	4805	GATTGGGTAGGTGGATTAAGTTG
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3543	CGCAACTTAATCCACCTACCCAA	4807	TTGGGTAGGTGGATTAAGTTGCG
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3545	TCCGCAACTTAATCCACCTACCC	4809	GGGTAGGTGGATTAAGTTGCGGA
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3547	GATCCGCAACTTAATCCACCTAC	4811	GTAGGTGGATTAAGTTGCGGATC
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3554	ATACATTGATCCGCAACTTAATC	4818	GATTAAGTTGCGGATCAATGTAT
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3557	CCCATACATTGATCCGCAACTTA	4821	TAAGTTGCGGATCAATGTATGGG
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3559	ATCCCATACATTGATCCGCAACT	4823	AGTTGCGGATCAATGTATGGGAT
3560	CATCCCATACATTGATCCGCAAC	4824	GTTGCGGATCAATGTATGGGATG
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3564	CATCCATCCCATACATTGATCCG	4828	CGGATCAATGTATGGGATGGATG
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3570	TCCATTCATCCATCCCATACATT	4834	AATGTATGGGATGGATGAATGGA
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3591	AACCACACATCCATCCATCCATC	4855	GATGGATGGATGGATGTGTGGTT
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3614	CTCTTCCAACCTTTCAGTAATTC	4878	GAATTACTGAAAGGTTGGAAGAG
3615	ACTCTTCCAACCTTTCAGTAATT	4879	AATTACTGAAAGGTTGGAAGAGT
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3617	CCACTCTTCCAACCTTTCAGTAA	4881	TTACTGAAAGGTTGGAAGAGTGG
3618	TCCACTCTTCCAACCTTTCAGTA	4882	TACTGAAAGGTTGGAAGAGTGGA
3619	ATCCACTCTTCCAACCTTTCAGT	4883	ACTGAAAGGTTGGAAGAGTGGAT
3620	CATCCACTCTTCCAACCTTTCAG	4884	CTGAAAGGTTGGAAGAGTGGATG
3621	CCATCCACTCTTCCAACCTTTCA	4885	TGAAAGGTTGGAAGAGTGGATGG
3622	CCCATCCACTCTTCCAACCTTTC	4886	GAAAGGTTGGAAGAGTGGATGGG
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3624	CACCCATCCACTCTTCCAACCTT	4888	AAGGTTGGAAGAGTGGATGGGTG
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3627	TTTCACCCATCCACTCTTCCAAC	4891	GTTGGAAGAGTGGATGGGTGAAA
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3633	CCCAAATTTCACCCATCCACTCT	4897	AGAGTGGATGGGTGAAATTTGGG
3634	CCCCAAATTTCACCCATCCACTC	4898	GAGTGGATGGGTGAAATTTGGGG
3635	ACCCCAAATTTCACCCATCCACT	4899	AGTGGATGGGTGAAATTTGGGGT
3636	TACCCCAAATTTCACCCATCCAC	4900	GTGGATGGGTGAAATTTGGGGTA
3637	CTACCCCAAATTTCACCCATCCA	4901	TGGATGGGTGAAATTTGGGGTAG
3638	ACTACCCCAAATTTCACCCATCC	4902	GGATGGGTGAAATTTGGGGTAGT
3639	AACTACCCCAAATTTCACCCATC	4903	GATGGGTGAAATTTGGGGTAGTT
3640	TAACTACCCCAAATTTCACCCAT	4904	ATGGGTGAAATTTGGGGTAGTTA

3641	CTAACTACCCCAAATTTCACCCA	4905	TGGGTGAAATTTGGGGTAGTTAG
3642	TCTAACTACCCCAAATTTCACCC	4906	GGGTGAAATTTGGGGTAGTTAGA
3643	ATCTAACTACCCCAAATTTCACC	4907	GGTGAAATTTGGGGTAGTTAGAT
3644	CATCTAACTACCCCAAATTTCAC	4908	GTGAAATTTGGGGTAGTTAGATG
3645	CCATCTAACTACCCCAAATTTCA	4909	TGAAATTTGGGGTAGTTAGATGG
3646	CCCATCTAACTACCCCAAATTTC	4910	GAAATTTGGGGTAGTTAGATGGG
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3648	CACCCATCTAACTACCCCAAATT	4912	AATTTGGGGTAGTTAGATGGGTG
3649	CCACCCATCTAACTACCCCAAAT	4913	ATTTGGGGTAGTTAGATGGGTGG
3650	CCCACCCATCTAACTACCCCAAA	4914	TTTGGGGTAGTTAGATGGGTGGG
3651	ACCCACCCATCTAACTACCCCAA	4915	TTGGGGTAGTTAGATGGGTGGGT
3652	CACCCACCCATCTAACTACCCCA	4916	TGGGGTAGTTAGATGGGTGGGTG
3653	ACACCCACCCATCTAACTACCCC	4917	GGGGTAGTTAGATGGGTGGGTGT
3654	CACACCCACCCATCTAACTACCC	4918	GGGTAGTTAGATGGGTGGGTGTG
3655	ACACACCCACCCATCTAACTACC	4919	GGTAGTTAGATGGGTGGGTGTGT
3656	CACACACCCACCCATCTAACTAC	4920	GTAGTTAGATGGGTGGGTGTGTG
3657	CCACACACCCACCCATCTAACTA	4921	TAGTTAGATGGGTGGGTGTGTGG
3658	TCCACACACCCACCCATCTAACT	4922	AGTTAGATGGGTGGGTGTGTGGA
3659	ATCCACACACCCACCCATCTAAC	4923	GTTAGATGGGTGGGTGTGTGGAT
3660	CATCCACACACCCACCCATCTAA	4924	TTAGATGGGTGGGTGTGTGGATG
3661	CCATCCACACACCCACCCATCTA	4925	TAGATGGGTGGGTGTGTGGATGG
3662	TCCATCCACACACCCACCCATCT	4926	AGATGGGTGGGTGTGTGGATGGA
3663	ATCCATCCACACACCCACCCATC	4927	GATGGGTGGGTGTGTGGATGGAT
3664	TATCCATCCACACACCCACCCAT	4928	ATGGGTGGGTGTGTGGATGGATA
3665	TTATCCATCCACACACCCACCCA	4929	TGGGTGGGTGTGTGGATGGATAA
3666	TTTATCCATCCACACACCCACCC	4930	GGGTGGGTGTGTGGATGGATAAA
3667	TTTTATCCATCCACACACCCACC	4931	GGTGGGTGTGTGGATGGATAAAA
3668	CTTTTATCCATCCACACACCCAC	4932	GTGGGTGTGTGGATGGATAAAAG
3669	TCTTTTATCCATCCACACACCCA	4933	TGGGTGTGTGGATGGATAAAAGA
3670	CTCTTTTATCCATCCACACACCC	4934	GGGTGTGTGGATGGATAAAAGAG
3671	ACTCTTTTATCCATCCACACACC	4935	GGTGTGTGGATGGATAAAAGAGT
3672	TACTCTTTTATCCATCCACACAC	4936	GTGTGTGGATGGATAAAAGAGTA
3673	CTACTCTTTTATCCATCCACACA	4937	TGTGTGGATGGATAAAAGAGTAG
3674	TCTACTCTTTTATCCATCCACAC	4938	GTGTGGATGGATAAAAGAGTAGA
3675	ATCTACTCTTTTATCCATCCACA	4939	TGTGGATGGATAAAAGAGTAGAT
3676	CATCTACTCTTTTATCCATCCAC	4940	GTGGATGGATAAAAGAGTAGATG
3677	TCATCTACTCTTTTATCCATCCA	4941	TGGATGGATAAAAGAGTAGATGA
3678	TTCATCTACTCTTTTATCCATCC	4942	GGATGGATAAAAGAGTAGATGAA
3679	ATTCATCTACTCTTTTATCCATC	4943	GATGGATAAAAGAGTAGATGAAT
3680	CATTCATCTACTCTTTTATCCAT	4944	ATGGATAAAAGAGTAGATGAATG
3681	TCATTCATCTACTCTTTTATCCA	4945	TGGATAAAAGAGTAGATGAATGA
3682	TTCATTCATCTACTCTTTTATCC	4946	GGATAAAAGAGTAGATGAATGAA

3683	ATTCATTCATCTACTCTTTTATC	4947	GATAAAAGAGTAGATGAATGAAT
3684	AATTCATTCATCTACTCTTTTAT	4948	ATAAAAGAGTAGATGAATGAATT
3685	TAATTCATTCATCTACTCTTTTA	4949	TAAAAGAGTAGATGAATGAATTA
3686	TTAATTCATTCATCTACTCTTTT	4950	AAAAGAGTAGATGAATGAATTAA
3687	ATTAATTCATTCATCTACTCTTT	4951	AAAGAGTAGATGAATGAATTAAT
3688	CATTAATTCATTCATCTACTCTT	4952	AAGAGTAGATGAATGAATTAATG
3689	TCATTAATTCATTCATCTACTCT	4953	AGAGTAGATGAATGAATTAATGA
3690	TTCATTAATTCATTCATCTACTC	4954	GAGTAGATGAATGAATTAATGAA
3691	ATTCATTAATTCATTCATCTACT	4955	AGTAGATGAATGAATTAATGAAT
3692	TATTCATTAATTCATTCATCTAC	4956	GTAGATGAATGAATTAATGAATA
3693	TTATTCATTAATTCATTCATCTA	4957	TAGATGAATGAATTAATGAATAA
3694	TTTATTCATTAATTCATTCATCT	4958	AGATGAATGAATTAATGAATAAA
3695	GTTTATTCATTAATTCATTCATC	4959	GATGAATGAATTAATGAATAAAC
3696	TGTTTATTCATTAATTCATTCAT	4960	ATGAATGAATTAATGAATAAACA
3697	CTGTTTATTCATTAATTCATTCA	4961	TGAATGAATTAATGAATAAACAG
3698	CCTGTTTATTCATTAATTCATTC	4962	GAATGAATTAATGAATAAACAGG
3699	GCCTGTTTATTCATTAATTCATT	4963	AATGAATTAATGAATAAACAGGC
3700	TGCCTGTTTATTCATTAATTCAT	4964	ATGAATTAATGAATAAACAGGCA
3701	CTGCCTGTTTATTCATTAATTCA	4965	TGAATTAATGAATAAACAGGCAG
3702	TCTGCCTGTTTATTCATTAATTC	4966	GAATTAATGAATAAACAGGCAGA
3703	ATCTGCCTGTTTATTCATTAATT	4967	AATTAATGAATAAACAGGCAGAT
3704	CATCTGCCTGTTTATTCATTAAT	4968	ATTAATGAATAAACAGGCAGATG
3705	CCATCTGCCTGTTTATTCATTAA	4969	TTAATGAATAAACAGGCAGATGG
3706	TCCATCTGCCTGTTTATTCATTA	4970	TAATGAATAAACAGGCAGATGGA
3707	ATCCATCTGCCTGTTTATTCATT	4971	AATGAATAAACAGGCAGATGGAT
3708	CATCCATCTGCCTGTTTATTCAT	4972	ATGAATAAACAGGCAGATGGATG
3709	TCATCCATCTGCCTGTTTATTCA	4973	TGAATAAACAGGCAGATGGATGA
3710	ATCATCCATCTGCCTGTTTATTC	4974	GAATAAACAGGCAGATGGATGAT
3711	CATCATCCATCTGCCTGTTTATT	4975	AATAAACAGGCAGATGGATGATG
3712	ACATCATCCATCTGCCTGTTTAT	4976	ATAAACAGGCAGATGGATGATGT
3713	TACATCATCCATCTGCCTGTTTA	4977	TAAACAGGCAGATGGATGATGTA
3714	TTACATCATCCATCTGCCTGTTT	4978	AAACAGGCAGATGGATGATGTAA
3715	CTTACATCATCCATCTGCCTGTT	4979	AACAGGCAGATGGATGATGTAAG
3716	GCTTACATCATCCATCTGCCTGT	4980	ACAGGCAGATGGATGATGTAAGC
3717	AGCTTACATCATCCATCTGCCTG	4981	CAGGCAGATGGATGATGTAAGCT
3718	CAGCTTACATCATCCATCTGCCT	4982	AGGCAGATGGATGATGTAAGCTG
3719	GCAGCTTACATCATCCATCTGCC	4983	GGCAGATGGATGATGTAAGCTGC
3720	GGCAGCTTACATCATCCATCTGC	4984	GCAGATGGATGATGTAAGCTGCC
3721	GGGCAGCTTACATCATCCATCTG	4985	CAGATGGATGATGTAAGCTGCCC
3722	GGGGCAGCTTACATCATCCATCT	4986	AGATGGATGATGTAAGCTGCCCC
3723	TGGGGCAGCTTACATCATCCATC	4987	GATGGATGATGTAAGCTGCCCCA
3724	CTGGGGCAGCTTACATCATCCAT	4988	ATGGATGATGTAAGCTGCCCCAG

3725	TCTGGGGCAGCTTACATCATCCA	4989	TGGATGATGTAAGCTGCCCCAGA
3726	GTCTGGGGCAGCTTACATCATCC	4990	GGATGATGTAAGCTGCCCCAGAC
3727	GGTCTGGGGCAGCTTACATCATC	4991	GATGATGTAAGCTGCCCCAGACC
3728	GGGTCTGGGGCAGCTTACATCAT	4992	ATGATGTAAGCTGCCCCAGACCC
3729	AGGGTCTGGGGCAGCTTACATCA	4993	TGATGTAAGCTGCCCCAGACCCT
3730	CAGGGTCTGGGGCAGCTTACATC	4994	GATGTAAGCTGCCCCAGACCCTG
3731	CCAGGGTCTGGGGCAGCTTACAT	4995	ATGTAAGCTGCCCCAGACCCTGG
3732	CCCAGGGTCTGGGGCAGCTTACA	4996	TGTAAGCTGCCCCAGACCCTGGG
3733	TCCCAGGGTCTGGGGCAGCTTAC	4997	GTAAGCTGCCCCAGACCCTGGGA
3734	GTCCCAGGGTCTGGGGCAGCTTA	4998	TAAGCTGCCCCAGACCCTGGGAC
3735	GGTCCCAGGGTCTGGGGCAGCTT	4999	AAGCTGCCCCAGACCCTGGGACC
3736	AGGTCCCAGGGTCTGGGGCAGCT	5000	AGCTGCCCCAGACCCTGGGACCT
3737	GAGGTCCCAGGGTCTGGGGCAGC	5001	GCTGCCCCAGACCCTGGGACCTC
3738	AGAGGTCCCAGGGTCTGGGGCAG	5002	CTGCCCCAGACCCTGGGACCTCT
3739	CAGAGGTCCCAGGGTCTGGGGCA	5003	TGCCCCAGACCCTGGGACCTCTG
3740	TCAGAGGTCCCAGGGTCTGGGGC	5004	GCCCCAGACCCTGGGACCTCTGA
3741	GTCAGAGGTCCCAGGGTCTGGGG	5005	CCCCAGACCCTGGGACCTCTGAC
3742	GGTCAGAGGTCCCAGGGTCTGGG	5006	CCCAGACCCTGGGACCTCTGACC
3743	GGGTCAGAGGTCCCAGGGTCTGG	5007	CCAGACCCTGGGACCTCTGACCC
3744	GGGGTCAGAGGTCCCAGGGTCTG	5008	CAGACCCTGGGACCTCTGACCCC
3745	GGGGGTCAGAGGTCCCAGGGTCT	5009	AGACCCTGGGACCTCTGACCCCC
3746	CGGGGGTCAGAGGTCCCAGGGTC	5010	GACCCTGGGACCTCTGACCCCCG
3747	CCGGGGGTCAGAGGTCCCAGGGT	5011	ACCCTGGGACCTCTGACCCCCGG
3748	GCCGGGGGTCAGAGGTCCCAGGG	5012	CCCTGGGACCTCTGACCCCCGGC
3749	CGCCGGGGGTCAGAGGTCCCAGG	5013	CCTGGGACCTCTGACCCCCGGCG
3750	TCGCCGGGGGTCAGAGGTCCCAG	5014	CTGGGACCTCTGACCCCCGGCGA
3751	GTCGCCGGGGGTCAGAGGTCCCA	5015	TGGGACCTCTGACCCCCGGCGAC
3752	GGTCGCCGGGGGTCAGAGGTCCC	5016	GGGACCTCTGACCCCCGGCGACC
3753	GGGTCGCCGGGGGTCAGAGGTCC	5017	GGACCTCTGACCCCCGGCGACCC
3754	GGGGTCGCCGGGGGTCAGAGGTC	5018	GACCTCTGACCCCCGGCGACCCC
3755	AGGGGTCGCCGGGGGTCAGAGGT	5019	ACCTCTGACCCCCGGCGACCCCT
3756	AAGGGGTCGCCGGGGGTCAGAGG	5020	CCTCTGACCCCCGGCGACCCCTT
3757	CAAGGGGTCGCCGGGGGTCAGAG	5021	CTCTGACCCCCGGCGACCCCTTG
3758	GCAAGGGGTCGCCGGGGGTCAGA	5022	TCTGACCCCCGGCGACCCCTTGC
3759	TGCAAGGGGTCGCCGGGGGTCAG	5023	CTGACCCCCGGCGACCCCTTGCA
3760	GTGCAAGGGGTCGCCGGGGGTCA	5024	TGACCCCCGGCGACCCCTTGCAC
3761	AGTGCAAGGGGTCGCCGGGGGTC	5025	GACCCCCGGCGACCCCTTGCACT
3762	GAGTGCAAGGGGTCGCCGGGGGT	5026	ACCCCCGGCGACCCCTTGCACTC
3763	AGAGTGCAAGGGGTCGCCGGGGG	5027	CCCCCGGCGACCCCTTGCACTCT
3764	GAGAGTGCAAGGGGTCGCCGGGG	5028	CCCCGGCGACCCCTTGCACTCTC
3765	GGAGAGTGCAAGGGGTCGCCGGG	5029	CCCGGCGACCCCTTGCACTCTCC
3766	TGGAGAGTGCAAGGGGTCGCCGG	5030	CCGGCGACCCCTTGCACTCTCCA

3767	ATGGAGAGTGCAAGGGGTCGCCG	5031	CGGCGACCCCTTGCACTCTCCAT
3768	CATGGAGAGTGCAAGGGGTCGCC	5032	GGCGACCCCTTGCACTCTCCATG
3769	TCATGGAGAGTGCAAGGGGTCGC	5033	GCGACCCCTTGCACTCTCCATGA
3770	GTCATGGAGAGTGCAAGGGGTCG	5034	CGACCCCTTGCACTCTCCATGAC
3771	TGTCATGGAGAGTGCAAGGGGTC	5035	GACCCCTTGCACTCTCCATGACA
3772	GTGTCATGGAGAGTGCAAGGGGT	5036	ACCCCTTGCACTCTCCATGACAC
3773	AGTGTCATGGAGAGTGCAAGGGG	5037	CCCCTTGCACTCTCCATGACACT
3774	AAGTGTCATGGAGAGTGCAAGGG	5038	CCCTTGCACTCTCCATGACACTT
3775	AAAGTGTCATGGAGAGTGCAAGG	5039	CCTTGCACTCTCCATGACACTTT
3776	GAAAGTGTCATGGAGAGTGCAAG	5040	CTTGCACTCTCCATGACACTTTC
3777	AGAAAGTGTCATGGAGAGTGCAA	5041	TTGCACTCTCCATGACACTTTCT
3778	GAGAAAGTGTCATGGAGAGTGCA	5042	TGCACTCTCCATGACACTTTCTC
3779	AGAGAAAGTGTCATGGAGAGTGC	5043	GCACTCTCCATGACACTTTCTCT
3780	GAGAGAAAGTGTCATGGAGAGTG	5044	CACTCTCCATGACACTTTCTCTC
3781	GGAGAGAAAGTGTCATGGAGAGT	5045	ACTCTCCATGACACTTTCTCTCC
3782	GGGAGAGAAAGTGTCATGGAGAG	5046	CTCTCCATGACACTTTCTCTCCC
3783	TGGGAGAGAAAGTGTCATGGAGA	5047	TCTCCATGACACTTTCTCTCCCA
3784	ATGGGAGAGAAAGTGTCATGGAG	5048	CTCCATGACACTTTCTCTCCCAT
3785	CATGGGAGAGAAAGTGTCATGGA	5049	TCCATGACACTTTCTCTCCCATG
3786	CCATGGGAGAGAAAGTGTCATGG	5050	CCATGACACTTTCTCTCCCATGG
3787	ACCATGGGAGAGAAAGTGTCATG	5051	CATGACACTTTCTCTCCCATGGT
3788	CACCATGGGAGAGAAAGTGTCAT	5052	ATGACACTTTCTCTCCCATGGTG
3789	CCACCATGGGAGAGAAAGTGTCA	5053	TGACACTTTCTCTCCCATGGTGG
3790	GCCACCATGGGAGAGAAAGTGTC	5054	GACACTTTCTCTCCCATGGTGGC
3791	TGCCACCATGGGAGAGAAAGTGT	5055	ACACTTTCTCTCCCATGGTGGCA
3792	CTGCCACCATGGGAGAGAAAGTG	5056	CACTTTCTCTCCCATGGTGGCAG

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

Table 2B. Example UNC13A Oligonucleotide Variant Sequences

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

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

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

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

[00193] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more locked nucleic acids (LNAs). In particular embodiments, an antisense oligonucleotide includes one LNA. In particular embodiments, an antisense oligonucleotide includes two LNAs. In particular

embodiments, an antisense oligonucleotide includes three LNAs. Generally, a LNA refers to nucleic acid monomers having a bridge (*e.g.*, methylene, ethylene, aminooxy, or oxyimino bridge) connecting two carbon atoms between the 4' and 2' position of the nucleoside sugar unit, thereby forming a bicyclic sugar.

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

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

[00196] In various embodiments, antisense oligonucleotides disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise three LNAs located at three different positions of the antisense oligonucleotide. In some embodiments, an antisense

oligonucleotide disclosed herein includes, if counting from 5' to 3', a first LNA at a 4th position of the antisense oligonucleotide, a second LNA at a 12th position of the antisense oligonucleotide, and a third LNA at a 20th position of the antisense oligonucleotide.

Antisense Oligonucleotides with One or more Spacers

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

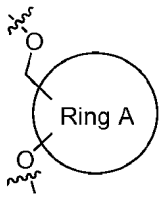
[00198] In certain embodiments, an oligonucleotide with one or more spacers, such as disclosed herein, may be an oligonucleotide with 5 to 100 oligonucleotide units in length, for example, 10 to 60 oligonucleotide units in length, for example, 12 to 50 oligonucleotide units in length, 14 to 40 oligonucleotide units in length, 10 to 30 oligonucleotide units in length, for example, 14 to 30 oligonucleotide units in length, for example, 14 to 25 or 15 to 22 oligonucleotide units in length, or 18, 19, 20, 21, 22, 23, 24, or 25 oligonucleotide units in length. As used herein, an "oligonucleotide unit" refers to either a nucleoside (e.g., a nucleoside which includes a sugar and/or a nucleobase) or a nucleoside-replacement group (e.g., a spacer) of the oligonucleotide.

[00199] In particular embodiments, oligonucleotides with one or more spacers are 25 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 23 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 21 oligonucleotide units in length. In particular embodiments, the oligonucleotides with one or more spacers are 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 18 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 19 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 20 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 21

oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 22 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 23 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 24 oligonucleotide units in length. In various embodiments, the oligonucleotides with one or more spacers are at least 25 oligonucleotide units in length.

[00200] In various embodiments, a UNC13A AON comprises a sequence that shares at least 80% identity with an equal length portion of any one of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, a UNC13A AON comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, a UNC13A AON comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, a UNC13A AON comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~. In various embodiments, a UNC13A AON comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

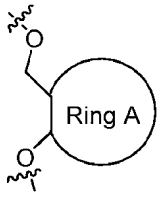
[00201] In some embodiments, the spacer is of Formula (X):



Formula (X)

wherein ring A is as defined herein.

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



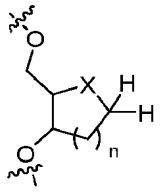
Formula (Xa)

wherein ring A is as defined herein and the -CH_2-O- group is on a ring A atom adjacent to the -O- group.

[00203] As generally defined herein, ring A of formulae (X) and (Xa), is an optionally substituted 4-8 member monocyclic cycloalkyl group (*e.g.* ring A is cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl) or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N (*e.g.* ring A is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl). In some embodiments, ring A is tetrahydrofuranyl. In some embodiments, ring A is tetrahydropyranyl. In some embodiments, ring A is pyrrolidinyl. In some embodiments, ring A is cyclopentyl. In some embodiments, the monocyclic cycloalkyl or monocyclic heterocyclyl is not further substituted. In some embodiments, the cycloalkyl or heterocyclyl is further substituted with 0, 1, 2 or 3 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN.

[00204] In some embodiments, tetrahydrofuranyl is substituted with 1 or 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 2 substituents selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with 1 substituent selected from halo (*e.g.*, -F, -Cl), -OMe, -OEt -O(CH_2)OMe, -O(CH_2)$_2$OMe and CN. In some embodiments, tetrahydrofuranyl is substituted with -O(CH_2)$_2$OMe.

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

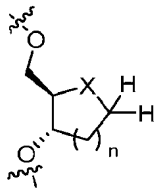


Formula (I)

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

n is 0, 1, 2 or 3.

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

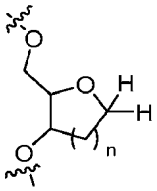


Formula (I')

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

n is 0, 1, 2 or 3.

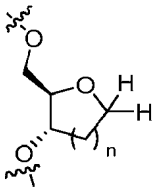
[00207] In some embodiments, the spacer is represented by Formula (Ia), wherein:



Formula (Ia)

and n is 0, 1, 2 or 3.

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



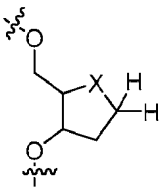
Formula (Ia')

and n is 0, 1, 2 or 3.

[00209] As generally defined herein, X is selected from -CH_2- and -O-. In some embodiments, X is -CH_2-. In other embodiments, X is -O-.

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

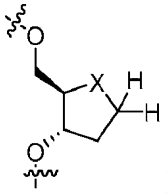
[00211] In some embodiments, the spacer is represented by Formula (II), wherein:



Formula (II)

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

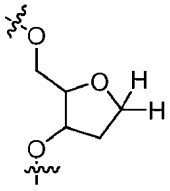
[00212] In some embodiments, the spacer is represented by Formula (II'), wherein:



Formula (II')

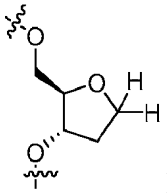
X is selected from -CH_2-and -O.

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



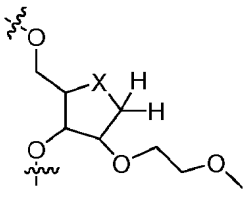
Formula (Iia).

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



Formula (Iia').

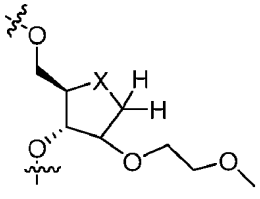
[00215] In some embodiments, the spacer is represented by Formula (IIi), wherein:



Formula (IIi)

X is selected from -CH_2- and -O-.

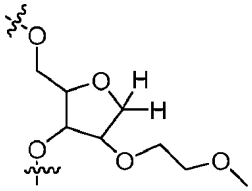
[00216] In some embodiments, the spacer is represented by Formula (IIi'), wherein:



Formula (IIi')

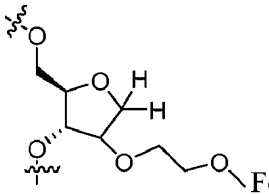
X is selected from -CH_2-and -O.

[00217] In some embodiments, the spacer is represented by Formula (IIib), wherein:



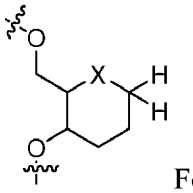
Formula (IIib).

[00218] In some embodiments, the spacer is represented by Formula (IIib'), wherein:



Formula (IIib').

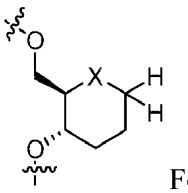
[00219] In some embodiments, the spacer is represented by Formula (III), wherein:



Formula (III)

X is selected from -CH_2- and -O-.

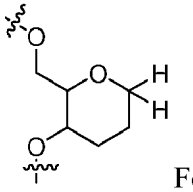
[00220] In some embodiments, the spacer is represented by Formula (III'), wherein:



Formula (III')

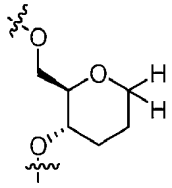
X is selected from -CH_2-and -O.

[00221] In some embodiments, the spacer is represented by Formula (IIIa), wherein:



Formula (IIIa).

[00222] In some embodiments, the spacer is represented by Formula (IIIa'), wherein:



Formula (IIIa').

[00223] In some embodiments, the open positions of Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') (*i.e.*, the positions not specifically depicted as bearing exclusively hydrogen atoms, including the -CH_2- group of X) are further substituted with 0-3 substituents independently selected from halo (*e.g.*, -F, -Cl), - OMe, -OEt -$O(CH_2)$OMe, -$O(CH_2)_2$OMe and CN. In some embodiments, Formulae (I), (I'), (Ia), (Ia'), (II), (II'), (Iia), (Iia'), (III), (III'), (IIIa) and (IIIa') are not further substituted.

[00224] As described further below, a UNC13A oligonucleotide with one or more spacers is described in reference to a corresponding UNC13A parent oligonucleotide or a corresponding UNC13A variant oligonucleotide. In various embodiments, a UNC13A oligonucleotide with a spacer differs from a UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide in that the spacer replaces a nucleoside in the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. As used hereafter, the "position" of the UNC13A oligonucleotide refers to a particular location as counted from the 5' end of the UNC13A oligonucleotide. In various embodiments, the spacer replaces a nucleoside at any one of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide. In particular embodiments, a spacer replaces a nucleoside at one of positions 7, 8, 11, 14, 16, 19, or 22 of the UNC13A parent oligonucleotide or an UNC13A variant oligonucleotide.

[00225] In various embodiments, a UNC13A oligonucleotide includes one spacer that replaces a nucleoside in the UNC13A oligonucleotide (e.g., one spacer replaces one nucleoside of the UNC13A oligonucleotide). In particular embodiments, the spacer replaces a nucleoside between positions 9 and 15 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between positions 9 and 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 10 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 12 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside between

positions 12 and 16 of the UNC13A oligonucleotide. In particular embodiments, the spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide.

[00226] In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 11 linked nucleosides. For example, the UNC13A oligonucleotide may be 23 oligonucleotide units in length, and the spacer can be located at position 12. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 11 nucleobases in length. In various embodiments, a UNC13A oligonucleotide including one spacer has 2 segments, where at least one of the 2 segments has at most 10 linked nucleosides. For example, the UNC13A oligonucleotide may be 21 oligonucleotide units in length, and the spacer can be located at position 11. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where both of the 2 segments are 10 nucleobases in length. As another example, the UNC13A oligonucleotide may be 25 oligonucleotide units in length, and the spacer can be located at position 15. Therefore, the UNC13A oligonucleotide has 2 segments divided by the spacer, where one of the 2 segments is 14 nucleobases in length and the second of the 2 segments is 10 nucleobases in length.

[00227] In various embodiments, a UNC13A oligonucleotide includes two spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., two spacers replace two separate nucleosides of the UNC13A oligonucleotide). In various embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, at least 7 nucleobases, at least 8 nucleobases, at least 9 nucleobases, or at least 10 nucleobases in the oligonucleotide. In particular embodiments, a first spacer and a second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases. In particular embodiments, the first spacer and the second spacer are not adjacent to one another in the oligonucleotide.

[00228] In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In various embodiments, the first spacer replaces a nucleoside between positions 8 and 11, positions 9 and 11, positions 10 and 11, positions 7 and 10, positions 7 and 9, positions 7 and 8, positions 8 and 10, positions 8 and 9, or positions 9 and 10 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In various embodiments, the second spacer replaces a nucleoside between positions 15 and 22, positions 16 and 22, positions 17 and 22, position 18 and 22, position 19 and 22, positions 20 and 22, positions 21 and 22, positions 15 and 21, position 16 and 21, positions 17 and 21, positions 18 and 21, positions 19 and 21, positions 20 and 21, positions 15 and 20, positions 16 and 20,

positions 17 and 20, positions 18 and 20, positions 19 and 20, positions 15 and 19, positions 16 and 19, positions 17 and 19, positions 18 and 19, positions 15 and 18, position 16 and 18, position 17 and 18, positions 15 and 17, positions 16 and 17, or positions 15 and 16 of the UNC13A oligonucleotide.

[00229] In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 14 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 7 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A parent oligonucleotide and the second spacer replaces a nucleoside at position 16 of the UNC13A parent oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 8 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 15 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 11 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 22 of the UNC13A oligonucleotide. In preferred embodiments, the first spacer replaces a nucleoside at position 9 of the UNC13A oligonucleotide and the second spacer replaces a nucleoside at position 19 of the UNC13A oligonucleotide.

[00230] In various embodiments, a UNC13A oligonucleotide includes three spacers that each replace a nucleoside in the UNC13A oligonucleotide (e.g., three spacers replace three separate nucleosides of the UNC13A oligonucleotide). In particular embodiments, the first spacer replaces a nucleoside between positions 7 and 11 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 14 and 22 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 21 and 24 of the UNC13A oligonucleotide. In some embodiments, the first spacer replaces a nucleoside between positions 2 and 5 of the UNC13A oligonucleotide. In particular embodiments, the second spacer replaces a nucleoside between positions 8 and 12 of the UNC13A oligonucleotide. In particular embodiments, the third spacer replaces a nucleoside between positions 18 and 22 of the UNC13A oligonucleotide.

[00231] In various embodiments, the three spacers in a UNC13A oligonucleotide are positioned such that each of the four segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. For example, a UNC13A oligonucleotide may have a first segment with 7 linked nucleosides connected to a first spacer, then a second segment with 7 linked nucleosides

connected on one end to the first spacer and connected on another end to a second spacer, then a third segment with 6 linked nucleosides connected on one end to the second spacer and connected on another end to a third spacer, then a fourth segment with 6 linked nucleosides connected to the third spacer.

[00232] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides (as opposed to guanine or cytosine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine adenosine or thymine nucleosides in the oligonucleotide. In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more guanine or cytosine nucleosides (as opposed to adenosine or thymine nucleosides). For example, the one or more spacers can replace one, two, three, four, five, six, seven, eight, or nine guanine or cytosine nucleosides in the oligonucleotide. In various embodiments, the spacers are positioned in the oligonucleotide to replace an equal number of adenosine/thymine nucleosides and guanine/cytosine nucleosides. For example, a first spacer in the oligonucleotide may replace an adenosine/thymine nucleoside and a second spacer in the oligonucleotide may replace a guanine/cytosine nucleoside.

[00233] In various embodiments, the one or more spacers are positioned in the oligonucleotide to control the sequence content in the oligonucleotide. For example, the one or more spacers are positioned such that at least one of the spacers is located adjacent to a guanine group. In various embodiments, an oligonucleotide with spacers can include one spacer adjacent to a guanine group, two spacers adjacent to guanine groups, three spacers adjacent to guanine groups, four spacers adjacent to guanine groups, or five spacers adjacent to guanine groups. In one embodiment, if counting from the 5' end of the oligonucleotide, a spacer immediately precedes a guanine group in the sequence. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately precedes a guanine group, two spacers that each immediately precede a guanine group, three spacers that each immediately precede a guanine group, four spacers that each immediately precede a guanine group, or five spacers that each immediately precede a guanine group. In one embodiment, if counting from the 5' end of the oligonucleotide, a guanine group is immediately succeeded by a spacer. Thus, in various embodiments, an oligonucleotide with spacers can include one spacer that immediately succeeds a guanine group, two spacers that each immediately succeed a guanine group, three spacers that each immediately succeed a guanine group, four spacers that each immediately succeed a guanine group, or five spacers that each immediately succeed a guanine group. In various

embodiments, the spacers in the oligonucleotide can be positioned to maximize the number of spacers adjacent to guanine groups.

[00234] In various embodiments, the one or more spacers are positioned in the oligonucleotide to replace one or more adenosine or thymine nucleosides such that the one or more spacers are located adjacent guanine groups. For example, two spacers can replace adenosine or thymine nucleosides in the oligonucleotide, each of the two spacers being located adjacent to a guanine group.

[00235] In various embodiments, the UNC13A oligonucleotide with one or more spacers has a particular GC content. As used herein, GC content (or guanine-cytosine content) is the percentage of nitrogenous bases in the oligonucleotide that are either guanine (G) or cytosine (C). In various embodiments, the UNC13A oligonucleotide with one or more spacers has at least 10% GC content, at least 20% GC content, at least 25% GC content, at least 30% GC content, at least 35% GC content, at least 40% GC content, at least 45% GC content, at least 50% GC content, at least 55% GC content, at least 60% GC content, at least 65% GC content, at least 75% GC content, at least 80% GC content, at least 85% GC content, at least 90% GC content, or at least 95% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 30% GC content. In particular embodiments, the UNC13A oligonucleotide with one or more spacers has at least 40% GC content. In various embodiments, the one or more spacers are positioned in the UNC13A oligonucleotide to maximize GC content. For example, instead of selecting a guanine or cytosine for replacement by a spacer in the UNC13A oligonucleotide, a thymine or adenine can be selected for replacement by a spacer.

[00236] In various embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) at least two, three, or four spacers are positioned adjacent to a guanine group. In some embodiments, a UNC13A oligonucleotide with spacers is designed such that 1) each segment of the UNC13A oligonucleotide has at most 7 linked nucleosides and 2) each of two spacers precede a guanine group.

[00237] In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in restoring full length UNC13A protein or full

length UNC13A mRNA in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide does not decrease the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a corresponding UNC13A parent oligonucleotide. In various embodiments, the inclusion of one or more spacers in the UNC13A oligonucleotide increases the effectiveness of the UNC13A oligonucleotide with the spacers in reducing quantity of UNC13A transcripts in comparison to the effect of a corresponding UNC13A parent oligonucleotide.

[00238] Tables 3A, 3B, 4, and 5 document example UNC13A oligonucleotides with one or more spacers and their relation to corresponding UNC13A parent oligonucleotides. Each UNC13A oligonucleotide is assigned a sequence name. As used hereafter, the nomenclature of the sequence name is expressed as "X_spA" (for a UNC13A AON with one spacer), "X_spA_spB" (for a UNC13A AON with two spacers), or "X_spA_spB_spC" (for a UNC13A AON with three spacers). Here, "X" refers to the length of the UNC13A AON, "A" refers to the position in the UNC13A AON where the first spacer is located, "B" refers to the position in the UNC13A AON where the second spacer is located, and if present, "C" refers to the position in the UNC13A AON where the third spacer is located.

[00239] In various embodiments, UNC13A oligonucleotides include one spacer. In various embodiments, the UNC13A oligonucleotides are oligonucleotide variants, such as any one of a 23mer, 21mer, or 19mer. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 11 linked nucleosides in length. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into two separate segments, where at least one of the segments is at most 10 linked nucleosides in length.

[00240] In various embodiments, the spacer is located between positions 10 and 15 of the oligonucleotide. In various embodiments, the spacer is located between positions 10 and 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 10 of the oligonucleotide. In particular embodiments, the spacer is located at position 11 of the oligonucleotide. In particular embodiments, the spacer is located at position 12 of the oligonucleotide. In particular embodiments, the spacer is located at position 15 of the oligonucleotide. Example UNC13A AONs with one spacer are documented below in Table 3A.

Table 3A: Identification of UNC13A AONs with one spacer. Here, each UNC13A AON has 2 segments, where at least one of the segments has at most 11 linked nucleosides.

Sequence name	**Relation to UNC13A oligonucleotide variant**	**~~Sequence ID Number (SEQ ID NO)~~**	**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A parent oligonucleotide	N/A	~~5066~~	XXXXXXXXXXXXXXXXXXXXXXXXX (25mer)
UNC13A Oligonucleotide (25mer) with Spacer at position 15 (UNC13A AON 25_sp15)	Nucleoside at position 15 of 25mer is substituted with a spacer	~~5067~~	XXXXXXXXXXXXXX$\mathbf{S_{15}}$XXXXXXXXXX
UNC13A oligonucleotide variant (23mer)	N/A	~~5068~~	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Oligonucleotide (23mer) with Spacer at position 12 (UNC13A AON 23_sp12)	Nucleoside at position 12 of 23mer is substituted with a spacer	~~5069~~	XXXXXXXXXXX$\mathbf{S_{12}}$XXXXXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A	~~5070~~	XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Oligonucleotide (21mer) with Spacer at position 11 (UNC13A AON 21_sp11)	Nucleoside at position 11 of 21mer is substituted with a spacer	~~5071~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX
UNC13A oligonucleotide variant (19mer)	N/A	~~5072~~	XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Oligonucleotide (19mer) with Spacer at position 10 (UNC13A AON 19_sp10)	Nucleoside at position 10 of 19mer is substituted with a spacer	~~5073~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate

(*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00241] In various embodiments, UNC13A oligonucleotides include two spacers. In various embodiments, the inclusion of a spacer divides up the UNC13A oligonucleotide into three separate segments, where at least one of the segments is at most 7 linked nucleosides in length. Example UNC13A AONs with two spacers are documented below in Table 3B.

Table 3B: Identification of UNC13A AONs with two spacers. Here, each UNC13A AON has 3 segments, where at least one of the segments has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A parent oligonucleotide**	~~**Sequence ID Number (SEQ ID NO)**~~	**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A parent oligonucleotide	N/A	~~5074~~	XXXXXXXXXXXXXXXXXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 22 (UNC13A AON 25_sp11sp22)	Nucleosides at positions 11 and 22 are each substituted with a spacer	~~5075~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXXX$\mathbf{S_{22}}$XXX
UNC13A Oligonucleotide with Spacers at positions 7 and 14 (UNC13A AON 25_sp7sp14)	Nucleosides at positions 7 and 14 are each substituted with a spacer	~~5076~~	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 19 (UNC13A AON 25_sp8sp19)	Nucleosides at positions 8 and 19 are substituted with spacers	~~5077~~	XXXXXXX$\mathbf{S_8}$XXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 14 (UNC13A AON 25_sp8sp14)	Nucleosides at positions 8 and 14 are substituted with spacers	~~5078~~	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 14 (UNC13A AON 25_sp9sp14)	Nucleosides at positions 9 and 14 are substituted with spacers	~~5079~~	XXXXXXXX$\mathbf{S_9}$XXXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 14 (UNC13A AON 25_sp10sp14)	Nucleosides at positions 10 and 14 are substituted with spacers	~~5080~~	XXXXXXXXX$\mathbf{S_{10}}$XXX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 14 (UNC13A AON 25_sp11sp14)	Nucleosides at positions 11 and 14 are substituted with spacers	~~5081~~	XXXXXXXXXX$\mathbf{S_{11}}$XX$\mathbf{S_{14}}$XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 15 (UNC13A AON 25_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	~~5082~~	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 15 (UNC13A AON 25_sp9sp15)	Nucleosides at positions 9 and 15 are substituted with spacers	~~5083~~	XXXXXXXX$\mathbf{S_9}$XXXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 15 (UNC13A AON 25_sp10sp15)	Nucleosides at positions 10 and 15 are substituted with spacers	~~5084~~	XXXXXXXXX$\mathbf{S_{10}}$XXXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 15 (UNC13A AON 25_sp11sp15)	Nucleosides at positions 11 and 15 are substituted with spacers	~~5085~~	XXXXXXXXXX$\mathbf{S_{11}}$XXX$\mathbf{S_{15}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 16 (UNC13A AON 25_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	~~5086~~	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 16 (UNC13A AON 25_sp9sp16)	Nucleosides at positions 9 and 16 are substituted with spacers	~~5087~~	XXXXXXXX$\mathbf{S_9}$XXXXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 16 (UNC13A AON 25_sp10sp16)	Nucleosides at positions 10 and 16 are substituted with spacers	~~5088~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 16 (UNC13A AON 25_sp11sp16)	Nucleosides at positions 11 and 16 are substituted with spacers	~~5089~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 17 (UNC13A AON 25_sp8sp17)	Nucleosides at positions 8 and 17 are substituted with spacers	~~5090~~	XXXXXXX$\mathbf{S_8}$XXXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 17 (UNC13A AON 25_sp9sp17)	Nucleosides at positions 9 and 17 are substituted with spacers	~~5091~~	XXXXXXXX$\mathbf{S_9}$XXXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 17 (UNC13A AON 25_sp10sp17)	Nucleosides at positions 10 and 17 are substituted with spacers	~~5092~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 17 (UNC13A AON 25_sp11sp17)	Nucleosides at positions 11 and 17 are substituted with spacers	~~5093~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXX$\mathbf{S_{17}}$XXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 18 (UNC13A ATON 25_sp8sp18)	Nucleosides at positions 8 and 18 are substituted with spacers	~~5094~~	XXXXXXX$\mathbf{S_8}$XXXXXXXXX$\mathbf{S_{18}}$XXXXXXX

UNC13A Oligonucleotide with Spacers at positions 9 and 18 (UNC13A AON 25_sp9sp18)	Nucleosides at positions 9 and 18 are substituted with spacers	~~5095~~	XXXXXXXX$\mathbf{S_9}$XXXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 18 (UNC13A AON 25_sp10sp18)	Nucleosides at positions 10 and 18 are substituted with spacers	~~5096~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 18 (UNC13A AON 25_sp11sp18)	Nucleosides at positions 11 and 18 are substituted with spacers	~~5097~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 19 (UNC13A AON 25_sp9sp19)	Nucleosides at positions 9 and 19 are substituted with spacers	~~5098~~	XXXXXXXX$\mathbf{S_9}$XXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 19 (UNC13A AON 25_sp10sp19)	Nucleosides at positions 10 and 19 are substituted with spacers	~~5099~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 19 (UNC13A AON 25_sp11sp19)	Nucleosides at positions 11 and 19 are substituted with spacers	~~5100~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 20 (UNC13A AON 25_sp9sp20)	Nucleosides at positions 9 and 20 are substituted with spacers	~~5101~~	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 20 (UNC13A AON 25_sp10sp20)	Nucleosides at positions 10 and 20 are substituted with spacers	~~5102~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXX$\mathbf{S_{20}}$XXXXX

UNC13A Oligonucleotide with Spacers at positions 11 and 20 (UNC13A AON 25_sp11sp20)	Nucleosides at positions 11 and 20 are substituted with spacers	~~5103~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 10 and 21 (UNC13A AON 25_sp10sp21)	Nucleosides at positions 10 and 21 are substituted with spacers	~~5104~~	XXXXXXXXX$\mathbf{S_{10}}$XXXXXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 11 and 21 (UNC13A AON 25_sp11sp21)	Nucleosides at positions 11 and 21 are substituted with spacers	~~5105~~	XXXXXXXXXX$\mathbf{S_{11}}$XXXXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 4 and 15 (UNC13A AON 25_sp4sp15)	Nucleosides at positions 4 and 15 are substituted with spacers	~~5106~~	XXXS_4XXXXXXXXXXS_{15}XXXXXXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 19 (UNC13A AON 25_sp7sp19)	Nucleosides at positions 7 and 19 are substituted with spacers	~~5107~~	XXXXXX$\mathbf{S_7}$XXXXXXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 18 (UNC13A AON 25_sp7sp18)	Nucleosides at positions 7 and 18 are substituted with spacers	~~5108~~	XXXXXX$\mathbf{S_7}$XXXXXXXXXX$\mathbf{S_{18}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 9 and 21 (UNC13A AON 25_sp9sp21)	Nucleosides at positions 9 and 21 are substituted with spacers	~~5109~~	XXXXXXXX$\mathbf{S_9}$XXXXXXXXXXX$\mathbf{S_{21}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate

(*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00242] In various embodiments, UNC13A oligonucleotides include three spacers. The inclusion of three spacers divides up the UNC13A oligonucleotide into four separate segments. In various embodiments, the three spacers are located at different positions of the UNC13A oligonucleotide such that each of the segments of the UNC13A oligonucleotide are at most 7 linked nucleosides in length. Example UNC13A AONs with three spacers are documented below in Table 4.

Table 4: Identification of UNC13A AONs or AON variants with three spacers. Here, each UNC13A AON has 4 segments, where each segment has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A parent oligonucleotide**	~~**Sequence ID Number (SEQ ID NO)**~~	**Sequence* (where *X* indicates a nucleoside of the UNC13A parent oligonucleotide and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 24 (UNC13A AON 25_sp8sp16sp24)	Nucleosides at positions 8 and 16 and 24 are substituted with spacers	~~5110~~	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX$\mathbf{S_{24}}$X
UNC13A Oligonucleotide with Spacers at positions 8 and 16 and 23 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 8 and 16 and 23 are substituted with spacers	~~5111~~	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXX$\mathbf{S_{23}}$XX
UNC13A Oligonucleotide with Spacers at positions 2 and 10 and 18 (UNC13A AON 25_sp8sp16sp23)	Nucleosides at positions 2 and 10 and 18 are substituted with spacers	~~5112~~	X$\mathbf{S_2}$XXXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 3 and 10	Nucleosides at positions 3 and 10 and 18	~~5113~~	XX$\mathbf{S_3}$XXXXXX$\mathbf{S_{10}}$XXXXXXX$\mathbf{S_{18}}$XXXXXXX

and 18 (UNC13A AON 25_sp8sp16sp23)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 4 and 12 and 19 (UNC13A AON 25_sp4sp12sp19)	Nucleosides at positions 4 and 12 and 19 are substituted with spacers	~~5114~~	XXX$\mathbf{S_4}$XXXXXXX$\mathbf{S_{12}}$XXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 13 and 18 (UNC13A AON 25_sp8sp13sp18)	Nucleosides at positions 8 and 13 and 18 are substituted with spacers	~~5115~~	XXXXXXX$\mathbf{S_8}$XXXX$\mathbf{S_{13}}$XXXX$\mathbf{S_{18}}$XXXXXXX
UNC13A Oligonucleotide with Spacers at positions 5 and 13 and 21 (UNC13A AON 25_sp5sp13sp21)	Nucleosides at positions 5 and 13 and 21 are substituted with spacers	~~5116~~	XXXX$\mathbf{S_5}$XXXXXXX$\mathbf{S_{13}}$XXXXXXX$\mathbf{S_{21}}$XXXX
UNC13A Oligonucleotide with Spacers at positions 7 and 13 and 19 (UNC13A AON 25_sp7sp13sp19)	Nucleosides at positions 7 and 13 and 19 are substituted with spacers	~~5117~~	XXXXXX$\mathbf{S_7}$XXXXX$\mathbf{S_{13}}$XXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 6 and 13 and 20 (UNC13A AON 25_sp6sp13sp20)	Nucleosides at positions 6 and 13 and 20 are substituted with spacers	~~5118~~	XXXXX$\mathbf{S_6}$XXXXXX$\mathbf{S_{13}}$XXXXXX$\mathbf{S_{20}}$XXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11 and 19 (UNC13A AON 25_sp8sp11sp19)	Nucleosides at positions 8 and 11 and 19 are substituted with spacers	~~5119~~	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXXXXX$\mathbf{S_{19}}$XXXXXX
UNC13A Oligonucleotide with Spacers at positions 8 and 11	Nucleosides at positions 8 and 11 and 16	~~5120~~	XXXXXXX$\mathbf{S_8}$XX$\mathbf{S_{11}}$XXXX$\mathbf{S_{16}}$XXXXXX

and 16 (UNC13A AON 23_sp8sp11sp16)	are substituted with spacers		
UNC13A Oligonucleotide with Spacers at positions 7 and 14 and 22 (UNC13A AON 23_sp7sp14sp22)	Nucleosides at positions 7 and 14 and 22 are substituted with spacers	~~5121~~	XXXXXX$\mathbf{S_7}$XXXXXX$\mathbf{S_{14}}$XXXXXXX$\mathbf{S_{22}}$XXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00243] In various embodiments, UNC13A AONs with one or more spacers are reduced in length in comparison to the UNC13A AONs described above in Tables 3B and 4. For example, such UNC13A AONs may be UNC13A oligonucleotide variants with one or more spacers. In various embodiments, the UNC13A oligonucleotide variants with one or more spacers are 23mers, 21mers, or 19mers. In various embodiments, UNC13A oligonucleotide variants include two spacers such that the UNC13A oligonucleotide variant includes three segments that are divided up by the two spacers. In various embodiments, at least one of the three segments has at most 7 linked nucleosides. In various embodiments, each of the three segments has at most 7 linked nueclosides. Example UNC13A oligonucleotide variants with one or more spacers are shown below in Table 5.

Table 5: Example UNC13A AON variants with two spacers. Here, each UNC13A AON variant has 3 segments, where at least one segment has at most 7 linked nucleosides.

Sequence name	**Relation to UNC13A oligonucleotide variant**	**~~Sequence ID Number (SEQ ID NO)~~**	**Sequence* (where *X* indicates a nucleoside of the UNC13A oligonucleotide variant and S_y indicates presence of a Spacer where *y* denotes the position)** (5' → 3')

UNC13A oligonucleotide variant (23mer)	N/A	~~5122~~	XXXXXXXXXXXXXXXXXXXXXXX (23mer)
UNC13A Variant Oligonucleotide (23mer) with Spacers at positions 8 and 16 (UNC13A AON variant 23_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	~~5123~~	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXXXX
UNC13A oligonucleotide variant (21mer)	N/A	~~5124~~	XXXXXXXXXXXXXXXXXXXXX (21mer)
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 5 and 12 (UNC13A AON variant 21_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	~~5125~~	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 16 (UNC13A AON variant 21_sp8sp16)	Nucleosides at positions 8 and 16 are substituted with spacers	~~5126~~	XXXXXXX$\mathbf{S_8}$XXXXXXX$\mathbf{S_{16}}$XXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 6 and 14 (UNC13A AON variant 21_sp6sp14)	Nucleosides at positions 6 and 14 are substituted with spacers	~~5127~~	XXXXX$\mathbf{S_6}$XXXXXXX$\mathbf{S_{14}}$XXXXXXX
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A	Nucleosides at positions 8 and 14 are substituted with spacers	~~5128~~	XXXXXXX$\mathbf{S_8}$XXXXX$\mathbf{S_{14}}$XXXXXXX

AON variant 21_sp8sp14)			
UNC13A Variant Oligonucleotide (21mer) with Spacers at positions 8 and 14 (UNC13A AON variant 21_sp8sp14)	Nucleosides at positions 6 and 20 are substituted with spacers	~~5129~~	XXXXX$\mathbf{S_6}$XXXXXXXXXXXXX$\mathbf{S_{20}}$X
UNC13A oligonucleotide variant (19mer)	N/A	~~5130~~	XXXXXXXXXXXXXXXXXXX (19mer)
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 5 and 12 (UNC13A AON variant 19_sp5sp12)	Nucleosides at positions 5 and 12 are substituted with spacers	~~5131~~	XXXX$\mathbf{S_5}$XXXXXX$\mathbf{S_{12}}$XXXXXXX
UNC13A Variant Oligonucleotide (19mer) with Spacers at positions 8 and 15 (UNC13A AON variant 19_sp8sp15)	Nucleosides at positions 8 and 15 are substituted with spacers	~~5132~~	XXXXXXX$\mathbf{S_8}$XXXXXX$\mathbf{S_{15}}$XXXX

* At least one nucleoside linkage of the nucleobase sequence is selected from a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

[00244] In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprise one or more spacers

as well as one or more locked nucleic acids (LNAs). In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and two LNAs. In some embodiments, an antisense oligonucleotide disclosed herein (e.g., UNC13A parent oligonucleotides and/or UNC13A oligonucleotide variants) comprises two spacers and three LNAs.

[00245] In various embodiments, a spacer and a LNA are located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 7th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 9th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 15th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a LNA can be located at a 17th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide.

[00246] In particular embodiments, a first spacer is located adjacent to a first LNA and a second spacer is located adjacent to a second LNA in an antisense oligonucleotide. For example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 15th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 7th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. As another example, if counting from 5' to 3', a first LNA can be located at a 9th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 17th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide.

[00247] In various embodiments, one or more spacers and one or more LNAs are not located adjacent to one another in an antisense oligonucleotide. For example, if counting from 5' to 3', a LNA can be located at a 4th position of the antisense oligonucleotide and a spacer can be located at a 8th position of the antisense oligonucleotide. As example, if counting from 5' to 3', a LNA

can be located at a 20th position of the antisense oligonucleotide and a spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 20th position of the antisense oligonucleotide, and a second spacer can be located at a 16th position of the antisense oligonucleotide. In particular embodiments, if counting from 5' to 3', a first LNA can be located at a 4th position of the antisense oligonucleotide, a first spacer can be located at a 8th position of the antisense oligonucleotide, a second LNA can be located at a 12th position of the antisense oligonucleotide, a second spacer can be located at a 16th position of the antisense oligonucleotide, and a third LNA can be located at a 20th position of the antisense oligonucleotide.

Performance of UNC13A Oligonucleotides

[00248] Generally, UNC13A oligonucleotides and/or UNC13A parent oligonucleotides (*e.g.*, UNC13A oligonucleotides with sequences of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~) target UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208 in order to increase, restore, rescue, or stabilize levels of expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein (*e.g.*, full length UNC13A). In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of mis-spliced UNC13A mRNA. In various embodiments, UNC13A AONs can exhibit at least a 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein. In various embodiments, UNC13A AONs can exhibit at least a 100%, 200%, 300%, or 400% increase of full length UNC13A protein. In some embodiments, the percent increase of the full length UNC13A protein is an increase in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide. For example, a TDP43 antisense oligonucleotide can be used to deplete full length UNC13A protein followed by increase of the full length UNC13A protein using a UNC13A AON.

[00249] In some embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein. In some embodiments, the percent rescue of full length UNC13A refers to the % of full length UNC13A following depletion using a TDP43 antisense oligonucleotide and a treatment using UNC13A AONs in comparison to a negative control (*e.g.*, cells that did not undergo depletion or treatment or cells that were treated with a vehicle solution).

[00250] In various embodiments, UNC13A AONs can exhibit at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon. In various embodiments, UNC13A AONs can exhibit at least a 100% reduction of an UNC13A transcript with a cryptic exon. In various embodiments, reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide. In various embodiments, UNC13A AONs can exhibit at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

Modifications

[00251] A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

[00252] Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased activity.

[00253] Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

[00254] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

[00255] Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

[00256] In certain embodiments, antisense compounds targeted to a UNC13A nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are interspersed throughout the antisense compound. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage. In certain embodiments, the antisense compounds targeted to a UNC13A nucleic acid comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Modified Sugar Moieties

[00257] Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substituent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or C(R_1)(R_2) (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (*see* PCT International Application WO 2008/101157 Published on Aug. 21, 2008 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl

ring oxygen atom with S with further substitution at the 2'-position (*see* published U.S. Patent Application US2005-0130923, published on Jun. 16, 2005) or alternatively 5'-substitution of a BNA (*see* PCT International Application WO 2007/134181 Published on Nov. 22, 2007 wherein LNA is substituted with for example a 5'-methyl or a 5'-vinyl group).

[00258] Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (R or 5), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-O CH_2 CH_2F and 2'-$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O—C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2S$ CH_3, $O(CH_2)_2$—O—$N(R_m)(R_n)$, O—CH_2—C(=O)—$N(R_m)(R_n)$, and O—CH_2—C(=O)—$N(R_1)$—($CH_2)_2$—$N(R_m)(R_n)$- , where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

[00259] Additional examples of modified sugar moieties include a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00260] As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)—O-2' (LNA); 4'-(CH_2)—S-2'; 4'-$(CH_2)_2$—O-2' (ENA); 4'-$CH(CH_3)$—O-2' and 4'-$CH(CH_2OCH_3)$—O-2' (and analogs thereof see U.S. Pat. No. 7,399,845, issued on Jul. 15, 2008); 4'-$C(CH_3)(CH_3)$—O-2' (and analogs thereof see published International Application WO/2009/006478, published Jan. 8, 2009); 4'-CH_2—$N(OCH_3)$-2' (and analogs thereof see published International Application WO/2008/150729, published Dec. 11, 2008); 4'-CH_2—O—$N(CH_3)$-2' (see published U.S. Patent Application US2004-0171570, published Sep. 2, 2004); 4'- CH_2—N(R)—O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008); 4'-CH_2—$C(H)(CH_3)$-2' (see Chattopadhyaya et al., J. Org. Chem., 2009, 74, 118-134); and 4'-CH_2—C—$(=CH_2)$-2' (and analogs thereof see published International Application WO 2008/154401, published on Dec. 8, 2008).

[00261] Further reports related to bicyclic nucleosides can also be found in published literature (*see* for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron,

1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U.S.A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 2007, 129(26) 8362-8379; Elayadi et al., Curr. Opinion Invest. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; and Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Ser. No. 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; and 61/099,844; Published PCT International applications WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; and WO 2009/006478. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on Mar. 25, 1999 as WO 99/14226).

[00262] In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from $—[C(R_a)(R_b)]_n—$, $—C(R_a)=C(R_b)—$, $—C(R_a)=N—$, $—C(=O)—$, $—C(=NR_a)—$, $—C(=S)—$, $—O—$, $—Si(R_a)_2—$, $—S(=O)_x—$, and $—N(R_a)—$; wherein:

x is 0, 1, or 2;

n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)—H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); and

each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group.

[00263] In certain embodiments, the bridge of a bicyclic sugar moiety is $—[C(R_a)(R_b)]_n—$, $—[—[C(R_a)(R_b)]_n—O—$, $—C(R_aR_b)—N(R)—O—$ or $—C(R_aR_b)—O—N(R)—$. In certain

embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2—O-2', 4'-$(CH_2)_2$—O-2', 4'-CH_2—O—N(R)-2' and 4'-CH_2—N(R)—O-2'- wherein each R is, independently, H, a protecting group or C_1-C_{12} alkyl, each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)—H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl or a protecting group; and R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00264] In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2—O-2') BNA's have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[00265] In certain embodiments, bicyclic nucleosides include, but are not limited to, α-L-methyleneoxy (4'-CH_2—O-2') BNA, β-D-methyleneoxy (4'-CH_2—O-2') BNA, ethyleneoxy (4'-$(CH_2)_2$—O-2) BNA, aminooxy (4'-CH_2—O—N(R)-2') BNA, oxyamino (4'-CH_2—N(R)—O-2') BNA, methyl(methyleneoxy) (4'-$CH(CH_3)$—O-2') BNA, methylene-thio (4'-CH_2—S-2') BNA, methylene-amino (4'-CH_2—N(R)-2') BNA, methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, and propylene carbocyclic (4'-$(CH_2)_3$-2') BNA; wherein R is H, C_1-C_{12} alkyl, or a protecting group (see U.S. Pat. No. 7,427,672, issued on Sep. 23, 2008).

[00266] The present disclosure provide, in some embodiments, methods for treating, ameliorating, or preventing a neurological disease and/or a neuropathy further include methods of administering, to a patient, a pharmaceutically acceptable composition, for example, a pharmaceutically acceptable formulation that includes one or more UNC13A oligonucleotides. UNC13A oligonucleotides can increase, restore, or stabilize UNC13A activity, for example, UNC13A activity, and/or levels of UNC13A expression, for example, UNC13A mRNA and/or protein expression.

[00267] The present disclosure also provides pharmaceutical compositions comprising a UNC13A oligonucleotide formulated together with one or more pharmaceutically or cosmetically acceptable excipients. These formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use, *e.g.*, as part of a composition suitable for applying topically to skin and/or mucous membrane, for example, a composition in the form of a gel, a paste, a wax, a cream, a spray, a liquid, a foam, a lotion, an ointment, a topical solution, a transdermal patch, a powder, a vapor, or a tincture. Although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular UNC13A oligonucleotide being used.

[00268] The present disclosure also provides a pharmaceutical composition comprising a UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof (for example, a UNC13A AON that includes a sequence of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~).

[00269] The present disclosure also provides methods that include the use of pharmaceutical compositions comprising a UNC13A AON is formulated together with one or more pharmaceutically acceptable excipients. Exemplary compositions provided herein include compositions comprising a UNC13A AON, and one or more pharmaceutically acceptable excipients. Formulations include those suitable for oral, sublingual, intratracheal, intranasal, transdermal, pulmonary, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, intraduodenal, or intravenous) administration, transmucosal (*e.g.*, buccal, vaginal, and rectal), or for topical use. The most suitable form of administration in any given case will depend on the clinical symptoms, complications, or biochemical indicia of the state, disorder, disease, or condition that one is trying to prevent in a subject; the state, disorder, disease, or condition one is trying to prevent in a subject; and/or on the nature of the particular compound and/or the composition being used.

Additional Chemically Modified UNC13A Oligonucleotides

[00270] UNC13A AONs described herein, can include chemically modified nucleosides, including modified ribonucleosides and modified deoxyribonucleosides. Chemically modified

nucleosides include, but are not limited to, uracine, uridine, 2'-O-(2-methoxyethyl) modifications, for example, 2'-O-(2-methoxyethyl)guanosine, 2'-O-(2-methoxyethyl)adenosine, 2'-O-(2-methoxyethyl)cytosine, and 2'-O-(2-methoxyethyl)thymidine. In certain embodiments, mixed modalities, *e.g.*, a combination of a UNC13A peptide nucleic acid (PNA) and a UNC13A locked nucleic acid (LNA). Chemically modified nucleosides also include, but are not limited to, locked nucleic acids (LNAs), 2'-O-methyl, 2'-fluoro, and 2'-fluoro-β-D-arabinonucleotide (FANA), and Fluoro Cyclohexenyl nucleic acid (F-CeNA) modifications. Chemically modified nucleosides that can be included in UNC13A AONs described herein are described in Johannes and Lucchino, (2018) "Current Challenges in Delivery and Cytosolic Translocation of Therapeutic RNAs" *Nucleic Acid Ther.* 28(3): 178–93; Rettig and Behlke, (2012) "Progress toward in vivo use of siRNAs-II" *Mol Ther* 20:483–512; and Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of each of which are incorporated by reference herein.

[00271] UNC13A AONs described herein can include chemical modifications that promote stabilization of an oligonucleotide's terminal 5'-phosphate and phosphatase-resistant analogs of 5′-phosphate. Chemical modifications that promote oligonucleotide terminal 5'-phosphate stabilization or which are phosphatase-resistant analogs of 5′-phosphate include, but are not limited to, 5′-methyl phosphonate, 5′-methylenephosphonate, 5′-methylenephosphonate analogs, 5′-*E*-vinyl phosphonate (5′-*E*-VP), 5′-phosphorothioate, and 5′-*C*-methyl analogs. Chemical modifications that promote AON terminal 5'-phosphate stabilization and phosphatase-resistant analogues of 5′-phosphate are described in Khvorova and Watts, (2017) "The chemical evolution of oligonucleotide therapies of clinical utility" *Nat Biotechnol.*, 35(3):238-48, the contents of which are incorporated by reference herein.

[00272] In some embodiments described herein, UNC13A AONs described herein can include chemically modified nucleosides, for example, 2' O-methyl ribonucleosides, for example, 2' O-methyl cytidine, 2' O-methyl guanosine, 2' O-methyl uridine, and/or 2' O-methyl adenosine. UNC13A AONs described herein can include one or more chemically modified bases, including a 5-methylpyrimidine, for example, 5-methylcytosine, and/or a 5-methylpurine, for example, 5-methylguanine. Chemically modified nucleosides can further include pseudo-uridine or 5'methoxyuridine. UNC13A AONs described herein can include any of the following chemically modified nucleosides: 5-methyl-2'-O-methylcytidine, 5-methyl-2'-O-methylthymidine, 5-methylcytidine, 5-methyluridine, and/or 5-methyl 2'-deoxycytidine.

[00273] UNC13A AONs described herein can include a phosphate backbone where one or more of the oligonucleoside linkages is a phosphate linkage. UNC13A AONs described herein may include a modified oligonucleotide backbone, where one or more of the nucleoside linkages of the sequence is selected from the group consisting of a phosphorothioate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate (*e.g.*, comprising a phosphorodiamidate morpholino (PMO), 3' amino ribose, or 5' amino ribose) linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage. In some embodiments of UNC13A AONs described herein, at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. For example, in some embodiments of UNC13A AONs described herein, one, two, three, or more internucleoside linkages of the oligonucleotide is a phosphorothioate linkage. In preferred embodiments of UNC13A AONs described herein, all internucleoside linkages of the oligonucleotide are phosphorothioate linkages. Thus, in some embodiments, all of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ are phosphorothioate linkages. In some embodiments, one or more of the nucleotide linkages of a UNC13A AON of any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ are phosphorothioate linkages.

[00274] In various embodiments, nucleotide linkages of UNC13A AON described herein such as any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ include a mix of phosphodiester and phosphorothioate linkages.

[00275] In some embodiments, nucleoside linkages linking a base at position 3 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 3 can be denoted as:

XXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00276] In some embodiments, one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 3 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00277] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00278] In various embodiments, in addition to one of the nucleoside linkages linking a base at position 3 of a UNC13A AON described herein being a phosphodiester bond, the UNC13A AON further includes two spacers. The two spacers can be positioned in the UNC13A AON such that the UNC13A AON includes a segment with at most 7 linked nucleosides. An example 25mer UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a preceding base can be denoted as:

XxoD$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXXXXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00279] An example 25mer UNC13A AON with two spacers and with a phosphodiester bond linking the base at position 3 to a succeeding base can be denoted as:

XXDoXXXXXXX$\mathbf{S}_1$XXXXXXXXX$\mathbf{S}_2$XXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond and "D" represents the base at position 3. Any nucleobase in the AON can be a nucleobase analog.

[00280] In some embodiments, nucleoside linkages linking a base at position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the base at position 4 can be denoted as:

XXXoDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00281] In some embodiments, one of the nucleoside linkages linking a base at position 4 of a UNC13A AON described herein is a phosphodiester bond. For example, the base at position 4 may be linked to either the preceding base or the succeeding base through a phosphodiester bond. An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a preceding base can be denoted as:

XXXoDXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00282] An example 25mer UNC13A AON with a phosphodiester bond linking the base at position 4 to a succeeding base can be denoted as:

XXXDoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond and "D" represents the base at position 4. Any nucleobase in the AON can be a nucleobase analog.

[00283] In some embodiments, nucleoside linkages linking both bases at position 3 and position 4 of a UNC13A AON described herein are phosphodiester bonds. For example, the base at position 3 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond, and the base at position 4 may be linked to each adjacent base (e.g., preceding base and succeeding base) through a phosphodiester bond. An example 25mer UNC13A AON with phosphodiester bonds linking the bases at positions 3 and 4 can be denoted as:

XXoDoEoXXXXXXXXXXXXXXXXXXXXX

where "o" represents a phosphodiester bond, "D" represents the base at position 3, and "E" represents the base at position 4. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00284] In various embodiments, UNC13A AON described herein include one or more spacers and phosphodiester bonds are located relative to the one or more spacers. In some embodiments, the Y number of bases immediately preceding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In particular embodiments, Y is two bases. For example, if the spacer is located at position 15, the bases at positions 13 and 14 of the UNC13A AON are each linked to their respective adjacent bases through phosphodiester bonds. As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the 2 bases immediately preceding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00285] In various embodiments, the UNC13A AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers are linked to respective preceding bases through phosphorothioate bonds. In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A AON have Y number of bases immediately preceding the spacers that are linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds.

[00286] In some embodiments, Y number of bases immediately preceding a spacer and Z number of bases immediately succeeding a spacer are linked through phosphodiester bonds. In various embodiments, Y is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. In various embodiments, Z is one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve bases. Y and Z can be independent of each other. In particular embodiments, Y is one base and Z is one base. For example, if the spacer is located at position 15, the bases at positions 14 and 16 of the UNC13A AON are each linked to their respective adjacent bases through phosphodiester bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXXXXXXXXXXoDo**S**oEoXXXXXXXXX

where "S" represents a spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00287] As described herein, the spacer can be located at various positions in the UNC13A AON and therefore, the bases immediately preceding or immediately succeeding the spacer can vary within the UNC13A AON depending on where the spacer is situated.

[00288] In various embodiments, the UNC13A AON may include more than one spacer. In some embodiments, only one of the spacers has Y number of bases immediately preceding the spacer and Z number of bases immediately succeeding the spacer that are linked through phosphodiester bonds. In such embodiments, the other spacers of the UNC13A AON are linked to respective preceding and succeeding bases through phosphorothioate bonds. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXoDo**S$_1$**oEoXXXXXXXXXXX**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00289] As another example, such a UNC13A AON (e.g., 25mer) can be denoted as:

XXXXX**S$_1$**XXXXXXXXXXXoDo**S$_2$**oDoXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the spacer, and "E" represents the base immediately succeeding the spacer. Any nucleobase in the AON can be a nucleobase analog.

[00290] In some embodiments, one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXo**S$_1$**XXXXXXXXXXX**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00291] As another example, a UNC13A AON includes a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S$_1$**XXXXXXXXXXXo**S$_2$**XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00292] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXXo**S**$_1$XXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00293] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately preceding base through a phosphodiester bond, which can be denoted as:

XXXXXXX**S**$_1$XXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00294] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately preceding base through a phosphodiester bond and the immediately preceding base is further linked to the preceding base through a phosphodiester bond. An example 21mer UNC13A AON can be denoted as:

XXXEoDo**S**$_1$XXXXXX**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00295] As another example, a 21mer UNC13A AON can be denoted as:

XXXXX**S**$_1$XXXXEoDo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Any nucleobase in the AON can be a nucleobase analog.

[00296] In some embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where a base that immediately precedes a first spacer is linked to another base through a phosphodiester bond. The base that immediately precedes the first spacer may be linked to the first spacer through a non-phosphodiester bond, such as a phosphorothioate bond. Additionally a second spacer is linked to an immediately preceding base through a phosphodiester bond. An example of a 21mer UNC13A AON can be denoted as:

XXXEoD**S**$_1$XXXXXXo**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_1 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the first spacer S_1 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The second spacer S_2 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00297] Another example of such a 21mer UNC13A AON can be denoted as:

XXXXXo**S**$_1$XXXXEoD**S**$_2$XXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents the base immediately preceding S_2 and "E" represents the base immediately preceding "D." Here, the base "D" is linked to the second spacer S_2 through a non-phosphodiester bond (e.g., phosphorothioate bond). Additionally, the base "D" is linked to base "E" through a phosphodiester bond. The first spacer S_1 is linked to an immediately preceding base through a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00298] In some embodiments, one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, a UNC13A AON includes a first spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S**$_1$oXXXXXXXXXXX**S**$_2$XXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00299] As another example, a UNC13A AON includes a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

XXXXXX**S**$_1$XXXXXXXXXXX**S**$_2$oXXXXXX

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00300] In various embodiments, the UNC13A AON may be a AON variant (e.g., a 23mer, a 21mer, or a 19mer) where one of the spacers is linked to the immediately succeeding base through a phosphodiester bond. For example, the UNC13A AON may be a 21mer with a first

spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1oXXXXX\mathbf{S}_2XXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00301] As another example, the UNC13A AON may be a 21mer with a second spacer that is linked to the immediately succeeding base through a phosphodiester bond, which can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXXX\mathbf{S}_2oXXXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond. Any nucleobase in the AON can be a nucleobase analog.

[00302] In various embodiments, two of the spacers have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. In various embodiments, each of the spacers in the UNC13A AON have Y number of bases immediately preceding the spacers and Z number of bases immediately succeeding the spacers that are linked through phosphodiester bonds. An example of such a UNC13A AON (e.g., 25mer) can be denoted as:

$$XXXXoDo\mathbf{S_1}oEoXXXXXXXXXXoFo\mathbf{S_2}oHoXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, "o" represents a phosphodiester bond, "D" represents a base immediately preceding the first spacer, "E" represents the base immediately succeeding the first spacer, "F" represents a base immediately preceding the second spacer, and "H" represents the base immediately succeeding the second spacer. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00303] In various UNC13A AON includes two or more spacers and a range of bases located between the two spacers are linked through phosphodiester bonds. In various embodiments, the range of bases include two, three, four, five, six, or seven bases linked through phosphodiester bonds. In particular embodiments, the range of bases include two bases linked through phosphodiester bonds. In particular embodiments, the range of bases include four bases linked through phosphodiester bonds. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00304] In various embodiments, the range of bases linked through phosphodiester bonds are positioned Y number of bases succeeding the first spacer and Z number of preceding the second spacer. In various embodiments, Y is one, two, three, four, five, six, or seven bases. In various embodiments, Z is one, two, three, four, five, six, or seven bases. Y and Z can be independent on each other. Any nucleobase in the AON can be a nucleobase analog.

[00305] In particular embodiments, Y is five bases and Z is four bases. To provide an example, such a UNC13A AON (e.g., 25mer) can be denoted as:

$$XXXXXXXX\mathbf{S}_1XXXXoDoEoFoHoXXX\mathbf{S}_2XXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D," "E," "F," and "H" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located five bases after the first spacer (e.g., D is positioned five bases after the first spacer) and the range of bases is located four bases preceding the second spacer (e.g., H is positioned four bases before the second spacer). Any nucleobase in the AON can be a nucleobase analog.

[00306] In particular embodiments, Y is four bases and Z is three bases. To provide an example, such a UNC13A AON (e.g., 23mer) can be denoted as:

$$XXXXXXX\mathbf{S}_1XXXoDoEoXX\mathbf{S}_2XXXXXX$$

where "S_1" represents a first spacer, "S_2" represents a second spacer, and "o" represents a phosphodiester bond. The bases "D" and "E" represent the range of bases that are linked through phosphodiester bonds. In this example, the range of bases is located four bases after the first spacer (e.g., D is positioned four bases after the first spacer) and the range of bases is located three bases preceding the second spacer (e.g., E is positioned three bases before the second spacer). In various embodiments, the positions of the two spacers differ than shown above and therefore, the range of bases linked through phosphodiester bonds are differently positioned. In various embodiments, all other bases of the UNC13A AON are linked through phosphorothioate bonds. Any nucleobase in the AON can be a nucleobase analog.

[00307] In some embodiments, a disclosed UNC13A AON may have at least one modified nucleobase, *e.g.*, 5-methylcytosine, and/or at least one methylphosphonate nucleotide, which is placed, for example, either at only one of the 5′ or 3′ ends or at both 5′ and 3′ ends or along the oligonucleotide sequence.

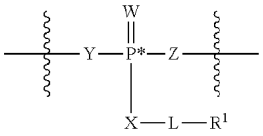
[00308] UNC13A AONs may include at least one modified sugar. For example, the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2′-OH group may be replaced by any one selected from the group consisting of OR, R, R′OR, SH, SR,

NH_2, NR_2, N_3, CN, F, Cl, Br, and I (wherein R is an alkyl or aryl and R′ is an alkylene). Examples of a modified sugar moiety include a 2'-Ome modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'MOE or MOE), 2'-O-(N-methylacetamide), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

[00309] In some embodiments, UNC13A AONs comprise 2'OMe (*e.g.*, a UNC13A AON comprising one or more 2'OMe modified sugar), 2'MOE or MOE (*e.g.*, a UNC13A AON comprising one or more 2'MOE modified sugar), PNA (*e.g.*, a UNC13A AON comprising one or more *N*-(2-aminoethyl)-glycine units linked by amide bonds or carbonyl methylene linkage as repeating units in place of a sugar-phosphate backbone), LNA (*e.g.*, a UNC13A AON comprising one or more locked ribose, and can be a mixture of 2'-deoxy nucleotides or 2'OMe nucleotides), c-ET (*e.g.*, a UNC13A AON comprising one or more cET sugar), cMOE (*e.g.*, a UNC13A AON comprising one or more cMOE sugar), morpholino oligomer (*e.g.*, a UNC13A AON comprising a backbone comprising one or more PMO), deoxy-2'-fluoro nucleoside (*e.g.*, a UNC13A AON comprising one or more 2'-fluoro-β-D-arabinonucleoside), tcDNA (*e.g.*, a UNC13A AON comprising one or more tcDNA modified sugar), ENA (*e.g.*, a UNC13A AON comprising one or more ENA modified sugar), or HNA (*e.g.*, a UNC13A AON comprising one or more HNA modified sugar). In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, morpholino linkage, PNA linkage, or any combination of phosphorothioate linkage, phosphodiester linkage, a phosphotriester linkage, methylphosphonate linkage, phosphoramidate linkage, morpholino linkage, and PNA linkage. In some embodiments, a UNC13A AON comprises one or more phosphorothioate linkage, phosphodiester linkage, or a combination of phosphorothioate and phosphodiester linkages.

[00310] In some embodiments, UNC13A AONs with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ is a chirally controlled oligonucleotide, such as a chirally controlled oligonucleotide described in any of US Patent No. 9,982,257, US Patent No. 10,590,413, US 10,724,035, US 10,450,568, and PCT Publication No. WO2019200185, each of which is hereby incorporated by reference in its entirety.

[00311] For example, a UNC13A AON with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and ~~55292~~ is a chirally controlled oligonucleotide comprising a plurality of oligonucleotides of at least one type, wherein each type is defined by: 1) base sequence; 2) pattern of backbone linkages; 3) pattern of backbone chiral centers; and 4) pattern of backbone X-moieties (—X-L-R^1); wherein: the oligonucleotides of the at least one type comprise one or more phosphorothioate triester internucleotidic linkages and one or more phosphate diester linkage; the oligonucleotides of the at least one type comprise at least two consecutive modified internucleotidic linkages; and oligonucleotides of the at least one oligonucleotide type comprise one or more modified internucleotidic linkages independently having the structure of:



wherein: P* is an asymmetric phosphorus atom and is either Rp or Sp;

W is O, S or Se; each of X, Y and Z is independently —O—, —S—, —N(-L-R^1)—, or L; L is a covalent bond or an optionally substituted, linear or branched C_1-C_{50} alkylene, wherein one or more methylene units of L are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; R^1 is halogen, R, or an optionally substituted C_1-C_{10} aliphatic wherein one or more methylene units are optionally and independently replaced by an optionally substituted C_1-C_6 alkylene, C_1-C_6 alkenylene, —C≡C—, —C(R′)$_2$—, -Cy-, —O—, —S—, —S—S—, —N(R′)—, —C(O)—, —C(S)—, —C(NR′)—, —C(O)N(R′)—, —N(R′)C(O)N(R′)—, —N(R′)C(O)—, —N(R′)C(O)O—, —OC(O)N(R′)—, —S(O)—, —S(O)$_2$—, —S(O)$_2$N(R′)—, —N(R′)S(O)$_2$—, —SC(O)—, —C(O)S—, —OC(O)—, or —C(O)O—; each R′ is independently —R, —C(O)R, —CO$_2$R, or —SO$_2$R, or: two R′ on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heterocyclic or heteroaryl ring, or two R′ on the same carbon are taken together with their intervening atoms to form an optionally substituted aryl, carbocyclic, heterocyclic, or heteroaryl ring; -Cy- is an optionally substituted bivalent ring selected from phenylene, carbocyclylene, arylene, heteroarylene, or heterocyclylene; each R is independently hydrogen, or an optionally

substituted group selected from C_1-C_6 aliphatic, phenyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl; and each  independently represents a connection to a nucleoside. In some embodiments, a UNC13A AON with a sequence of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 ~~5292~~is a chirally controlled oligonucleotide comprising certain chemical modifications (e.g., 2'F (2' Fluoro, which contains a fluorine molecule at the 2' ribose position (instead of 2'-hydroxyl group in an RNA monomer)), 2'-OMe, phosphorothioate linkages, lipid conjugation, etc.), as described in U.S. Patent No. 10,450,568.

Motor Neuron Diseases

[00312] Motor neuron diseases are a group of diseases characterized by loss of function of motor neurons that coordinate voluntary movement of muscles by the brain. Motor neuron diseases may affect upper and/or lower motor neurons, and may have sporadic or familial origins. Motor neuron diseases include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, post-polio syndrome, and ALS with frontotemporal dementia.

[00313] Symptoms of motor neuron diseases include muscle decay or weakening, muscle pain, spasms, slurred speech, difficulty swallowing, loss of muscle control, joint pain, stiff limbs, difficulty breathing, drooling, and complete loss of muscle control, including over basic functions such as breathing, swallowing, eating, speaking, and limb movement. These symptoms are also sometimes accompanied by depression, loss of memory, difficulty with planning, language deficits, altered behavior, and difficulty assessing spatial relationships and/or changes in personality.

[00314] Motor neuron diseases can be assessed and diagnosed by a clinician of skill, for example, a neurologist, using various tools and tests. For example, the presence or risk of developing a motor neuron disease can be assessed or diagnosed using blood and urine tests (for example, tests that assay for the presence of creatinine kinase), magnetic resonance imaging (MRI), electromyography (EMG), nerve conduction study (NCS), spinal tap, lumbar puncture, and/or muscle biopsy. Motor neuron diseases can be diagnosed with the aid of a physical exam and/or a neurological exam to assess motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior.

Amyotrophic Lateral Sclerosis

[00315] ALS is a progressive motor neuron disease that disrupts signals to all voluntary muscles. ALS results in atrophy of both upper and lower motor neurons. Symptoms of ALS include weakening and wasting of the bulbar muscles, general and bilateral loss of strength, spasticity, muscle spasms, muscle cramps, fasciculations, slurred speech, and difficulty breathing or loss of ability to breathe. Some individuals with ALS also suffer from cognitive decline. At the molecular level, ALS is characterized by protein and RNA aggregates in the cytoplasm of motor neurons, including aggregates of the RNA-binding protein TDP43.

[00316] ALS is most common in males above 40 years of age, although it can also occur in women and children. Risk of ALS is also heightened in individuals who smoke, are exposed to chemicals such as lead, or who have served in the military. Most instances of ALS are sporadic, while only about 10% of cases are familial. Causes of ALS include sporadic or inherited genetic mutations, high levels of glutamate, protein mishandling. Genetic mutations associated with ALS include mutations in the genes SOD1, C9orf72, TARDBP, FUS, ANG, ATXN2, CHCHD10, CHMP2B, DCTN1, ErbB4, FIG4, HNRPA1, MATR3, NEFH, OPTN, PFN1, PRPH, SETX, SIGMAR1, SMN1, SPG11, SQSTM1, TBK1, TRPM7, TUBA4A, UBQLN2, VAPB, and VCP.

Frontotemporal Dementia

[00317] Frontotemporal dementia (FTD) is a form of dementia that affects the frontal and temporal lobes of the brain. FTD includes frontotemporal lobar degeneration (FTLD). It has an earlier average age of onset than Alzheimer's disease – 40 years of age. Symptoms of FTD include extreme changes in behavior and personality, speech and language problems, and movement-related symptoms such as tremor, rigidity, muscle spasm, weakness, and difficulty swallowing. Subtypes of FTD include behavior variant frontotemporal dementia (bvFTD), characterized by changes in personality and behavior, and primary progressive aphasia (PPA), which affects language skills, speaking, writing and comprehension. FTD is associated with tau protein accumulation (Pick bodies) and altered TDP43 function. About 30% of cases of FTD are familial, and no other risk factors other than family history of the disease are known. Genetic mutations associated with FTD include mutations in the genes C9orf72, Progranulin (GRN), microtubule-associated protein tau (MAPT), UBQLN2, VPC, CHMP2B, TARDBP, FUS, ITM2B, CHCHD10, SQSTM1, PSEN1, PSEN2, CTSF, CYP27A1, TBK1 and TBP.

Amyotrophic lateral sclerosis with frontotemporal dementia

[00318] Amyotrophic lateral sclerosis with frontotemporal dementia (ALS with FTD) is a clinical syndrome in which FTD and ALS occur in the same individual. Interestingly, mutations in C9orf72 are the most common cause of familial forms of ALS and FTD. Additionally, mutations in TBK1, VCP, SQSTM1, UBQLN2 and CHMP2B are also associated with ALS with FTD. Symptoms of ALS with FTD include dramatic changes in personality, as well as muscle weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and degeneration of the spinal cord, motor neurons, and frontal and temporal lobes of the brain. At the molecular level, ALS with FTD is characterized by the accumulation of TDP-43 and/or FUS proteins. TBK1 mutations are associated with ALS, FTD, and ALS with FTD.

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

[00319] Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by accumulation of misfolded TDP-43 protein in the brain, specifically in the limbic system. LATE is a neurological disorder that typically manifests in older patients (e.g., greater than 80 years old). LATE can be a diagnosis for dementia and LATE often mimics the symptoms of Alzheimer's Disease including memory loss, confusion, and mood changes.

Methods of Treatment

[00320] The disclosure contemplates, in part, treating neurological diseases including any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), Limbic-predominant age-related TDP-43 encephalopathy (LATE), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism) in a patient in need thereof comprising administering a UNC13A AON. In some embodiments, provided herein are methods for treatment of a neurological disease in a patient in need thereof, comprising administering a disclosed UNC13A AON. In some embodiments of the disclosure, an effective amount of a disclosed UNC13A oligonucleotide may be administered to a patient in need thereof to treat a neurological disease, and/or to increase, restore, or stabilize expression of UNC13A mRNA that is capable of translation to produce a functional UNC13A protein, thereby increase, restore, or stabilize UNC13A activity and/or function.

[00321] In some embodiments, treating a neurological disease comprises at least ameliorating or reducing one symptom associated with the neurological disease (for example, reducing muscle weakness in a patient with ALS). Methods of treating a neurological disease (for example, ALS, FTD, or ALS with FTD) in a patient suffering therefrom are provided, that include administering a disclosed UNC13A AON. In some embodiments, methods of slowing the progression of a neurological disease, for example, a motor neuron disease, are provided.

[00322] Provided herein are methods of treating, reducing the risk of developing, or delaying the onset of a neurological disease in a subject in need thereof comprising administering a disclosed UNC13A AON. The methods include for example, treating a subject at risk of developing a neurological disease; *e.g.*, administering to the subject an effective amount of a disclosed UNC13A AON. Neurological diseases that can be treated in this manner include motor neuron diseases, ALS, FTD, ALS with FTD, progressive bulbar palsy, pseudobulbar palsy, progressive muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and post-polio syndrome.

[00323] Methods of preventing or treating neurological diseases (for example, PD, ALS, FTD, and ALS with FTD) form part of this disclosure. Such methods may comprise administering to a patient in need thereof or a patient at risk, a pharmaceutical preparation comprising a UNC13A AON disclosed herein. For example, a method of preventing or treating a neurological disease is provided comprising administering to a patient in need thereof a UNC13A AON disclosed herein.

[00324] Patients treated using an above method may experience an increase, restoration of, or stabilization of UNC13A mRNA expression, which is capable of translation to produce a functional UNC13A protein, of at least about 5%, 10%, 20%, 30%, 40% or even 50%, thereby increase, restore, or stabilize UNC13A activity and/or function in a target cell (for example, a motor neuron) after administering a UNC13A oligonucleotide *e.g.* after 1 day, 2 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 1 month, 2 months, 3, months, 4 months, 5, months, or 6 months or more. In some embodiments, administering such a UNC13A oligonucleotide may be on, *e.g.*, at least a daily basis. The UNC13A oligonucleotide may be administered orally. In some embodiments, the UNC13A oligonucleotide is administered intrathecally, intrathalamically, or intracisternally. For example, in an embodiment described herein, a UNC13A oligonucleotide is administered intrathecally, intrathalamically or intracisternally about every 3 months. The delay or amelioration of clinical manifestation of a neurological disease in a patient as a consequence of administering a UNC13A oligonucleotide disclosed here may be at least *e.g.*, 6 months, 1 year, 18 months or even 2 years or more as

compared to a patient who is not administered a UNC13A oligonucleotide, such as one disclosed herein.

[00325] UNC13A oligonucleotides can be used alone or in combination with each other whereby at least two UNC13A oligonucleotides are used together in a single composition or as part of a treatment regimen. UNC13A oligonucleotides may also be used in combination with other drugs or AON for treating neurological diseases or conditions.

[00326] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00327] In various embodiments, disclosed herein is a method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221,

or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

[00328] In various embodiments, disclosed herein is a method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof; wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or wherein at least one

(*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally wherein the oligonucleotide further comprises a spacer.

Treatment and Evaluation

[00329] A patient, as described herein, refers to any animal at risk for, suffering from or diagnosed with a neurological disease, including, but not limited to, mammals, primates, and humans. In certain embodiments, the patient may be a non-human mammal such as, for example, a cat, a dog, or a horse. A patient may be an individual diagnosed with a high risk of developing a neurological disease, someone who has been diagnosed with a neurological disease, someone who previously suffered from a neurological disease, or an individual evaluated for symptoms or indications of a neurological disease, for example, any of the signs or symptoms associated with neurological diseases such as: amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

[00330] "A patient in need," as used herein, refers to a patient suffering from any of the symptoms or manifestations of a neurological disease, a patient who may suffer from any of the symptoms or manifestations of a neurological disease, or any patient who might benefit from a method of the disclosure for treating a neurological disease. A patient in need may include a patient who is diagnosed with a risk of developing a neurological disease, a patient who has suffered from a neurological disease in the past, or a patient who has previously been treated for a neurological disease.

[00331] "Effective amount," as used herein, refers to the amount of an agent that is sufficient to at least partially treat a condition when administered to a patient. The therapeutically effective amount will vary depending on the severity of the condition, the route of administration of the component, and the age, weight, etc. of the patient being treated. Accordingly, an effective amount of a disclosed UNC13A oligonucleotide is the amount of the UNC13A oligonucleotide necessary to treat a neurological disease in a patient such that administration of the agent prevents a neurological disease from occurring in a subject, prevents neurological disease progression (*e.g.*, prevents the onset or increased severity of symptoms of the neurological such as muscle weakening, spasms, or fasciculation), or relieves or completely ameliorates all associated symptoms of a neurological disease, *i.e.* causes regression of the disease.

[00332] Efficacy of treatment may be evaluated by means of evaluation of gross symptoms associated with a neurological disease, analysis of tissue histology, biochemical assay, imaging methods such as, for example, magnetic resonance imaging, or other known methods. For instance, efficacy of treatment may be evaluated by analyzing gross symptoms of the disease such as changes in muscle strength and control or other aspects of gross pathology associated with a neurological disease following administration, to a patient suffering from a neurological disease, a disclosed UNC13A oligonucleotide.

[00333] Efficacy of treatment may also be evaluated at the tissue or cellular level, for example, by means of obtaining a tissue biopsy (*e.g.*, a brain, spinal, muscle, motor neuron tissue biopsy, or olfactory neurosphere cell biopsy) and evaluating gross tissue or cell morphology or staining properties. Biochemical assays that examine protein or RNA expression may also be used to evaluate efficacy of treatment. For instance, one may evaluate levels of a protein or gene product indicative of a neurological disease, in dissociated cells or non-dissociated tissue via immunocytochemical, immunohistochemical, Western blotting, or Northern blotting methods, or methods useful for evaluating RNA levels such as quantitative or semi-quantitative polymerase chain (*e.g.*, digital PCR (DigitalPCR, dPCR, or dePCR), qPCR etc.) reaction. One may also evaluate the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43 or p75 extracellular domain ($p75^{ECD}$)) found in spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, exosome-like cerebrospinal fluid extracellular vesicles ("CSF exosomes"), such as those described in Welton *et al.*, (2017) "Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery in neurological disease; multiple sclerosis" *J Extracell Vesicles.*, 6(1):1-10; and Street *et al.*, (2012) "Identification and proteomic profiling of exosomes in human cerebrospinal fluid" *J*

Transl. Med., 10:5), urine, fecal matter, lymphatic fluid, blood, plasma, or serum to evaluate disease state and efficacy of treatment. One may also evaluate the presence or level of expression of useful biomarkers found in the plasma, neuronal extracellular vesicles/exosomes. Additional measurements of efficacy may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential (CMAP), and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease status and survival in *C9ORF72*-associated amyotrophic lateral sclerosis (c9ALS) patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00334] In evaluating efficacy of treatment, suitable controls may be chosen to ensure a valid assessment. For instance, one can compare symptoms evaluated in a patient with a neurological disease following administration of a disclosed UNC13A oligonucleotide to those symptoms in the same patient prior to treatment or at an earlier point in the course of treatment or in another patient not diagnosed with the neurological disease. Alternatively, one may compare the results of biochemical or histological analysis of tissue following administration of a disclosed UNC13A oligonucleotide with those of tissue from the same patient or from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. Additionally, one may compare blood, plasma, serum, cell, urine, lymphatic fluid, spinal cord fluid, cerebrospinal fluid, or fecal samples following administration of the UNC13A oligonucleotide with comparable samples from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide. In some embodiments one may compare extracellular vesicles (for example CSF exosomes), following administration of the UNC13A oligonucleotide with extracellular vesicles from an individual not diagnosed with the neurological disease or from the same patient prior to administration of the UNC13A oligonucleotide.

[00335] Validation of UNC13A oligonucleotides may be determined by direct or indirect assessment of UNC13A expression levels or activity. For instance, biochemical assays that measure UNC13A protein or RNA expression may be used to evaluate overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to

any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. For instance, one may measure UNC13A protein levels in cells or tissue by Western blot to evaluate overall UNC13A levels. One may also measure UNC13A mRNA levels by means of Northern blot or quantitative polymerase chain reaction to determine overall effect on UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. One may also evaluate UNC13A protein levels or levels of another protein indicative of UNC13A signaling activity in dissociated cells, non-dissociated tissue, extracellular vesicles (for example, CSF exosomes), blood, serum, or fecal matter via immunocytochemical or immunohistochemical methods.

[00336] Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of useful biomarkers (*e.g.*, neurofilament light (NEFL), neurofilament heavy (NEFH), TDP-43, or $p75^{ECD}$ found in plasma, spinal cord fluid, cerebrospinal fluid, extracellular vesicles (for example, CSF exosomes), blood, urine, lymphatic fluid, fecal matter, or tissue to evaluate the modulation of expression of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208. Modulation of expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208 may also be evaluated indirectly by measuring parameters such as autophagy, endocytosis, protein aggregation, and the presence or level of expression of physiological biomarkers such as compound muscle action potential (CMAP). Additional measurements may include strength duration time constant (SDTC), short interval cortical inhibition (SICI), dynamometry, accurate test of limb isometric strength (ATLIS), compound muscle action potential, and ALSFRS-R. In certain embodiments, urinary neurotrophin receptor p75 extracellular domain ($p75^{ECD}$) is a disease progression and prognostic biomarker in amyotrophic lateral sclerosis (ALS). Phosphorylated neurofilament heavy chain (pNFH) in cerebrospinal fluid (CSF) predict disease

status and survival in c9ALS patients. CSF pNFH as a prognostic biomarker for clinical trials, which will increase the likelihood of successfully developing a treatment for c9ALS.

[00337] The disclosure also provides methods of restoring expression of full length UNC13A transcripts in cells of a patient suffering from a neurological disease. Full length UNC13A transcripts may be restored in any cell in which UNC13A expression or activity occurs, including cells of the nervous system (including the central nervous system (e.g., spinal cord or brain), the peripheral nervous system, motor neurons, glial cells, astrocytes, oligodendrocytes, microglia, the brain, the brain stem, the frontal lobes, the temporal lobes, the spinal cord), the musculoskeletal system, spinal fluid, and cerebrospinal fluid. Cells of the musculoskeletal system include skeletal muscle cells (*e.g.*, myocytes). Motor neurons include upper motor neurons and lower motor neurons.

Pharmaceutical Compositions and Routes of Administration

[00338] The present disclosure also provides methods for treating a neurological disease via administration of a pharmaceutical composition comprising a disclosed UNC13A oligonucleotide. In another aspect, the disclosure provides a pharmaceutical composition for use in treating a neurological disease. The pharmaceutical composition may be comprised of a disclosed UNC13A oligonucleotide, and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutical composition" means, for example, a mixture containing a specified amount of a therapeutic compound, *e.g.*, a therapeutically effective amount, of a therapeutic compound in a pharmaceutically acceptable carrier to be administered to a mammal, *e.g.*, a human, in order to treat a neurological disease. In some embodiments, described herein are pharmaceutical compositions comprising a disclosed UNC13A oligonucleotide, and a pharmaceutically acceptable carrier. In another aspect, the disclosure provides use of a disclosed UNC13A oligonucleotide in the manufacture of a medicament for treating a neurological disease. "Medicament," as used herein, has essentially the same meaning as the term "pharmaceutical composition."

[00339] As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings,

isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. In one embodiment the pharmaceutical composition is administered orally and includes an enteric coating suitable for regulating the site of absorption of the encapsulated substances within the digestive system or gut. For example, an enteric coating can include an ethylacrylate-methacrylic acid copolymer.

[00340] In one embodiment, a disclosed UNC13A oligonucleotide and any pharmaceutical composition thereof may be administered by one or several routes, including topically, intrathecally, intrathalamically, intracisternally, intracerebroventricularly, parenterally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, or intraduodenally. The term parenteral as used herein includes subcutaneous injections, intrapancreatic administration, intravenous, intracisternal, intracerebroventricular, intrathecal, intrathalamic, intramuscular, intraperitoneal, intrasternal injection or infusion techniques. For example, a disclosed UNC13A oligonucleotide may be administered subcutaneously to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered orally to a subject. In another example, a disclosed UNC13A oligonucleotide may be administered directly to the nervous system, or specific regions or cells of the nervous system (*e.g.*, the brain, brain stem, lower motor neurons, spinal cord, upper motor neurons) via parenteral administration, for example, a disclosed UNC13A oligonucleotide may be administered intrathecally, intrathalamically intracisternally, or intracerebroventricularly.

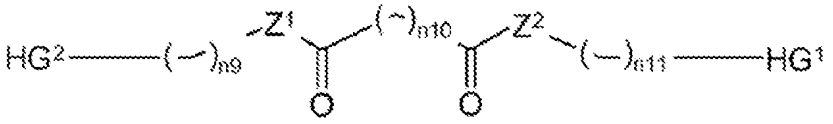
[00341] In various embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be exposed to calcium-containing buffers prior to administration. Such calcium-containing buffers can mitigate toxicity adverse effects of the UNC13A oligonucleotide. Further details of exposing an example antisense oligonucleotide to calcium-containing buffers is described in Moazami, et al., Quantifying and Mitigating Motor Phenotypes Induced by Antisense Oligonucleotides in the Central Nervous System, bioRxiv 2021.02.14.431096, which is hereby incorporated by reference in its entirety.

[00342] In some embodiments, a UNC13A oligonucleotide, for example a UNC13A AON, can be encapsulated in a nanoparticle coating. It is believed that nanoparticle encapsulation prevents AON degradation and enhances cellular uptake. For example, in some embodiments a UNC13A oligonucleotide is encapsulated in a coating of a cationic polymer, for example, a synthetic polymer (*e.g.*, poly-L-lysine, polyamidoamine, a poly(β-amino ester), and polyethyleneimine) or a naturally occurring polymer (*e.g.*, chitosan and a protamine). In some embodiments, a

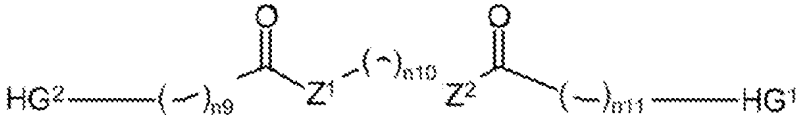
UNC13A oligonucleotide is encapsulated in a lipid or lipid-like material, for example, a cationic lipid, a cationic lipid-like material, or an ionizable lipid that is positively charged only at an acidic pH. An example of a lipid nanoparticle nucleotide therapy includes Exicure's XCUR-FXN, a lipid-nanoparticle spherical nucleic acid (SNA)-based therapeutic candidate. For example, in some embodiments, a UNC13A oligonucleotide is encapsulated in a lipid nanoparticle that includes hydrophobic moieties, *e.g.*, cholesterol and/or a polyethylene glycol (PEG) lipid.

[00343] In various embodiments, a pharmaceutical composition comprising a disclosed UNC13A oligonucleotide may further comprise a bolaamphiphilic compound. Example bolaamphiphilic compounds are described in WO2014039493A1, WO2014039500A1, WO2014039502A1, WO2014039503A1, and WO2014039504A1, each of which is hereby incorporated by reference in its entirety. In particular embodiments, a bolaamphiphilic compound is a compound according to formula I: HG^2 L^1 HG^1, or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, isotopic variant, or N-oxide thereof, or a combination thereof; wherein: each HG^1 and HG^2 is independently a hydrophilic head group; and L^1 is alkylene, alkenyl, heteroalkylene, or heteroalkenyl linker; unsubstituted or substituted with C1-C20 alkyl, hydroxyl, or oxo.

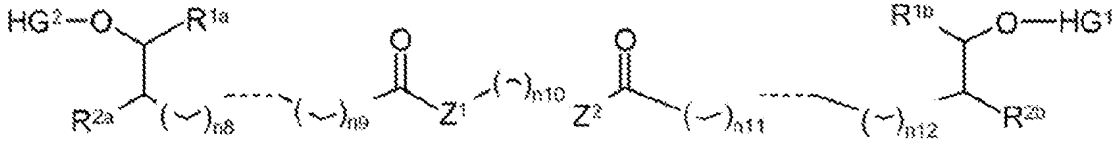
[00344] In one embodiment, with respect to the bolaamphiphilic compound of formula I, the bolaamphiphilic compound is a compound according to formula II, III, IV, V, or VI:



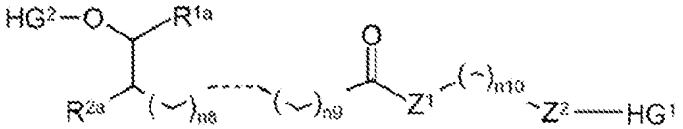
II



III

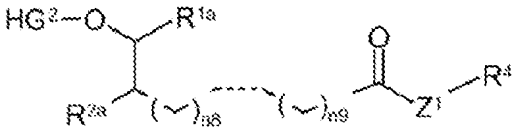


IV



V

; or



VI

[00345] or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, stereoisomer, tautomer, isotopic variant, or N-oxide thereof, or a combination thereof;

wherein:

each HG^1 and HG^2 is independently a hydrophilic head group;

each Z^1 and Z^2 is independently $-C(R^3)_2-$, $-N(R^3)-$ or -0-;

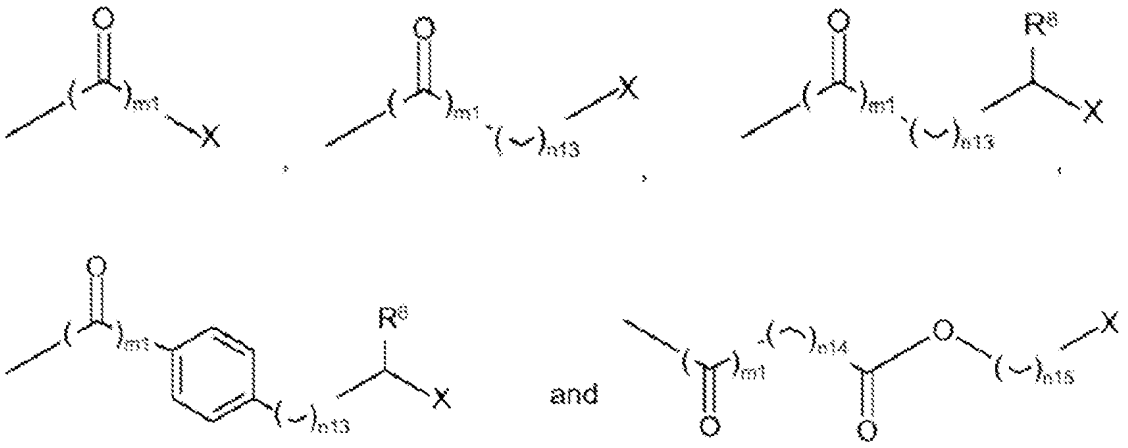
each R^{la}, R^{lb}, R^3, and R^4 is independently H or Ci-C8 alkyl;

each R^{2a} and R^{2b} is independently H , Ci-C8 alkyl, OH, alkoxy, or O-HG^1 or O-HG^2; each n8, n9, n11, and n12 is independently an integer from 1-20;

n10 is an integer from 2-20; and

each dotted bond is independently a single or a double bond.

[00346] In one embodiment, with respect to the bolaamphiphilic compound of formula I, II, III, IV, V, or VI, each HG^1 and HG^2 is independently selected from:



[00347] wherein: X is $-NR^{5a}R^{5b}$, or $-N^{+}R^{5a}R^{5b}R^{5c}$; each R^{5a}, and R^{5b} is independently H or substituted or unsubstituted C_1-C_{20} alkyl or R^{5a} and R^{5b} may join together to form an N containing substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl; each R^{5c} is independently substituted or unsubstituted C_1-C_{20} alkyl; each R^8 is independently H, substituted or unsubstituted C_1-C_{20} alkyl, alkoxy, or carboxy; ml is 0 or 1; and each n13, n14, and n15 is independently an integer from 1-20.

[00348] In various embodiments, pharmaceutical compositions disclosed herein comprise complexes between bolaamphiphiles and pharmacologically or biologically active compounds (e.g., an UNC13A oligonucleotide disclosed herein). In various embodiments, the pharmaceutical compositions disclosed herein comprise a bolaamphiphile vesicle complexes comprising one or more bolaamphiphilic compounds and the biologically active compound is an oligonucleotide (e.g., an UNC13A oligonucleotide disclosed herein).

[00349] Pharmaceutical compositions containing a disclosed UNC13A oligonucleotide, such as those disclosed herein, can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990).

[00350] Pharmaceutical formulations, in some embodiments, are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Parenteral Administration

[00351] The pharmaceutical compositions of the disclosure can be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intracisternal, intracerebroventricular, intramuscular, subcutaneous, intrathecal, intrathalamic, intralesional, or intraperitoneal routes. The preparation of an aqueous composition, such as an aqueous pharmaceutical composition containing a disclosed UNC13A oligonucleotide, will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

[00352] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including normal saline, artificial cerebrospinal fluid, sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00353] Solutions of active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In one embodiment, a disclosed UNC13A antisense oligonucleotide may be suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethylcellulose and 0.1% (v/v) TWEEN™ 80. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00354] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and

the required other ingredients from those enumerated above. Sterile injectable solutions of the disclosure may be prepared by incorporating a disclosed UNC13A antisense oligonucleotide in the required amount of the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter.

[00355] The preparation of more, or highly concentrated solutions for intramuscular injection is also contemplated. In this regard, the use of DMSO as solvent is preferred as this will result in extremely rapid penetration, delivering high concentrations of the disclosed oligonucleotide to a small area.

[00356] Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about pH 6 and pH 8, and for example, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose , petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like.

Oral Administration

[00357] In some embodiments, contemplated herein are compositions suitable for oral delivery of a disclosed UNC13A oligonucleotide, *e.g.*, tablets that include an enteric coating, *e.g.*, a gastro-resistant coating, such that the compositions may deliver a UNC13A oligonucleotide to, *e.g.*, the gastrointestinal tract of a patient.

[00358] For example, a tablet for oral administration is provided that comprises granules (*e.g.*, is at least partially formed from granules) that include a disclosed UNC13A oligonucleotide, *e.g.*, a

UNC13A oligonucleotide represented by any SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and pharmaceutically acceptable excipients. Such a tablet may be coated with an enteric coating. Contemplated tablets may include pharmaceutically acceptable excipients such as fillers, binders, disintegrants, and/or lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring such as wintergreen, orange, xylitol, sorbitol, fructose, and maltodextrin, and perfuming agents, preservatives and/or antioxidants.

[00359] In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5 ~~5292~~that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable salt. In some embodiments, contemplated pharmaceutical formulations include an intra-granular phase that includes a disclosed UNC13A oligonucleotide, *e.g.*, a UNC13A oligonucleotide represented by any of SEQ ID NOs: 1-1264, SEQ ID NO: 2529-3792, SEQ ID NOs: 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~ that targets a UNC13A transcript comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, and a pharmaceutically acceptable filler. For example, a disclosed UNC13A oligonucleotide and a filler may be blended together, optionally, with other excipients, and formed into granules. In some embodiments, the intragranular phase may be formed using wet granulation, *e.g.*, a liquid (*e.g.*, water) is added to the blended UNC13A oligonucleotide and filler, and then the combination is dried, milled and/or sieved to produce granules. One of skill in the art would understand that other processes may be used to achieve an intragranular phase.

[00360] In some embodiments, contemplated formulations include an extra-granular phase, which may include one or more pharmaceutically acceptable excipients, and which may be blended with the intragranular phase to form a disclosed formulation.

[00361] A disclosed formulation may include an intragranular phase that includes a filler. Exemplary fillers include, but are not limited to, cellulose, gelatin, calcium phosphate, lactose, sucrose, glucose, mannitol, sorbitol, microcrystalline cellulose, pectin, polyacrylates, dextrose, cellulose acetate, hydroxypropylmethyl cellulose, partially pre-gelatinized starch, calcium carbonate, and others including combinations thereof.

[00362] In some embodiments, a disclosed formulation may include an intragranular phase and/or an extragranular phase that includes a binder, which may generally function to hold the ingredients of the pharmaceutical formulation together. Exemplary binders of the disclosure may include, but are not limited to, the following: starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, pre-gelatinized maize starch, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, low substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, sugar alcohols and others including combinations thereof.

[00363] Contemplated formulations, *e.g.*, that include an intragranular phase and/or an extragranular phase, may include a disintegrant such as but not limited to, starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, alginates, corn starch, crosmellose sodium, crosslinked carboxymethyl cellulose, low substituted hydroxypropyl cellulose, acacia, and others including combinations thereof. For example, an intragranular phase and/or an extragranular phase may include a disintegrant.

[00364] In some embodiments, a contemplated formulation includes an intra-granular phase comprising a disclosed UNC13A oligonucleotide and excipients chosen from: mannitol, microcrystalline cellulose, hydroxypropylmethyl cellulose, and sodium starch glycolate or combinations thereof, and an extra-granular phase comprising one or more of: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate or mixtures thereof.

[00365] In some embodiments, a contemplated formulation may include a lubricant, *e.g.* an extra-granular phase may contain a lubricant. Lubricants include but are not limited to talc, silica, fats, stearin, magnesium stearate, calcium phosphate, silicone dioxide, calcium silicate, calcium phosphate, colloidal silicon dioxide, metallic stearates, hydrogenated vegetable oil, corn starch, sodium benzoate, polyethylene glycols, sodium acetate, calcium stearate, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate, talc, and stearic acid.

[00366] In some embodiments, the pharmaceutical formulation comprises an enteric coating. Generally, enteric coatings create a barrier for the oral medication that controls the location at which the drug is absorbed along the digestive track. Enteric coatings may include a polymer that disintegrates at different rates according to pH. Enteric coatings may include for example, cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxylpropylmethyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymers, ethylacrylate-methacrylic acid copolymers, methacrylic acid copolymer type C, polyvinyl acetate-phthalate, and cellulose acetate phthalate.

[00367] Exemplary enteric coatings include Opadry® AMB, Acryl-EZE®, Eudragit® grades. In some embodiments, an enteric coating may comprise about 5% to about 10%, about 5% to about 20%, 8% to about 15%, about 8% to about 20%, about 10% to about 20%, or about 12% to about 20%, or about 18% of a contemplated tablet by weight. For example, enteric coatings may include an ethylacrylate-methacrylic acid copolymer.

[00368] For example, in a contemplated embodiment, a tablet is provided that comprises or consists essentially of about 0.5% to about 70%, *e.g.*, about 0.5% to about 10%, or about 1% to about 20%, by weight of a disclosed UNC13A oligonucleotide or a pharmaceutically acceptable salt thereof. Such a tablet may include for example, about 0.5% to about 60% by weight of mannitol, *e.g.*, about 30% to about 50% by weight mannitol, *e.g.*, about 40% by weight mannitol; and/or about 20% to about 40% by weight of microcrystalline cellulose, or about 10% to about 30% by weight of microcrystalline cellulose. For example, a disclosed tablet may comprise an intragranular phase that includes about 30% to about 60%, *e.g.* about 45% to about 65% by weight, or alternatively, about 5 to about 10% by weight of a disclosed UNC13A oligonucleotide, about 30% to about 50%, or alternatively, about 5% to about 15% by weight mannitol, about 5% to about 15% microcrystalline cellulose, about 0% to about 4%, or about 1% to about 7% hydroxypropylmethylcellulose, and about 0% to about 4%, *e.g.*, about 2% to about 4% sodium starch glycolate by weight.

[00369] In another contemplated embodiment, a pharmaceutical tablet formulation for oral administration of a disclosed UNC13A oligonucleotide comprises an intra-granular phase, wherein the intra-granular phase includes a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof (such as a sodium salt), and a pharmaceutically acceptable filler, and which may also include an extra-granular phase, that may include a pharmaceutically acceptable excipient such as a disintegrant. The extra-granular phase may include components chosen from microcrystalline cellulose, magnesium stearate, and mixtures thereof. The pharmaceutical

composition may also include an enteric coating of about 12% to 20% by weight of the tablet. For example, a pharmaceutically acceptable tablet for oral use may comprise about 0.5% to 10% by weight of a disclosed UNC13A AON, *e.g.*, a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof, about 30% to 50% by weight mannitol, about 10% to 30% by weight microcrystalline cellulose, and an enteric coating comprising an ethylacrylate-methacrylic acid copolymer.

[00370] In another example, a pharmaceutically acceptable tablet for oral use may comprise an intra-granular phase, comprising about 5 to about 10% by weight of a disclosed UNC13A AON, *e.g.*, a disclosed UNC13A AON or a pharmaceutically acceptable salt thereof, about 40% by weight mannitol, about 8% by weight microcrystalline cellulose, about 5% by weight hydroxypropylmethyl cellulose, and about 2% by weight sodium starch glycolate; an extra-granular phase comprising about 17% by weight microcrystalline cellulose, about 2% by weight sodium starch glycolate, about 0.4% by weight magnesium stearate; and an enteric coating over the tablet comprising an ethylacrylate-methacrylic acid copolymer.

[00371] In some embodiments the pharmaceutical composition may contain an enteric coating comprising about 13% or about 15%, 16%, 17% or 18% by weight, *e.g.*, AcyrlEZE® (*see, e.g.*, PCT Publication No. WO 2010/054826, which is hereby incorporated by reference in its entirety).

[00372] The rate at which the coating dissolves and the active ingredient is released is its dissolution rate. In an embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 7.2, of about 50% to about 100% of the UNC13A oligonucleotide releasing after about 120 minutes to about 240 minutes, for example after 180 minutes. In another embodiment, a contemplated tablet may have a dissolution profile, *e.g.*, when tested in a USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in diluted HCl with a pH of 1.0, where substantially none of the UNC13A oligonucleotide is released after 120 minutes. A contemplated tablet, in another embodiment, may have a dissolution profile, *e.g.*, when tested in USP/EP Type 2 apparatus (paddle) at 100 rpm and 37 °C in a phosphate buffer with a pH of 6.6, of about 10% to about 30%, or not more than about 50% of the UNC13A oligonucleotide releasing after 30 minutes.

[00373] In some embodiments, methods provided herein may further include administering at least one other agent that is directed to treatment of diseases and disorders disclosed herein. In

one embodiment, contemplated other agents may be co-administered (*e.g.*, sequentially or simultaneously).

Dosage and Frequency of Administration

[00374] The dosage or amounts described below refer either to the oligonucleotide or a pharmaceutically acceptable salt thereof.

[00375] In some embodiments, methods described herein include administering at least 1 μg, at least 5 μg, at least 10 μg, at least 20 μg, at least 30 μg, at least 40 μg, at least 50 μg, at least 60 μg, at least 70 μg, at least 80 μg, at least 90 μg, or at least 100 μg of a UNC13A antisense oligonucleotide *e.g.*, a UNC13A oligonucleotide. In some embodiments, methods include administering from 10 mg to 500 mg, from 1 mg to 10 mg, from 10 mg to 20 mg, from 20 mg to 30 mg, from 30 mg to 40 mg, from 40 mg to 50 mg, from 50 mg to 60 mg, from 60 mg to 70 mg, from 70 mg to 80 mg, from 80 mg to 90 mg, from 90 mg to 100 mg, from 100 mg to 150 mg, from 150 mg to 200 mg, from 200 mg to 250 mg, from 250 mg to 300 mg, from 300 mg to 350 mg, from 350 mg to 400 mg, from 400 mg to 450 mg, from 450 mg to 500 mg, from 500 mg to 600 mg, from 600 mg to 700 mg, from 700 mg to 800 mg, from 800 mg to 900 mg, from 900 mg to 1 g, from 1 mg to 50 mg, from 20 mg to 40 mg, or from 1 mg to 500 mg of a UNC13A antisense oligonucleotide.

[00376] In some embodiments, methods described herein include administering formulations that include about 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, 4.0 g, 4.5 g, or 5.0 g of a disclosed UNC13A oligonucleotide. In some embodiments, a formulation may include about 40 mg, 80 mg, or 160 mg of a disclosed UNC13A oligonucleotide. In some embodiments, a formulation may include at least 100 μg of a disclosed UNC13A oligonucleotide. For example, formulations may include about 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg of a disclosed UNC13A oligonucleotide. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health and size of the patient, the *in vivo* potency of the UNC13A oligonucleotide, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study. Dosing

frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. In some embodiments, dosing is once per day for 7 days. In some embodiments, dosing is once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, or once every 12 weeks. In some embodiments, dosing is once a month to every three months. In some embodiments, dosing is once every 2 weeks for three dose, then monthly, bimonthly, or every three or four months.

Combination Therapies

[00377] In various embodiments, a UNC13A AON as disclosed herein can be administered in combination with one or more additional therapies. The combination therapy of the disclosed oligonucleotide and the one or more additional therapies can, in some embodiments, be synergistic in treating any of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Parkinson's disease, Parkinson's disease with or without dementia, and Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

[00378] Non-limiting examples of therapies for Parkinson's disease (PD) include: deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, Symmetrel, osmolex), benztropine (Cogentin), trihexyphenidyl (artane), selegiline (eldepryl, zelapar), rasagiline, entacapone (comtan), opicapone (ongentys), tolcapone (tasmar), apomorphine (apokyn, kynmobi), exenatide, lingzhi, BIIB054, BIIB094, Caffeine, sarizotan, Nuplazid, and embryonic dopamine cell implantation.

[00379] Non-limiting examples of therapies for Alzheimer's disease (AD) include aducanamab (Aduhlem), memantine (Namenda), Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (razadyne), Namzeric, Suvorexant (belsomra), and lecanemab.

[00380] A non-limiting example of a therapy for amyotrophic lateral sclerosis (ALS) is pridopidine.

[00381] Non-limiting examples of therapies for frontotemporal dementia (FTD) include olanzapine (Zyprexa), quetiapine (Seroquel), SSRIs (citalopram (Cipramil), dapoxetine (Priligy), escitalopram (Cipralex), fluoxetine (Prozac or Oxactin), fluvoxamine (Faverin), paroxetine (Seroxat), sertraline (Lustral), vortioxetine (Brintellix)), divalproex sodium (Depakote), carbamazepine (Tegretol), and medroxyprogestrone.

[00382] Non-limiting examples of therapies for epilepsy include Brivaracetam (briviact), cannabidiol (epidiolex), carbamazepine (carbatrol, Tegretol), cenobamate (xcopri), diazepam (valium), lorazepam (Ativan), clonazepam (klonopin), eslicarbazepine (aptiom), ethosuximide (zarontin), felbamate (felbatol), fenfluramine (fintepla), lacosamide (VIMPAT), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (oxtellar xr, Trileptal), perampanel (fycompa), phenobarbital, phenytoin (dilantin), pregabalin (lyrica), tiagabine (gabitril), topiramate (topamax), valproate (depakene, depakote), and zonisamide (zonegran).

[00383] Example additional therapies include any of Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, 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), medroxyprosterone, KCNQ2/KCNQ3 openers (e.g., retigabine, XEN1101, or QRL-101), bioactive scaffolds, anticonvulsants and psychostimulant agents. Additional therapies can further include breathing care, physical therapy, occupational therapy, speech therapy, and nutritional support. Further non-limiting examples of additional therapies include any of deep brain stimulation, levodopa and carbidopa (duopa, rytary, Sinemet, inbrija), istradefylline (nourianz), safinamide (xadago), pramipexole (Mirapex), rotigotine (neupro), ropinirole (requip), amantadine (gocovri, 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 zonisamide (zonegran). In various embodiments, an additional therapy can be a second antisense oligonucleotide. As an example, the second antisense oligonucleotide may target a UNC13A transcript (*e.g.*, UNC13A pre-mRNA, mature UNC13A mRNA) to modulate the expression levels of full length UNC13A protein.

[00384] Non-limiting examples of therapies for spinal cord injury includes bioactive scaffolds, such as bioactive scaffolds with enhanced supramolecular motion. Further details of example bioactive scaffolds as therapies for spinal cord injury is described in Alvarez et al., "Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury." Science, 374, 848-856 (2021), which is hereby incorporated by reference in its entirety.

[00385] In various embodiments, the disclosed oligonucleotide and the one or more additional therapies can be conjugated to one another and provided in a conjugated form. Further description regarding conjugates involving the disclosed oligonucleotide is described below. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided concurrently. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided simultaneously. In various embodiments, the disclosed oligonucleotide and one or more additional therapies are provided sequentially.

Conjugates

[00386] In certain embodiments, provided herein are oligomeric compounds, which comprise an oligonucleotide (*e.g.*, UNC13A oligonucleotide) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups include one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or

terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

[00387] Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

Conjugate Groups

[00388] In certain embodiments, a UNC13A AON is covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge, and clearance. In particular embodiments, conjugate groups modify the circulation time (e.g., increase) of the oligonucleotides in the bloodstream such that increased concentrations of the oligonucleotides are delivered to the brain. In particular embodiments, conjugate groups modify the residence time (e.g., increase residence time) of the oligonucleotides in a target organ (e.g., brain) such that increased residence time of the oligonucleotides improves their performance (e.g., efficacy). In particular embodiments, conjugate groups increase the delivery of the oligonucleotide to the brain through the blood brain barrier and/or brain parenchyma (e.g., through receptor mediated transcytosis). In particular embodiments, conjugate groups enable the oligonucleotide to target a specific organ (e.g., the brain). In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. NY. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac -glycerol or triethyl -ammonium l,2-di-0-

hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937), a tocopherol group (Nishina *et al.*, Molecular Therapy Nucleic Acids, 2015, 4, e220; and Nishina *et al.*, Molecular Therapy, 2008, 16, 734-740), or a GalNAc cluster (*e.g.*, WO2014/179620).

Conjugate Moieties

[00389] Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, dyes, bile acids, and phenylbutyric acid. In particular embodiments, conjugate moieties are selected from a peptide, a lipid, N-acetylgalactosamine (GalNAc), cholesterol, vitamin E, lipoic acid, panthothenic acid, polyethylene glycol, an antibody (*e.g.*, an antibody for crossing the blood brain barrier such as anti-transferrin receptor antibody), or a cell-penetrating peptide (*e.g.*, transactivator of transcription (TAT) and penetratine).

[00390] In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (*S*)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

Conjugate Linkers

[00391] Conjugate moieties are attached to a UNC13A AON through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbon chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

[00392] In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In certain such embodiments, the conjugate linker comprises groups selected from alkyl, amino,

oxo, amide and ether groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

[00393] In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, *e.g.*, those known in the art to be useful for attaching conjugate groups to parent compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to bind to a particular site on a parent compound and the other is selected to bind to a conjugate group. Examples of functional groups used in a bifunctional linking moiety include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[00394] Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane- l-carboxylate (SMCC) and 6-aminohexanoic acid (AHEX or AHA). Other conjugate linkers include but are not limited to substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[00395] In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise 3 linker-nucleosides.

[00396] In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N -benzoyl-5 -methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is

typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

[00397] Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid.

[00398] In certain embodiments, it is desirable for a conjugate group to be cleaved from the UNC13A AON. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

[00399] In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

[00400] In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain

embodiments, a cleavable moiety is 2'-deoxy nucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxy adenosine.

Terminal Groups

[00401] In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic nucleosides and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides. In certain such embodiments, the 2'-linked nucleoside is an abasic nucleoside. In various embodiments, terminal groups comprise one or more spacers.

Diagnostic Methods

[00402] The disclosure also provides a method of diagnosing a patient with a neurological disease that relies upon detecting levels of UNC13A expression signal in one or more biological samples of a patient. As used herein, the term "UNC13A expression signal" can refer to any indication of UNC13A gene expression, or gene or gene product activity. UNC13A gene products include RNA (*e.g.*, mRNA), peptides, and proteins. Indices of UNC13A gene expression that can be assessed include, but are not limited to, UNC13A gene or chromatin state, UNC13A gene interaction with cellular components that regulate gene expression, UNC13A gene product expression levels (*e.g.*, expression levels of UNC13A transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, or interaction of UNC13A RNA or protein with transcriptional, translational, or post-translational processing machinery.

[00403] Detection of UNC13A expression signal may be accomplished through *in vivo*, *in vitro*, or *ex vivo* methods. In a preferred embodiment, methods of the disclosure may be carried out *in vitro*. Methods of detecting may involve detection in blood, serum, fecal matter, tissue, cerebrospinal fluid, spinal fluid, urine, extracellular vesicles (for example, CSF exosomes), or cells of a patient. Detection may be achieved by measuring expression signal of UNC13A

transcripts (for example, a UNC13A pre-mRNA) comprising a sequence that shares at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identity to SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208 in whole tissue, tissue explants, cell cultures, dissociated cells, cell extract, extracellular vesicles (for example, CSF exosomes), or body fluids, including blood, spinal fluid, cerebrospinal fluid, urine, lymphatic fluid, plasma, or serum. Methods of detection include assays that measure levels of UNC13A gene product expression such as Western blotting, FACS, ELISA, other quantitative binding assays, cell or tissue growth assays, Northern blots, quantitative or semi-quantitative polymerase chain reaction, medical imaging methods (*e.g.*, MRI), or immunostaining methods (*e.g.*, immunohistochemistry or immunocytochemistry).

Modifications in General

[00404] While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

[00405] Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of a uracil of RNA). Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence "ATCGATCG" encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as

"AT^{m}CGAUCG," wherein ^{m}C indicates a cytosine base comprising a methyl group at the 5-position.

[00406] Certain compounds described herein (*e.g.*, modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), as α or β such as for sugar anomers, or as (D) or (L), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that contain stereocenters that are drawn or described with undefined stereochemistry included all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, all tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated, compounds described herein are intended to include corresponding salt forms.

[00407] The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ^{1}H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ^{2}H or ^{3}H in place of ^{1}H, ^{13}C or ^{14}C in place of ^{12}C, ^{15}N in place of ^{14}N, ^{17}O or ^{18}O in place of ^{16}O, and ^{33}S, ^{34}S, ^{35}S, or ^{36}S in place of ^{32}S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool.

EXAMPLES

[00408] The disclosure is further illustrated by the following examples. The examples are provided for illustrative purposes only, and are not to be construed as limiting the scope or content of the disclosure in any way.

Example 1: Design and Selection of UNC13A Oligonucleotides

[00409] UNC13A AONs oligonucleotides that target a UNC13A transcript are designed and tested to identify UNC13A AONs capable of reducing quantity of UNC13A transcripts (e.g., mis-spliced UNC13A transcripts). Such UNC13A AONs include UNC13A parent oligonucleotides represented by any of SEQ ID NOs: 1-1264 or UNC13A oligonucleotide variants represented by SEQ ID NOs: 2529-3792. The UNC13A parent oligonucleotides are 25 nucleosides in length. Each of the nucleosides of the UNC13A parent oligonucleotides are modified nucleosides with 2'MOE sugar moieties, and each "C" is replaced with a 5-MeC.

Additionally, each of the internucleoside linkages between the nucleosides of the UNC13A oligonucleotides are phosphorothioate internucleoside linkages.

[00410] Generally, the length of the UNC13A antisense oligonucleotides are 25 oligonucleotide units in length. However, variants of the UNC13A antisense oligonucleotides were also designed with varying lengths (*e.g.*, 23mers, 21mers, or 19mers). Examples of these variant UNC13A antisense oligonucleotides were designed to include a subset of the sequences of SEQ ID NOs: 2529-3792.

[00411] Table 6A: Example UNC13A AONs (including UNC13A oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence (where S indicates presence of a Spacer)* (5' → 3')	Length
5133	GGGCAGSCAGGAATGGTGSGTGGAA	25
5134	AGGGAGSAGTTTTCCAGGSAAAGGG	25
5135	GCAGCTSGAAGAGACATASCCAGAC	25
5136	TCCACCSGCCACTCACAASCATCCA	25
5137	GAAAGTSTCATGGAGAGTSCAAGGG	25
5138	GGGCAGGCSGGAATGGTGSGTGGAA	25
5139	AGGGAGGASTTTTCCAGGSAAAGGG	25
5140	GCAGCTGGSAGAGACATASCCAGAC	25
5141	TCCACCAGSCACTCACAASCATCCA	25
5142	GAAAGTGTSATGGAGAGTSCAAGGG	25
5143	GCAGGCASGAATGGTSAGTGGAA	23
5144	GGGCAGGSAGGAATGSTGAGTGG	23
5145	GGCAGGCSGGAATGGSGAGTGGA	23
5146	GTAAAGGSAATGGCASGGCGGGC	23
5147	AGGTAAASGGAATGGSATGGCGG	23
5148	GGTAAAGSGAATGGCSTGGCGGG	23
5149	AGGAGGTSACCCTGASTCTGGAC	23
5150	AGAGGAGSTGACCCTSAATCTGG	23
5151	GAGGAGGSGACCCTGSATCTGGA	23
5152	ACAAACGSCCCAATCSTGAGTGG	23

5153	ACACAAASGGCCCAASCCTGAGT	23
5154	CACAAACSGCCCAATSCTGAGTG	23
5155	TCTTTCCSGGAAACCSAGGCAGC	23
5156	GTTCTTTSCAGGAAASCCAGGCA	23
5157	TTCTTTCSAGGAAACSCAGGCAG	23
5158	TCCGCAASTTAATCCSCCTACCC	23
5159	GATCCGCSACTTAATSCACCTAC	23
5160	ATCCGCASCTTAATCSACCTACC	23
5161	CCCACCCSTCTAACTSCCCCAAA	23
5162	CACCCACSCATCTAASTACCCCA	23
5163	ACCCACCSATCTAACSACCCCAA	23
5164	AAGTGTCSTGGAGAGSGCAAGGG	23
5165	GAAAGTGSCATGGAGSGTGCAAG	23
5166	AAAGTGTSATGGAGASTGCAAGG	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (Iia') as disclosed herein.

[00412] Table 6B: Example UNC13A AONs (including UNC13A oligonucleotides with two spacers)

SEQ ID No:	Oligonucleotide Sequence (where **S** indicates presence of a Spacer)* (5' → 3')	Length
5168	AGTTCASCCACACATCCTSCCATTC	25
5169	AGTTCAACSACACATCCTSCCATTC	25
5170	GTTCAACSACACATCSTTCCATT	23
5171	AGTTCAASCACACATSCTTCCAT	23
5172	TTCAACCSCACATCCSTCCATTC	23
5173	CTTGCASTAGTTCAACCASACATCC	25
5174	CTTGCAATSGTTCAACCASACATCC	25

5175	TTGCAATSGTTCAACSACACATC	23
5176	CTTGCAASAGTTCAASCACACAT	23
5177	TGCAATASTTCAACCSCACATCC	23
5178	ACACATSCATCCATCCATSCATTCA	25
5179	ACACATCCSTCCATCCATSCATTCA	25
5180	CACATCCSTCCATCCSTCCATTC	23
5181	ACACATCSATCCATCSATCCATT	23
5182	ACATCCASCCATCCASCCATTCA	23
5183	CAGTAASTCAACCACACASCCATCC	25
5184	CAGTAATTSAACCACACASCCATCC	25
5185	AGTAATTSAACCACASATCCATC	23
5186	CAGTAATSCAACCACSCATCCAT	23
5187	GTAATTCSACCACACSTCCATCC	23
5188	ACCTTTSAGTAATTCAACSACACAT	25
5189	ACCTTTCASTAATTCAACSACACAT	25
5190	CCTTTCASTAATTCASCCACACA	23
5191	ACCTTTCSGTAATTCSACCACAC	23
5192	CTTTCAGSAATTCAASCACACAT	23
5193	CTCTTTSATCCATCCACASACCCAC	25
5194	CTCTTTTASCCATCCACASACCCAC	25
5195	TCTTTTASCCATCCASACACCCA	23
5196	CTCTTTTSTCCATCCSCACACCC	23
5197	CTTTTATSCATCCACSCACCCAC	23
5198	ATCTACSCTTTTATCCATSCACACA	25
5199	ATCTACTCSTTTATCCATSCACACA	25
5200	TCTACTCSTTTATCCSTCCACAC	23
5201	ATCTACTSTTTTATCSATCCACA	23
5202	CTACTCTSTTATCCASCCACACA	23

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages.

A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (Iia') as disclosed herein.

Example 2: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00413] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 50,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13a transcript. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00414] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C"is 5-MeC.

[00415] To evaluate UNC13a AON ability to restore full length UNC13A (UNC13A FL) mRNA (also referred to as correctly spliced UNC13A (UNC13A CS) mRNA), antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After 72 additional hours, RNA was collected from the 96-well plates for RT-qPCR.RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A full length transcript and reference GAPDH quantification.

[00416] Transcript levels (e.g., UNC13A full length transcript or TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. RT-qPCR was performed for detecting UNC13A-FL transcripts using Thermofisher® TaqMan Gene Expression Assay Hs00392638_m1.

[00417] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00418] UNC13A-FL (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-FL), the normalized UNC13A-FL signal was further

normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A FL were normalized using the following formula:

$$(((RQAON - RQTDP43)/(RQendo-RQTDP43))*100$$

[00419] Table 7 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons. UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers were tested for their ability to increase or restore full-length UNC13A mRNA (*i.e.*, mRNA from which full-length UNC13A protein is translated) levels. In some cases, UNC13A AONs with spacers increased full-length UNC13A mRNA ("UNC13A FL"), also referred to herein as correctly spliced UNC13A (UNC13A CS). In some cases, UNC13A AONs without spacers increased full-length UNC13A mRNA or correctly spliced UNC13A mRNA (UNC13A CS)). Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00420] As shown in Table 7, a 500 nM dose of SEQ ID NO: ~~5153~~ 5326 (ACACAAASGGCCCAASCCTGAGT with two spacers) rescued full length UNC13A mRNA to 55.69%. Comparatively, a 500 nM dose of SEQ ID NO: ~~2788~~ 5325 (ACACAAACGGCCCAATCCTGAGT with no spacers) rescued full length UNC13A mRNA to 41.87%. This indicates that the addition of spacers of SEQ ID NO: ~~5153~~ 5326 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~2788~~5325).

[00421] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: ~~5159~~ 5352 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 55.88%. A 500 nM dose of SEQ ID NO: ~~5159~~ 5352 (GATCCGCSACTTAATSCACCTAC with two spacers) rescued full length UNC13A mRNA to 66.62%. Comparatively, a 200 nM dose of SEQ ID NO: 3547 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 43.88%. A 500 nM dose of SEQ ID NO: ~~3547~~ 5351 (GATCCGCAACTTAATCCACCTAC with no spacers) rescued full length UNC13A mRNA to 66.98%. This indicates that at 200 nM and 500 nM doses, the performance of an AON with SEQ ID NO: ~~5159~~ 5352 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~3547~~5351).

[00422] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: ~~5162~~ 5359 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to

47.94%. A 500 nM dose of SEQ ID NO: ~~5162~~ 5359 (CACCCACSCATCTAASTACCCCA with two spacers) rescued full length UNC13A mRNA to 83.19%. Comparatively, a 200 nM dose of SEQ ID NO: ~~3652~~ 5358 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 47.68%. A 500 nM dose of SEQ ID NO: ~~3652~~ 5358 (CACCCACCCATCTAACTACCCCA with no spacers) rescued full length UNC13A mRNA to 41.16%. This indicates that at a 200 nM dose, the performance of SEQ ID NO: ~~5162~~ 5359 (with spacers) is similar to the performance of the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~3652~~5358). However, at a 500 nM dose, the addition of spacers of SEQ ID NO: ~~5162~~ 5359 improves the performance in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~3652~~5358).

[00423] Additionally shown in Table 7, a 500 nM dose of SEQ ID NO: ~~5161~~ 5361 (CCCACCCSTCTAACTSCCCCAAA with two spacers) rescued full length UNC13A mRNA to 43.10%. Comparatively, a 500 nM dose of SEQ ID NO: ~~3650~~ 5360 (CCCACCCATCTAACTACCCCAAA with no spacers) rescued full length UNC13A mRNA to 23.37%. This indicates that at a 500 nM dose, the addition of spacers improves the performance of an AON with SEQ ID NO: ~~5161~~ 5361 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~3650~~5360).

[00424] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: ~~5164~~ 5368 (AAGTGTCSTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 35.39%. A 500 nM dose of SEQ ID NO: ~~5164~~ 5368 (AAGTGTCSTGGAGAGSGCAAGGG with two spacers) rescued full length UNC13A mRNA to 6.60%. Comparatively, a 200 nM dose of SEQ ID NO: ~~3774~~ 5367 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 19.04%. A 500 nM dose of SEQ ID NO: ~~3774~~ 5367 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to -34.58%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 5164 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: ~~3774~~5367).

[00425] Additionally shown in Table 7, a 200 nM dose of SEQ ID NO: 5370 ~~5142~~ (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 67.77%. A 500 nM dose of SEQ ID NO: 5370 ~~5142~~ (GAAAGTGTSATGGAGAGTSCAAGGG with two spacers) rescued full length UNC13A mRNA to 84.79%. Comparatively, a 200 nM dose of SEQ ID NO: 5362 ~~1248~~ (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A

mRNA to 22.48%. A 500 nM dose of SEQ ID NO: 5362 ~~1248~~ (GAAAGTGTCATGGAGAGTGCAAGGG with no spacers) rescued full length UNC13A mRNA to 24.84%. This indicates that at 200 nM and 500 nM doses, the addition of spacers improves the performance of an AON with SEQ ID NO: 5142 in comparison to the UNC13A AON counterpart without spacers (e.g., SEQ ID NO: 1248).

[00426] Altogether, these results demonstrate that different UNC13A AONs including two spacers are capable of increasing UNC13A-FL mRNA to levels that are comparable to or improved beyond their non-spacer counterparts.

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Table 7: Performance of UNC13A AONs in UNC13A full length assay (UNC13A oligonucleotides without spacers, or with one or two spacers).

SEQ ID NO:	Oligonucleotide Sequence* (where **S** indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	500 nM	500 nM
		Normalized CS	Normalized CS SD	Normalized CS	Normalized CS SD
529342	GAAGAGCTGGGCAGGCAGGAATGGT	3.79367	0.480565	-63.053	0.19433
529466	TGTGGATGGTGTGGCCAGAAAGAGG	60.6986	0.724229	-23.435	0.36397
529577	GGCCAGGAGAGTGTGGATGGTGTGG	154.828	1.127288	434.631	2.32539
5296101	ATGGCATGGCGGGCAGTCTCAGAGG	37.1601	0.448286	12.6634	0.41631
5297108	AAAGGGAATGGCATGGCGGGCAGTC	-26.139	0.13718	22.9464	0.49028
5298112	AGGTAAAGGGAATGGCATGGCGGGC	-5.3242	0.383369	-37.199	0.17903
52992639	GGTAAAGGGAATGGCATGGCGGG	-29.228	0.227001	-33.566	0.20089
53005148	GGTAAAG**S**GAATGGC**S**TGGCGGG	-16.331	0.304608	-29.739	0.22392
53012640	AGGTAAAGGGAATGGCATGGCGG	-13.385	0.322337	-40.436	0.15956
53025147	AGGTAAA**S**GGAATGG**S**ATGGCGG	-13.664	0.320657	-24.027	0.2583
53032638	GTAAAGGGAATGGCATGGCGGGC	-29.989	0.222419	-26.677	0.24235
53045146	GTAAAGG**S**AATGGCA**S**GGCGGGC	25.771	0.557959	-18.428	0.29199
5305115	TCCAGGTAAAGGGAATGGCATGGCG	-7.8349	0.268854	40.2877	0.61503
5306127	AGGGAGGAGTTTTCCAGGTAAAGGG	-32.255	0.392785	-25.109	0.4256
53075134	AGGGAG**S**AGTTTTCCAGG**S**AAAGGG	6.97605	0.572906	-3.6889	0.52394
53085139	AGGGAGGA**S**TTTTCCAGG**S**AAAGGG	-70.51	0.217148	-78.696	0.17957
5309162	AGAGGAGGTGACCCTGAATCTGGAC	129.033	0.93262	110.34	1.0505

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5310~~2689~~	GAGGAGGTGACCCTGAATCTGGA	169.855	1.024819	164.814	1.30762
5311~~5151~~	GAGGAGGSGACCCTGSATCTGGA	-72.457	0.658323	138.629	1.28191
5312~~2690~~	AGAGGAGGTGACCCTGAATCTGG	171.498	1.135638	3.26987	0.54512
5313~~5150~~	AGAGGAGSTGACCCTSAATCTGG	7.49253	0.565048	-57.946	0.25617
5314~~2688~~	AGGAGGTGACCCTGAATCTGGAC	44.7095	0.740715	125.001	1.1197
5315~~5149~~	AGGAGGTSACCCTGASTCTGGAC	-44.26	0.320771	12.8179	0.59018
5316~~195~~	GAGAGTCAACCTGGAGGCCAAGGTG	32.5688	0.559505	57.0338	0.7355
5317~~200~~	GTAGTGAGAGTCAACCTGGAGGCCA	70.681	0.905428	67.6819	0.88671
5318~~203~~	TGAGTAGTGAGAGTCAACCTGGAGG	91.2119	1.033573	59.7857	0.83742
5319~~244~~	CCTGAGTGGTTAGGGCTGGAATAGA	46.7792	0.756244	-24.332	0.3124
5320~~248~~	CAATCCTGAGTGGTTAGGGCTGGAA	-8.5	0.411217	73.8646	0.9253
5321~~254~~	ACGGCCCAATCCTGAGTGGTTAGGG	66.8521	0.88153	45.3726	0.74746
5322~~260~~	ACACAAACGGCCCAATCCTGAGTGG	-11.42	0.462541	75.8487	0.8839
5323~~2787~~	CACAAACGGCCCAATCCTGAGTG	-11.128	0.463949	-41.939	0.31518
5324~~5154~~	CACAAACSGCCCAATSCTGAGTG	50.7872	0.762897	-14.314	0.44857
5325~~2788~~	ACACAAACGGCCCAATCCTGAGT	-27.43	0.385239	41.8694	0.71984
5326~~5153~~	ACACAAASGGCCCAASCCTGAGT	-14.732	0.44655	55.6902	0.78657
5327~~2786~~	ACAAACGGCCCAATCCTGAGTGG	-49.751	0.277462	-20.306	0.41964
5328~~5152~~	ACAAACGSCCCAATCSTGAGTGG	105.349	1.026341	47.8744	0.74883
5329~~263~~	CAGACACAAACGGCCCAATCCTGAG	-40.7843	0.3272	-5.4793	0.5486
5330~~269~~	CATACCCAGACACAAACGGCCCAAT	-21.2475	0.3317	14.4015	0.5542
5331~~273~~	GAGACATACCCAGACACAAACGGCC	47.2141	0.7590	116.3656	1.1906

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5332~~283~~	GCAGCTGGAAGAGACATACCCAGAC	4.7146	0.5625	-66.6389	0.2349
5333~~5135~~	GCAGCTSGAAGAGACATASCCAGAC	33.7840	0.6960	-6.4957	0.5111
5334~~5140~~	GCAGCTGGSAGAGACATASCCAGAC	3.7461	0.5581	35.3538	0.7032
5335~~301~~	TCTTTCCAGGAAACCCAGGCAGCTG	17.5514	0.5395	30.5680	0.5952
5336~~303~~	GTTCTTTCCAGGAAACCCAGGCAGC	41.1141	0.5932	-27.3254	0.2666
5337~~2830~~	TTCTTTCCAGGAAACCCAGGCAG	-31.8396	0.2450	-7.7732	0.3599
5338~~5157~~	TTCTTTCSAGGAAACSCAGGCAG	-72.0800	0.0530	-37.1813	0.2196
5339~~2831~~	GTTCTTTCCAGGAAACCCAGGCA	-14.5643	0.3275	44.7209	0.6104
5340~~5156~~	GTTCTTTSCAGGAAASCCAGGCA	-38.7597	0.2120	-22.4863	0.2897
5341~~2829~~	TCTTTCCAGGAAACCCAGGCAGC	2.0002	0.4065	-15.1244	0.3248
5342~~5155~~	TCTTTCCSGGAAACCSAGGCAGC	-59.9899	0.1107	-64.5153	0.0891
5343~~454~~	CACGAATCTACCCACCAACTCATCC	-39.5824	0.2948	-56.2924	0.2233
5344~~460~~	TCTAGCCACGAATCTACCCACCAAC	75.4170	0.7873	-12.0685	0.4126
5345~~927~~	GTCTGTCCACCAGCCACTCACAACC	121.2337	0.9834	-62.7895	0.1955
5346~~930~~	TTCGTCTGTCCACCAGCCACTCACA	-18.2285	0.3863	-45.7096	0.2686
5347~~937~~	TCCATTTTTCGTCTGTCCACCAGCC	-63.8195	0.2479	-54.2647	0.2917
5348~~1019~~	GATCCGCAACTTAATCCACCTACCC	88.0305	0.9091	44.9905	0.5436
5349~~3546~~	ATCCGCAACTTAATCCACCTACC	30.7027	0.4223	45.1113	0.5446
5350~~5160~~	ATCCGCASCTTAATCSACCTACC	38.8278	0.4913	50.8796	0.5936
5351~~3547~~	GATCCGCAACTTAATCCACCTAC	43.8789	0.5342	66.9823	0.7303
5352~~5159~~	GATCCGCSACTTAATSCACCTAC	**55.8768**	**0.6360**	**66.6162**	**0.7272**
5353~~3545~~	TCCGCAACTTAATCCACCTACCC	64.3790	0.7082	67.3066	0.7331

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5354~~5158~~	TCCGCAASTTAATCCSCCTACCC	53.4236	0.6152	51.3988	0.5980
5355~~1124~~	CACCCACCCATCTAACTACCCCAAA	64.1844	0.6729	44.6783	0.4941
5356~~3651~~	ACCCACCCATCTAACTACCCCAA	41.2908	0.4631	64.1844	0.6729
5357~~5163~~	ACCCACCSATCTAACSACCCCAA	46.9810	0.4070	58.8250	0.6238
5358~~3652~~	CACCCACCCATCTAACTACCCCA	47.6810	0.5217	41.0564	0.4609
5359~~5162~~	CACCCACSCATCTAASTACCCCA	47.9432	0.5241	83.1895	0.8471
5360~~3650~~	CCCACCCATCTAACTACCCCAAA	72.0651	0.5775	23.3677	0.2988
5361~~5161~~	CCCACCCSTCTAACTSCCCCAAA	41.8445	0.4682	43.0965	0.4796
5362~~1248~~	GAAAGTGTCATGGAGAGTGCAAGGG	22.4754	0.5041	24.8358	0.5167
5363~~3775~~	AAAGTGTCATGGAGAGTGCAAGG	82.5919	0.8245	7.0300	0.4218
5364~~5166~~	AAAGTGTSATGGAGASTGCAAGG	61.0070	0.7095	-4.8799	0.3583
5365~~3776~~	GAAAGTGTCATGGAGAGTGCAAG	55.7844	0.6816	-19.7864	0.2789
5366~~5165~~	GAAAGTGSCATGGAGSGTGCAAG	40.0402	0.5977	3.6974	0.4040
5367~~3774~~	AAGTGTCATGGAGAGTGCAAGGG	19.0435	0.4858	-34.5807	0.2001
5368~~5164~~	AAGTGTCSTGGAGAGSGCAAGGG	35.3880	0.5729	6.6020	0.4195
5369~~5137~~	GAAAGTSTCATGGAGAGTSCAAGGG	-10.6183	0.3278	50.6900	0.6545
5370~~5142~~	GAAAGTGTSATGGAGAGTSCAAGGG	67.7691	0.7455	84.7852	0.8362
5371~~1260~~	CACCATGGGAGAGAAAGTGTCATGG	17.7544	0.4529	64.3335	0.7880

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (IIa') as disclosed herein.

Example 3: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00427] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00428] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C"is 5-MeC.

[00429] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[00430] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detect using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 5203)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 5204)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 5203)

[00431] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00432] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt). Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

$$(((RQAON - RQendo)/(RQTDP43- RQendo))*100$$

[00433] Table 8 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[00434] As shown in Table 8, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00435] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~273~~ 5372 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 4.4%. A 50 nM dose of SEQ ID NO: ~~273~~ 5372 (GAGACATACCCAGACACAAACGGCC with no spacers) reduced UNC13A cryptic exon levels to 20.3%.

[00436] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~2831~~ 5373 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 5.1%. A 50 nM dose of SEQ ID NO: ~~2831~~ 5373 (GTTCTTTCCAGGAAACCCAGGCA with no spacers) reduced UNC13A cryptic exon levels to 26.0%.

[00437] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5156~~ 5374 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 6.6%. A 50 nM dose of SEQ ID NO: ~~5156~~ 5374 (GTTCTTTSCAGGAAASCCAGGCA with two spacers) reduced UNC13A cryptic exon levels to 41.2%.

[00438] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5140~~ 5375 (GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 8.3%. A 50 nM dose of SEQ ID NO: 5375 ~~5140~~

(GCAGCTGGSAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 31.0%.

[00439] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~303~~ 5376 (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 8.8%. A 50 nM dose of SEQ ID NO: 5376 ~~303~~ (GTTCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 35.4%.

[00440] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5135~~ 5377 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 11.8%. A 50 nM dose of SEQ ID NO: ~~5135~~ 5377 (GCAGCTSGAAGAGACATASCCAGAC with two spacers) reduced UNC13A cryptic exon levels to 30.6%.

[00441] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~283~~ 5378 (GCAGCTGGAAGAGACATACCCAGACwith no spacers) reduced UNC13A cryptic exon levels to 13.8%. A 50 nM dose of SEQ ID NO: ~~283~~ 53787 (GCAGCTGGAAGAGACATACCCAGACwith no spacers) reduced UNC13A cryptic exon levels to 66.0%.

[00442] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~2830~~ 5379 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 15.2%. A 50 nM dose of SEQ ID NO: ~~2830~~ 5379 (TTCTTTCCAGGAAACCCAGGCAG with no spacers) reduced UNC13A cryptic exon levels to 34.4%.

[00443] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~3585~~ 5380 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 15.8%. A 50 nM dose of SEQ ID NO: ~~3585~~ 5380 (ACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 45.4%.

[00444] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5155~~ 5381 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 18.2%. A 50 nM dose of SEQ ID NO: ~~5155~~ 5381 (TCTTTCCSGGAAACCSAGGCAGC with two spacers) reduced UNC13A cryptic exon levels to 41.9%.

[00445] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5157~~ 5382 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 20.1%. A 50 nM dose of SEQ ID NO: ~~5157~~ 5382 (TTCTTTCSAGGAAACSCAGGCAG with two spacers) reduced UNC13A cryptic exon levels to 42.8%.

[00446] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~1059~~ 5383 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 23.1%. A 50 nM dose of SEQ ID NO: ~~1059~~ 5383 (ACACATCCATCCATCCATCCATTCA with no spacers) reduced UNC13A cryptic exon levels to 50.2%.

[00447] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~2829~~ 5384 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 25%. A 50 nM dose of SEQ ID NO: ~~2829~~ 5384 (TCTTTCCAGGAAACCCAGGCAGC with no spacers) reduced UNC13A cryptic exon levels to 40.6%.

[00448] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~269~~ 5385 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 27.2%. A 50 nM dose of SEQ ID NO: ~~269~~ 5385 (CATACCCAGACACAAACGGCCCAAT with no spacers) reduced UNC13A cryptic exon levels to 43.4%.

[00449] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~1142~~ 5386 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 34.4%. A 50 nM dose of SEQ ID NO: ~~1142~~ 5386 (CTCTTTTATCCATCCACACACCCAC with no spacers) reduced UNC13A cryptic exon levels to 64.3%.

[00450] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~3670~~ 5387 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 40.5%. A 50 nM dose of SEQ ID NO: ~~3670~~ 5387 (CTCTTTTATCCATCCACACACCC with no spacers) reduced UNC13A cryptic exon levels to 82.2%.

[00451] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~301~~ 5388 (TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 41.6%. A 50 nM dose of SEQ ID NO: ~~301~~ 5388

(TCTTTCCAGGAAACCCAGGCAGCTG with no spacers) reduced UNC13A cryptic exon levels to 54.2%.

[00452] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5165~~ 5389 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 42.0%. A 50 nM dose of SEQ ID NO: ~~5165~~ 5389 (GAAAGTGSCATGGAGSGTGCAAG with two spacers) reduced UNC13A cryptic exon levels to 54.0%.

[00453] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5198~~ 5390 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 44.5%. A 50 nM dose of SEQ ID NO: ~~5198~~ 5390 (ATCTACSCTTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 45.5%.

[00454] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~1147~~ 5391 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 46.4%. A 50 nM dose of SEQ ID NO: ~~1147~~ 5391 (ATCTACTCTTTTATCCATCCACACA with no spacers) reduced UNC13A cryptic exon levels to 69.7%.

[00455] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~3587~~ 5392 (ACACATCCATCCATCCATCCATT with no spacers) reduced UNC13A cryptic exon levels to 47.8%.

[00456] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5202~~ 5393 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.1%. A 50 nM dose of SEQ ID NO: ~~5202~~ 5393 (CTACTCTSTTATCCASCCACACA with two spacers) reduced UNC13A cryptic exon levels to 76.5%.

[00457] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5199~~ 5394 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 48.2%. A 50 nM dose of SEQ ID NO: ~~5199~~ 5394 (ATCTACTCSTTTATCCATSCACACA with two spacers) reduced UNC13A cryptic exon levels to 62.8%.

[00458] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~5192~~ 5395 (CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 49.6%. A 50 nM dose of SEQ ID NO: ~~5192~~ 5395

(CTTTCAGSAATTCAASCACACAT with two spacers) reduced UNC13A cryptic exon levels to 70.9%.

[00459] As shown in Table 8, a 200 nM dose of SEQ ID NO: ~~3774~~ 5396 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 49.8%. A 50 nM dose of SEQ ID NO: ~~3774~~ 5396 (AAGTGTCATGGAGAGTGCAAGGG with no spacers) reduced UNC13A cryptic exon levels to 67.0%.

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Table 8. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

SEQ ID NO:	Oligonucleotide Sequence* (where S indicates presence of a Spacer) (5' → 3')	QPCR potency		QPCR potency	
		200 nM	200 nM	50 nM	50 nM
		Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon	Normalized UNC13A Cryptic Exon	SD Normalized UNC13A Cryptic Exon
5372~~273~~	GAGACATACCCAGACACAAACGGCC	4.38	4.41	20.3	14.4
5373~~2831~~	GTTCTTTCCAGGAAACCCAGGCA	5.11	4.14	26	15.2
5374~~5156~~	GTTCTTTSCAGGAAASCCAGGCA	6.62	6.06	41.2	15.2
5375~~5140~~	GCAGCTGGSAGAGACATASCCAGAC	8.3	7.86	31	26.4
5376~~303~~	GTTCTTTCCAGGAAACCCAGGCAGC	8.84	7.85	35.4	22.4
5377~~5135~~	GCAGCTSGAAGAGACATASCCAGAC	11.8	10.7	30.6	13
5378~~283~~	GCAGCTGGAAGAGACATACCCAGAC	13.8	7.11	66	45.9
5379~~2830~~	TTCTTTCCAGGAAACCCAGGCAG	15.2	7.39	34.4	25.1
5380~~3585~~	ACATCCATCCATCCATCCATTCA	15.8	8.84	45.4	14
5381~~5155~~	TCTTTCCSGGAAACCSAGGCAGC	18.2	9.18	41.9	24.2
5382~~5157~~	TTCTTTCSAGGAAACSCAGGCAG	20.1	9.33	42.8	27.7
5383~~1059~~	ACACATCCATCCATCCATCCATTCA	23.1	15.7	50.2	21.5
5384~~2829~~	TCTTTCCAGGAAACCCAGGCAGC	25	11.7	40.6	22.9
5385~~269~~	CATACCCAGACACAAACGGCCCAAT	27.2	20.6	43.4	28
5386~~1142~~	CTCTTTTATCCATCCACACACCCAC	34.4	20.1	64.3	34.7

5387~~3670~~	CTCTTTTATCCATCCACACACCC	40.5	15.2	82.2	45.5
5388~~301~~	TCTTTCCAGGAAACCCAGGCAGCTG	41.6	30.5	54.2	20.8
5389~~5165~~	GAAAGTGSCATGGAGSGTGCAAG	42	38.1	54	32.5
5390~~5198~~	ATCTACSCTTTTATCCATSCACACA	44.5	22.4	45.5	34.4
5391~~1147~~	ATCTACTCTTTTATCCATCCACACA	46.4	29.9	69.7	47.6
5392~~3587~~	ACACATCCATCCATCCATCCATT	47.8	24.9	122	41.9
5393~~5202~~	CTACTCTSTTATCCASCCACACA	48.1	35.4	76.5	37.9
5394~~5199~~	ATCTACTCSTTTATCCATSCACACA	48.2	21.5	62.8	44.3
5395~~5192~~	CTTTCAGSAATTCAASCACACAT	49.6	39.2	70.9	46.3
5396~~3774~~	AAGTGTCATGGAGAGTGCAAGGG	49.8	39.3	67	59.7
5397~~3586~~	CACATCCATCCATCCATCCATTC	51.6	14.2	80.3	41.4
5398~~248~~	CAATCCTGAGTGGTTAGGGCTGGAA	54.2	18.8	59.6	16.2
5399~~263~~	CAGACACAAACGGCCCAATCCTGAG	54.4	19.2	73.2	43.7
5400~~3668~~	CTTTTATCCATCCACACACCCAC	55.4	30.5	59	34.2
5401~~3669~~	TCTTTTATCCATCCACACACCCA	55.7	29.2	61.1	45.6
5402~~5196~~	CTCTTTTSTCCATCCSCACACCC	55.9	29.8	83.8	50.9
5403~~2562~~	GGGCAGGCAGGAATGGTGAGTGG	56.6	41	73.6	47.2
5404~~5141~~	TCCACCAGSCACTCACAASCATCCA	58	17.7	86.1	36.5
5405~~1124~~	CACCCACCCATCTAACTACCCCAAA	58.2	42.7	91	34.4
5406~~2561~~	GGCAGGCAGGAATGGTGAGTGGA	59.1	43.9	57.9	41.1
5407~~5195~~	TCTTTTASCCATCCASACACCCA	63.1	23.5	54.3	40.7

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5408~~3652~~	CACCCACCCATCTAACTACCCCA	63.1	44.6	74.3	51.2
5409~~5166~~	AAAGTGTSATGGAGASTGCAAGG	63.7	39.2	55.5	53
5410~~5177~~	TGCAATASTTCAACCSCACATCC	64.1	25.7	75.7	42.9
5411~~5138~~	GGGCAGGCSGGAATGGTGSGTGGAA	64.2	32	73	39
5412~~34~~	GGGCAGGCAGGAATGGTGAGTGGAA	64.6	42.2	91.2	48.4
5413~~5145~~	GGCAGGCSGGAATGGSGAGTGGA	64.6	49.5	92.8	65
5414~~5193~~	CTCTTTSATCCATCCACASACCCAC	65.1	34.1	53	32.2
5415~~3775~~	AAAGTGTCATGGAGAGTGCAAGG	65.3	45.4	71.2	64.2
5416~~5186~~	CAGTAATSCAACCACSCATCCAT	65.5	23.7	92.7	24.1
5417~~5194~~	CTCTTTTASCCATCCACASACCCAC	65.6	37.8	67.8	29.5
5418~~3673~~	CTACTCTTTTATCCATCCACACA	67.1	32	50.5	34
5419~~1078~~	ACCTTTCAGTAATTCAACCACACAT	67.5	52.3	87.4	58
5420~~3776~~	GAAAGTGTCATGGAGAGTGCAAG	68.3	52.7	52.7	38.7
5421~~5197~~	CTTTTATSCATCCACSCACCCAC	68.7	58.9	59.2	33.2
5422~~5189~~	ACCTTTCASTAATTCAACSACACAT	69.2	35.5	115	79.8
5423~~5153~~	ACACAAASGGCCCAASCCTGAGT	69.3	54.9	114	67.4
5424~~5162~~	CACCCACSCATCTAASTACCCCA	71.4	65.7	111	77.3
5425~~5185~~	AGTAATTSAACCACASATCCATC	72	16	58	21.7
5426~~5164~~	AAGTGTCSTGGAGAGSGCAAGGG	72.1	51.9	70.7	59.6
5427~~2788~~	ACACAAACGGCCCAATCCTGAGT	72.4	18.3	99.8	34.6
5428~~3386~~	TGCAATAGTTCAACCACACATCC	74	35.8	124	53.6

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5429~~3604~~	CTTTCAGTAATTCAACCACACAT	74.1	39.5	65.7	57.3
5430~~260~~	ACACAAACGGCCCAATCCTGAGTGG	74.3	16.6	109	53.2
5431~~244~~	CCTGAGTGGTTAGGGCTGGAATAGA	75.2	42.7	92.4	35.7
5432~~3605~~	CCTTTCAGTAATTCAACCACACA	76.2	42.9	145	138
5433~~2787~~	CACAAACGGCCCAATCCTGAGTG	76.8	37.3	91.2	46.8
5434~~3651~~	ACCCACCCATCTAACTACCCCAA	77.1	52.6	87.2	59.1
5435~~5200~~	TCTACTCSTTTATCCSTCCACAC	78.2	43.6	88.6	71.7
5436~~5154~~	CACAAACSGCCCAATSCTGAGTG	78.2	45.6	86.8	45.4
5437~~5152~~	ACAAACGSCCCAATCSTGAGTGG	78.3	38.8	66.1	35
5438~~5136~~	TCCACCSGCCACTCACAASCATCCA	78.7	73.6	120	50.9
5439~~3650~~	CCCACCCATCTAACTACCCCAAA	78.9	50.3	71.8	60.4
5440~~5144~~	GGGCAGGSAGGAATGSTGAGTGG	82.7	67.3	142	100
5441~~5173~~	CTTGCASTAGTTCAACCASACATCC	86	34.4	140	132
5442~~5201~~	ATCTACTSTTTTATCSATCCACA	86.3	55.6	117	68.8
5443~~254~~	ACGGCCCAATCCTGAGTGGTTAGGG	86.9	44.1	108	78
5444~~3547~~	GATCCGCAACTTAATCCACCTAC	88.3	76.5	115	86.5
5445~~5137~~	GAAAGTSTCATGGAGAGTSCAAGGG	89.6	50.5	107	42.8
5446~~3675~~	ATCTACTCTTTTATCCATCCACA	91.1	60.9	89.8	70.4
5447~~2786~~	ACAAACGGCCCAATCCTGAGTGG	92.9	43.5	78.5	47.3
5448~~2560~~	GCAGGCAGGAATGGTGAGTGGAA	94	74.1	118	82.7
5449~~5191~~	ACCTTTCSGTAATTCSACCACAC	95.2	44.9	60.6	52.1

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5450~~112~~	AGGTAAAGGGAATGGCATGGCGGGC	96	49.3	115	57
5451~~3545~~	TCCGCAACTTAATCCACCTACCC	96	82.6	111	77.3
5452~~1248~~	GAAAGTGTCATGGAGAGTGCAAGGG	96.3	58.9	118	77.8
5453~~5176~~	CTTGCAASAGTTCAASCACACAT	98.9	42.4	90.8	40.8
5454~~3388~~	CTTGCAATAGTTCAACCACACAT	99.5	39	95.7	46.1
5455~~5161~~	CCCACCCSTCTAACTSCCCCAAA	99.7	71.7	112	82.8
5456~~5184~~	CAGTAATTSAACCACACASCCATCC	101	95.2	128	130
5457~~3387~~	TTGCAATAGTTCAACCACACATC	102	54.4	138	55.5
5458~~3606~~	ACCTTTCAGTAATTCAACCACAC	105	105	120	108
5459~~5187~~	GTAATTCSACCACACSTCCATCC	106	60.1	116	48.6
5460~~200~~	GTAGTGAGAGTCAACCTGGAGGCCA	107	21.8	92.6	27.2
5461~~3674~~	TCTACTCTTTTATCCATCCACAC	107	71.4	83.2	56.9
5462~~1260~~	CACCATGGGAGAGAAAGTGTCATGG	108	103	67.4	60.1
5463~~127~~	AGGGAGGAGTTTTCCAGGTAAAGGG	109	50.5	95.7	21.4
5464~~5143~~	GCAGGCASGAATGGTSAGTGGAA	109	74.8	150	98.2
5465~~5163~~	ACCCACCSATCTAACSACCCCAA	112	74.4	81.6	45.8
5466~~5178~~	ACACATSCATCCATCCATSCATTCA	114	36.7	135	39.5
5467~~5175~~	TTGCAATSGTTCAACSACACATC	115	54.7	98.6	51.2
5468~~5134~~	AGGGAGSAGTTTTCCAGGSAAAGGG	116	30	110	29.8
5469~~5182~~	ACATCCASCCATCCASCCATTCA	116	50.6	111	38
5470~~5188~~	ACCTTTSAGTAATTCAACSACACAT	116	81.4	101	74.7

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54715~~5142~~	GAAAGTGTSATGGAGAGTSCAAGGG	117	40.6	115	66.2
54725~~5139~~	AGGGAGGASTTTTCCAGGSAAAGGG	118	30.4	111	22.7
5473~~195~~	GAGAGTCAACCTGGAGGCCAAGGTG	118	43.8	96.1	17.9
54743~~3379~~	GTTCAACCACACATCCTTCCATT	119	70.8	186	142
5475~~860~~	CTTGCAATAGTTCAACCACACATCC	120	57.3	140	70.5
5476~~927~~	GTCTGTCCACCAGCCACTCACAACC	120	104	154	122
54773~~3380~~	AGTTCAACCACACATCCTTCCAT	121	55	161	77.7
54785~~5169~~	AGTTCAACSACACATCCTSCCATTC	122	71.7	129	96.7
54795~~5181~~	ACACATCSATCCATCSATCCATT	123	40.6	108	40.9
54803~~3378~~	TTCAACCACACATCCTTCCATTC	124	9.97	143	48.5
54815~~5151~~	GAGGAGGSGACCCTGSATCTGGA	124	33.6	117	67.2
54822~~2639~~	GGTAAAGGGAATGGCATGGCGGG	125	50.2	110	68.5
54835~~5171~~	AGTTCAASCACACATSCTTCCAT	125	81.5	142	155
54845~~5180~~	CACATCCSTCCATCCSTCCATTC	128	67	89.1	32
54855~~5147~~	AGGTAAASGGAATGGSATGGCGG	128	77.5	149	85.4
54865~~5133~~	GGGCAGSCAGGAATGGTGSGTGGAA	129	72.2	105	58.4
54875~~5159~~	GATCCGCSACTTAATSCACCTAC	136	111	152	102
54883~~3598~~	GTAATTCAACCACACATCCATCC	137	54	107	52.1
54895~~5150~~	AGAGGAGSTGACCCTSAATCTGG	139	55.6	118	48.1
54905~~5170~~	GTTCAACSACACATCSTTCCATT	145	80.5	138	84.8
54913~~3600~~	CAGTAATTCAACCACACATCCAT	146	47.3	119	22.7

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5492~~5160~~	ATCCGCASCTTAATCSACCTACC	147	63.2	132	76.5
5493~~2640~~	AGGTAAAGGGAATGGCATGGCGG	147	82.1	148	92.8
5494~~5158~~	TCCGCAASTTAATCCSCCTACCC	148	97	180	93.3
5495~~5149~~	AGGAGGTSACCCTGASTCTGGAC	149	47.3	101	58.2
5496~~5168~~	AGTTCASCCACACATCCTSCCATTC	149	79	132	60.8
5497~~5183~~	CAGTAASTCAACCACACASCCATCC	149	84.3	116	53.3
5498~~852~~	AGTTCAACCACACATCCTTCCATTC	151	106	137	114
5499~~5148~~	GGTAAAGSGAATGGCSTGGCGGG	151	111	106	63.6
5500~~1072~~	CAGTAATTCAACCACACATCCATCC	155	85.5	133	58.7
5501~~5172~~	TTCAACCSCACATCCSTCCATTC	156	159	139	80.1
5502~~5174~~	CTTGCAATSGTTCAACCASACATCC	157	99.7	123	77
55034~~2~~	GAAGAGCTGGGCAGGCAGGAATGGT	158	99.8	160	79.5
5504~~1019~~	GATCCGCAACTTAATCCACCTACCC	161	73	154	72
5505~~5179~~	ACACATCCSTCCATCCATSCATTCA	163	45.7	163	44.5
5506~~203~~	TGAGTAGTGAGAGTCAACCTGGAGG	164	54.7	108	59.6
5507~~101~~	ATGGCATGGCGGGCAGTCTCAGAGG	168	99.2	166	76.5
5508~~3599~~	AGTAATTCAACCACACATCCATC	173	58.2	107	51.4
5509~~922~~	TCCACCAGCCACTCACAACCATCCA	173	134	84.3	45.9
5510~~2688~~	AGGAGGTGACCCTGAATCTGGAC	176	46.2	85.1	44.1
5511~~454~~	CACGAATCTACCCACCAACTCATCC	178	116	140	49.4
5512~~2689~~	GAGGAGGTGACCCTGAATCTGGA	182	60.1	108	36.8

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5513~~5190~~	CCTTTCASTAATTCASCCACACA	182	192	114	61.7
551~~466~~	TGTGGATGGTGTGGCCAGAAAGAGG	185	70.1	156	70.7
5515~~3546~~	ATCCGCAACTTAATCCACCTACC	186	58.2	149	63.5
5516~~5146~~	GTAAAGGSAATGGCASGGCGGGC	193	116	161	79.1
5517~~930~~	TTCGTCTGTCCACCAGCCACTCACA	193	125	119	81.2
5518~~937~~	TCCATTTTTCGTCTGTCCACCAGCC	196	122	113	51.4
5519~~2690~~	AGAGGAGGTGACCCTGAATCTGG	197	67.6	108	41.2
5520~~162~~	AGAGGAGGTGACCCTGAATCTGGAC	197	92.2	119	37.6
552177	GGCCAGGAGAGTGTGGATGGTGTGG	200	74.8	162	83.3
5522~~2638~~	GTAAAGGGAATGGCATGGCGGGC	205	79.8	80	52
5523~~115~~	TCCAGGTAAAGGGAATGGCATGGCG	215	102	149	127
5524~~108~~	AAAGGGAATGGCATGGCGGGCAGTC	226	99.9	178	113
5525~~277~~	GGAAGAGACATACCCAGACACAAAC	0.02	0.00	11.43	6.56
5526~~282~~	CAGCTGGAAGAGACATACCCAGACA	0.03	0.02	16.20	7.83
5527~~276~~	GAAGAGACATACCCAGACACAAACG	0.94	1.59	0.61	1.01
5528~~306~~	AGAGTTCTTTCCAGGAAACCCAGGC	1.47	2.28	19.61	9.44
5529~~307~~	AAGAGTTCTTTCCAGGAAACCCAGG	3.01	2.16	21.95	5.43
5530~~305~~	GAGTTCTTTCCAGGAAACCCAGGCA	3.49	2.07	29.80	2.76
5531~~304~~	AGTTCTTTCCAGGAAACCCAGGCAG	3.62	3.79	38.61	18.71
5532~~285~~	AGGCAGCTGGAAGAGACATACCCAG	4.63	5.37	32.99	2.70
5533~~274~~	AGAGACATACCCAGACACAAACGGC	5.98	6.18	12.51	6.77

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5534~~279~~	CTGGAAGAGACATACCCAGACACAA	6.26	10.82	58.24	12.87
5535~~275~~	AAGAGACATACCCAGACACAAACGG	9.32	5.24	16.02	3.73
5536~~272~~	AGACATACCCAGACACAAACGGCCC	12.07	2.14	29.94	15.81
5537~~284~~	GGCAGCTGGAAGAGACATACCCAGA	12.92	4.64	50.87	17.93
5538~~286~~	CAGGCAGCTGGAAGAGACATACCCA	14.04	2.17	32.22	17.05
5539~~280~~	GCTGGAAGAGACATACCCAGACACA	15.74	19.34	36.35	14.55
5540~~281~~	AGCTGGAAGAGACATACCCAGACAC	18.82	10.27	20.31	17.71
5541~~283~~	GCAGCTGGAAGAGACATACCCAGAC	18.87	22.30	55.59	34.27
5542~~271~~	GACATACCCAGACACAAACGGCCCA	19.96	11.08	28.25	4.42
5543~~273~~	GAGACATACCCAGACACAAACGGCC	21.01	9.29	26.91	8.72
5544~~1057~~	ACATCCATCCATCCATCCATTCATC	21.36	5.97	63.61	8.59
5545~~1058~~	CACATCCATCCATCCATCCATTCAT	23.52	1.80	108.40	54.14
5546~~287~~	CCAGGCAGCTGGAAGAGACATACCC	25.02	3.34	60.96	5.29
5547~~1055~~	ATCCATCCATCCATCCATTCATCCA	25.59	10.98	86.98	36.11
5548~~1059~~	ACACATCCATCCATCCATCCATTCA	27.76	4.11	72.26	37.32
5549~~302~~	TTCTTTCCAGGAAACCCAGGCAGCT	30.66	1.40	86.91	11.41
5550~~301~~	TCTTTCCAGGAAACCCAGGCAGCTG	31.13	5.45	52.43	7.09
5551~~1056~~	CATCCATCCATCCATCCATTCATCC	35.45	4.51	75.99	10.37
5552~~1060~~	CACACATCCATCCATCCATCCATTC	38.25	19.28	96.63	22.67
5553~~270~~	ACATACCCAGACACAAACGGCCCAA	38.57	4.68	44.89	1.89
5554~~1062~~	ACCACACATCCATCCATCCATCCAT	39.40	7.68	71.32	18.18

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5555~~1061~~	CCACACATCCATCCATCCATCCATT	39.80	8.88	77.72	2.82
5556~~1063~~	AACCACACATCCATCCATCCATCCA	41.07	10.10	97.41	24.31
5557~~300~~	CTTTCCAGGAAACCCAGGCAGCTGG	42.16	22.26	77.70	9.85
5558~~299~~	TTTCCAGGAAACCCAGGCAGCTGGA	51.84	9.47	72.21	10.14
5559~~269~~	CATACCCAGACACAAACGGCCCAAT	60.89	6.26	84.01	23.09

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer as indicated by **S** is not a nucleoside. **S** represents a spacer of Formula (Iia') as disclosed herein.

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Example 4: Methods for Evaluating UNC13A Antisense Oligonucleotides

[00460] UNC13A antisense oligonucleotides were evaluated in iPSC derived human motor neurons (hMN). The cells were seeded in 96-well plates at a density of 40,000 cells / well. Antisense oligonucleotide (AON) to TDP43 was transfected with Endoporter (Gene Tools, Philomath, OR, USA) to decrease expression of the full length UNC13A transcript and increase expression of UNC13A cryptic exon. Vehicle control consisted of motor neuron treatment with Endoporter alone. Positive controls included cells that were treated with TDP43 AON alone ("AON TDP43" or "TDP43 AON").

[00461] TDP43 AON is a gapmer oligonucleotide and has the following sequence and chemistry: 5' A*A*G*G*C*T*T*C*A*T*A*T*T*G*T*A*C*T*T*T 3' (SEQ ID NO: 5167) where * = phosphorothioate, underlined = DNA, other=2'MOE RNA;each "C"is 5-MeC.

[00462] To evaluate UNC13A AON ability to reduce UNC13A cryptic exon levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A cryptic exon, and reference GAPDH quantification.

[00463] Transcript levels (e.g., UNC13A cryptic exon, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a cryptic exon was detected using custom sequences.

UNC13a Cryptic Exon:

Forward Primer: ATTGTTCTGCACGTCGGT (SEQ ID NO: 5203)

Reverse Primer: GTCTGGGTATGTCTCTTCCAG (SEQ ID NO: 5204)

Probe Sequence: AGTTCTTTCCAGGAAACCCAGGCA (SEQ ID NO: 5203)

[00464] To evaluate UNC13A AON ability to reduce UNC13A correctly spliced (CS)exon junction 20/21 levels, antisense oligonucleotides to UNC13A were co-incubated with TDP43 AON in Endoporter in media before addition to the cells. After 72 hours, antisense oligonucleotides and Endoporter were washed out and replaced with fresh media alone. After six additional days, RNA was collected from the 96-well plates for RT-qPCR. RNA was

isolated, cDNA generated and multiplexed RT-qPCR assay performed with Taqman probes for UNC13A CS exon 20/21 junction, and reference GAPDH quantification.

[00465] Transcript levels (e.g., UNC13A exon junction 20/21, and TDP43 transcript) were detected by RT-qPCR using Taqman. Specifically, RT-qPCR was performed for detecting GAPDH using Thermofisher® TaqMan Gene Expression Assay Hs03929097_g1. UNC13a exon 20/21 junction was detect using TaqMan Gene Expression Assay Hs01000584_m1.

[00466] RT-qPCR was performed on Applied Biosystems ® 7500 Real-time PCR systems. One cycle of reverse transcription was performed at a temperature of 50°C for 5 min. One cycle of RT inactivation/initial denaturation was performed at a temperature of 95°C for 20 seconds. Forty five cycles of amplification were performed at a temperature of 95°C for 1 second followed by 60°C for 20 seconds.

[00467] UNC13A-cryptic (Ct) was normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % decrease of UNC13A-cryptic), the normalized UNC13A-cryptic signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt).

[00468] Relative quantity (RQ) of transcript level was calculated using the equation $RQ=2^{-deltadeltaCt}$ and is used to describe the treatment condition comparison to normal, healthy levels (1.0). RQ values for UNC13A cryptic were normalized using the following formula:

$$(((RQAON - RQendo)/(RQTDP43- RQendo))*100$$

[00469] Table 9 shows the RT-qPCR results of UNC13A AONs with spacers and performance of UNC13A AONs without spacers in human motor neurons.

[00470] As shown in Table 9, UNC13A AONs (*e.g.*, UNC13A oligonucleotides without spacers or with one or two spacers) were tested for their ability to reduce UNC13A transcripts with a cryptic exon. In some cases, UNC13A AONs with spacers reduced UNC13A cryptic exon levels. In some cases, UNC13A AONs without spacers reduced UNC13A cryptic exon levels. Specific AON sequences are labeled according to their corresponding SEQ ID NO.

[00471] Correctly spliced UNC13A (Ct) was also normalized to GAPDH (deltaCt). To visualize the quantitative changes (e.g., % increase of correctly spliced UNC13A), the normalized correctly spliced UNC13A signal was further normalized to the vehicle (treated with Endoporter alone, deltadeltaCt).

[00472] Relative quantity (RQ) of transcript level was calculated using the equation RQ=2^(-deltadeltaCt) and is used to describe the treatment condition comparison to normal, healthy

levels (1.0). RQ values for UNC13A corrected splicing were normalized using the following formula:

$$(((RQAON - RQTDP43)/(RQendo - RQTDP43))*$$

Table 9. Performance of Exemplary UNC13A AONs evaluated in human derived iPSC motor neurons

		UNC13A Corrected Splicing Normalized RQ				UNC13A Cryptic Splicing Normalized RQ			
		200nM		50nM		200nM		50nM	
SEQ ID NO:	Oligonucleotide Sequence* (5' to 3')	Mean	STD	Mean	STD	Mean	STD	Mean	STD
~~276~~5566	GAAGAGACATACCCAGACACAAACG	41.82	18.84	-27.56	73.08	3.16	1.03	18.87	12.38
~~2804~~5565	GAAGAGACATACCCAGACACAAA	8.93	7.32	-7.13	7.81	15.78	7.41	42.31	31.11
~~2803~~5563	AAGAGACATACCCAGACACAAAC	-28.45	72.83	-12.62	12.84	12.06	9.62	57.27	34.91
~~2802~~5564	AGAGACATACCCAGACACAAACG	13.03	15.19	9.48	11.41	14.78	6.73	61.44	25.31
~~2801~~5562	GAGACATACCCAGACACAAACGG	28.03	29.67	7.69	35.17	18.53	10.52	33.25	20.41
~~2800~~5560	AGACATACCCAGACACAAACGGC	24.21	33.06	23.24	30.63	29.74	33.32	50.76	39.49
~~2799~~5561	GACATACCCAGACACAAACGGCC	2.47	35.11	2.89	26.90	26.29	25.67	46.66	32.30
~~285~~5573	AGGCAGCTGGAAGAGACATACCCAG	47.19	57.85	15.52	30.16	2.07	3.30	13.45	13.12
~~2813~~5571	AGGCAGCTGGAAGAGACATACCC	37.80	13.72	1.51	9.33	2.32	3.41	22.31	14.52
~~2812~~5570	GGCAGCTGGAAGAGACATACCCA	39.83	25.50	19.20	21.74	7.01	5.73	25.13	28.23
~~2811~~5572	GCAGCTGGAAGAGACATACCCAG	43.08	23.32	4.48	7.87	5.11	6.91	32.17	23.76
~~2810~~5567	CAGCTGGAAGAGACATACCCAGA	-21.34	16.48	-144.30	28.86	7.59	6.87	21.20	16.74
~~2809~~5568	AGCTGGAAGAGACATACCCAGAC	-173.70	29.80	-75.73	8.72	4.20	7.60	165.20	96.22
5253	GCAGCTGSAAGAGACSTACCCAG	64.46	20.00	-11.79	20.17	2.34	1.77	17.01	6.37
5251	CAGCTGGSAGAGACASACCCAGA	87.01	8.70	28.35	13.19	5.72	3.41	22.86	10.45
5266	GTTCTTSCCAGGAAACCCSGGCAGC	-8.32	3.39	-10.50	8.45	29.49	14.34	51.95	12.36
5265	GTTCTTTCSAGGAAACCCSGGCAGC	6.29	22.23	6.58	3.64	8.10	5.42	28.87	7.85
5269	AGAGTTCSTTCCAGGSAACCCAG	61.99	21.81	-24.46	58.00	12.82	3.63	55.05	18.66
5267	GAGTTCTSTCCAGGASACCCAGG	38.47	29.10	-14.70	48.97	17.11	11.96	80.63	36.03
5268	AGTTCTTSCCAGGAASCCCAGGC	9.90	25.86	-7.31	26.47	26.33	9.18	92.35	32.38
5271	AGAGTTSTTTCCAGGAAASCCAGGC	44.52	32.61	57.40	14.54	9.44	4.83	22.79	6.99
5270	AGAGTTCTSTCCAGGAAASCCAGGC	44.46	8.40	48.23	22.36	3.31	2.76	14.18	10.22

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5243	GAGACATSCCCAGACSCAAACGG	84.50	29.82	47.59	10.35	31.74	13.09	79.61	17.53
5241	AGACATASCCAGACASAAACGGC	90.95	10.72	22.20	40.15	30.38	13.73	82.12	14.48
5242	GACATACSCAGACACSAACGGCC	73.81	41.97	36.23	29.75	22.06	9.58	70.87	9.37
5245	GAGACASACCCAGACACASACGGCC	80.40	19.16	23.13	19.81	31.05	15.73	88.26	28.47
5244	GAGACATASCCAGACACASACGGCC	126.50	25.60	88.00	43.30	17.80	10.45	77.70	25.98
5257	AGGCAGSTGGAAGAGACASACCCAG	96.50	22.07	44.00	25.12	10.88	6.15	35.95	13.92
5256	AGGCAGCTSGAAGAGACASACCCAG	103.10	12.62	66.18	15.49	4.04	2.80	27.84	10.66
5255	AGGCAGCSGGAAGAGSCATACCC	92.83	15.27	58.96	6.90	12.26	4.78	31.13	9.49
5254	GGCAGCTSGAAGAGASATACCCA	82.43	18.79	58.45	12.96	8.83	8.20	37.74	10.12
5252	AGCTGGASGAGACATSCCCAGAC	87.57	8.14	9.59	32.49	7.43	3.22	28.79	15.38
5250	GAAGAGSCATACCCAGACSCAAACG	102.70	14.83	54.28	31.30	29.53	14.04	75.86	28.78
5249	GAAGAGACSTACCCAGACSCAAACG	99.18	24.63	46.29	25.42	22.36	7.32	75.43	35.92
5248	GAAGAGASATACCCASACACAAA	49.24	20.69	21.53	23.44	89.72	39.56	135.70	43.02
5246	AAGAGACSTACCCAGSCACAAAC	28.09	21.14	22.72	15.94	52.17	11.17	112.70	38.44
5247	AGAGACASACCCAGASACAAACG	78.70	27.23	29.31	21.53	29.70	17.53	85.44	19.01
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	25.91	16.04	21.89	19.68	4.99	12.69	17.06	44.28
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	19.94	10.97	10.81	5.00	20.25	27.06	28.08	34.90
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	8.93	9.25	6.86	7.65	-1.28	1.43	7.60	13.16
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.18	4.96	12.23	11.77	-1.20	1.39	29.03	35.58
5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	14.39	10.91	10.40	7.95	6.29	12.97	21.83	31.86
5287	GCA[LNA-G]CTGGSAGAGACATASCC[LNA-A]GAC	-10.22	30.13	29.91	20.97	11.14	21.19	6.45	7.80
5286	GCA[LNA-G]CTGGSAGA[LNA-G]ACATASCC[LNA-A]GAC	10.40	16.54	5.17	18.78	12.36	10.45	32.23	21.90
5285	GCAGCTG[LNA-G]SAGAGACAT[LNA-A]SCCAGAC	0.57	12.49	-14.07	16.60	7.76	8.69	16.24	14.15
5284	GCAGCTG[LNA-G]SAGAGACATAS[LNA-C]CAGAC	-6.16	17.10	7.57	18.74	14.62	9.19	46.32	24.49
5283	GCAGCTGGS[LNA-A]GAGACATAS[LNA-C]CAGAC	18.14	16.98	9.28	26.20	8.90	6.17	40.24	12.47
5292	GTT[LNA-C]TTTSCAGGAAASCCA[LNA-G]GCA	4.16	16.50	4.89	11.13	15.39	21.60	19.66	21.58
5291	GTT[LNA-C]TTTSCAG[LNA-G]AAASCCA[LNA-G]GCA	-0.74	10.05	1.42	8.15	11.70	16.06	52.88	33.79
5290	GTTCTT[LNA-T]SCAGGAA[LNA-A]SCCAGGCA	-3.14	10.20	0.93	12.63	11.03	12.72	21.48	26.72
5289	GTTCTT[LNA-T]SCAGGAAAS[LNA-C]CAGGCA	0.43	5.96	0.99	9.62	6.88	15.65	39.99	36.29

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5288	GTTCTTTS[LNA-C]AGGAAAS[LNA-C]CAGGCA	-6.06	6.61	-11.46	10.35	6.58	11.97	20.12	30.75
5241	AGACATASCCAGACASAAACGGC	37.10	22.45	53.64	15.42	43.13	22.30	79.66	21.62
5242	GACATACSCAGACACSAACGGCC	50.01	21.60	21.58	15.74	67.02	35.41	83.55	61.27
5243	GAGACATSCCCAGACSCAAACGG	49.95	11.51	29.51	6.61	40.47	25.79	143.30	44.64
5237	AGACATA(S1)CCAGACA(S1)AAACGGC	41.00	21.58	27.91	8.85	51.69	49.87	103.79	37.66
5236	GACATAC(S1)CAGACAC(S1)AACGGCC	46.48	5.54	20.34	11.08	9.03	14.52	72.91	57.87
5235	GAGACAT(S1)CCCAGAC(S1)CAAACGG	45.33	8.89	33.99	13.59	23.89	18.73	133.34	42.50
5157	TTCTTTCSAGGAAACSCAGGCAG	11.16	8.04	9.91	7.60	5.90	10.52	94.03	74.88
5156	GTTCTTTSCAGGAAASCCAGGCA	5.10	4.93	-8.11	6.11	12.92	15.28	25.15	25.51
5155	TCTTTCCSGGAAACCSAGGCAGC	10.06	10.19	3.12	11.72	6.96	9.36	26.97	9.87
5261	TTCTTTC(S1)AGGAAAC(S1)CAGGCAG	11.38	11.69	7.69	15.12	11.99	14.32	54.16	41.27
5260	GTTCTTT(S1)CAGGAAA(S1)CCAGGCA	1.44	7.33	-4.17	4.75	9.79	9.57	27.69	15.98
5259	TCTTTCC(S1)GGAAACC(S1)AGGCAGC	7.18	11.81	-11.24	5.27	18.13	13.56	55.71	28.06
5182	ACATCCASCCATCCASCCATTCA	-37.97	26.85	-4.07	52.32	129.74	41.79	122.30	48.42
5181	ACACATCSATCCATCSATCCATT	5.77	35.61	-11.91	27.75	96.81	38.14	111.73	35.15
5180	CACATCCSTCCATCCSTCCATTC	-14.00	37.66	1.96	30.50	159.36	43.66	164.55	47.07
5274	ACATCCA(S1)CCATCCA(S1)CCATTCA	-16.66	14.80	-5.26	26.53	165.82	42.96	151.38	29.35
5273	ACACATC(S1)ATCCATC(S1)ATCCATT	-7.44	24.85	-21.89	16.44	162.48	39.49	116.38	15.71
5272	CACATCC(S1)TCCATCC(S1)TCCATTC	-9.65	36.42	-0.61	27.96	145.25	19.25	132.10	35.74
5209	TCTTTCCAGGAAACCCAGGCA	18.29	17.99	9.91	14.01	16.42	18.29	16.34	9.91
5220	CAGGAAACCCAGGCA	2.74	3.88	2.44	1.85	16.24	2.74	14.66	2.44
5221	TCTTTCCAGGAAACC	12.94	2.00	7.34	7.10	12.75	12.94	12.29	7.34
5218	CCAGGAAACCCAGGCA	0.00	0.00	0.74	1.05	13.49	0.00	16.04	0.74
5219	TCTTTCCAGGAAACCC	17.89	25.30	17.60	2.62	18.82	17.89	15.79	17.60
5216	TCCAGGAAACCCAGGCA	0.00	0.00	1.54	2.17	14.54	0.00	15.41	1.54
5217	TCTTTCCAGGAAACCCA	6.80	9.61	2.79	1.25	12.77	6.80	15.04	2.79
5214	TTCCAGGAAACCCAGGCA	0.70	0.98	0.00	0.00	16.31	0.70	11.42	0.00
5215	TCTTTCCAGGAAACCCAG	19.21	8.43	49.84	70.94	16.89	19.21	19.14	49.84
5212	TTTCCAGGAAACCCAGGCA	0.55	0.78	3.96	5.60	13.97	0.55	12.15	3.96

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5213	TCTTTCCAGGAAACCCAGG	11.47	8.56	2.24	3.17	16.52	11.47	15.47	2.24
5210	CTTTCCAGGAAACCCAGGCA	6.60	0.75	1.59	2.25	18.60	6.60	12.55	1.59
5211	TCTTTCCAGGAAACCCAGGC	15.08	15.12	11.29	4.48	15.92	15.08	12.81	11.29

* Unless otherwise noted, each of the nucleosides of antisense oligonucleotides shown are modified nucleosides with 2'-O-(2-methoxyethyl) (2'-MOE) sugar moieties, each "C" is replaced with a 5-methylcytosine (5-MeC), and all internucleoside linkages are phosphorothioate linkages. A spacer, as indicated by any of **S, S1, or S#,** is not a nucleoside. S represents a spacer of Formula (Iia') as disclosed herein. S1 represents a spacer of Formula (IIIa'); S# represents a spacer of Formula (IIib'). [LNA-X] refers to a locked nucleic acid with a corresponding base X (e.g., LNA-A refers to a locked nucleic acid with an adenine nucleobase, LNA-G refers to a locked nucleic acid with a guanine nucleobase, LNA-T refers to a locked nucleic acid with a thymine nucleobase, and LNA-C refers to a locked nucleic acid with a cytosine nucleobase).

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INCORPORATION BY REFERENCE

[00473] The entire disclosure of each of the patent documents and scientific articles cited herein is incorporated by reference for all purposes.

EQUIVALENTS

[00474] The disclosure can be embodied in other specific forms without departing from the essential characteristics thereof. The foregoing embodiments therefore are to be considered illustrative rather than limiting on the disclosure described herein. The scope of the disclosure is indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

AMENDMENTS TO THE CLAIMS

1. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

2. (Original) The compound of claim 1, wherein the modified oligonucleotide comprises a spacer.

3. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. (Original) An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

5. (Original) The oligonucleotide of claim 4, further comprising a spacer.

6. (Original) An oligonucleotide comprising a sequence that is at least 85 98% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. (Original) The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

8. (Original) The compound of claims 1-3 or 7, or oligonucleotides of claims 5-7, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

9. (Original) The compound of any one of claims 1-3 or 7-8 or oligonucleotide of any one of claims 44-8, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

10. (Original) The compound of any one of claims 1-3 or 7-9 or oligonucleotide of any one of claims 5-9, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

11. (Original) The compound of any one of claims 1-3 or 7-10 or oligonucleotide of any one of claims 5-10, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

12. (Currently Amended) The compound or oligonucleotide of any one of claims 7-11, wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; ~~5066~~5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-~~5292~~5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

13. (Currently Amended) The compound or oligonucleotide of any one of claims 7-12, wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

14. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

15. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs;

5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

16. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

17. (Currently Amended) The compound or oligonucleotide of claim 16, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

18. (Currently Amended) The compound or oligonucleotide of claim 16 or 17, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

19. (Original) The compound or oligonucleotide of any one of claims 1-18, wherein the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length.

20. (Original) The compound or oligonucleotide of claim 19, wherein the oligonucleotide is at least 19 oligonucleotide units in length.

21. (Original) The compound or oligonucleotide of any one of claims 1-3 and 5-20, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

22. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

23. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

24. (Original) The compound or oligonucleotide of claim 21 or 23, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

25. (Original) The compound or oligonucleotide of claim 24, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

26. (Original) The compound or oligonucleotide of claim 24 or 25, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

27. (Original) The compound or oligonucleotide of any one of claims 24-26, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

28. (Original) The compound or oligonucleotide of any one of claims 24-27, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

29. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

30. (Original) The compound or oligonucleotide of claim 29, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

31. (Original) The compound or oligonucleotide of claim 30, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

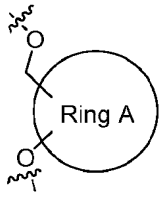
32. (Original) The compound or oligonucleotide of claim 21, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

33. (Original) The compound or oligonucleotide of claim 32, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

34. (Original) The compound or oligonucleotide of claim 33, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

35. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

36. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

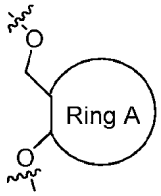


Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  symbol represents the point of connection to an internucleoside linkage.

37. (Original) The compound or oligonucleotide of claim 36, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



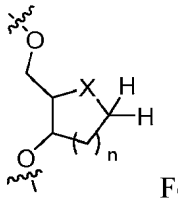
Formula (Xa).

38. (Original) The compound or nucleotide of claim 36 or 37, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, 266yrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

39. (Original) The compound or nucleotide of claim 38 wherein ring A is tetrahydrofuranyl.

40. (Original) The compound or nucleotide of claim 38 wherein ring A is tetrahydropyranyl.

41. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I, wherein:

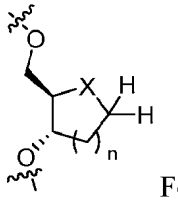


Formula (I)

X is selected from $-CH_2-$ and -O-; and

n is 0, 1, 2 or 3.

42. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I', wherein:

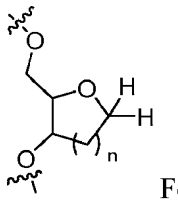


Formula (I')

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

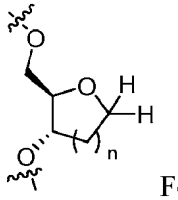
43. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

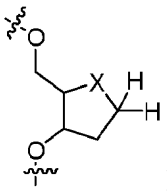
44. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

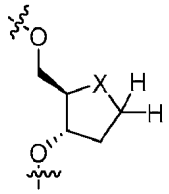
45. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

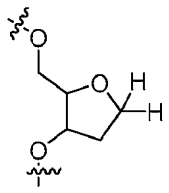
46. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

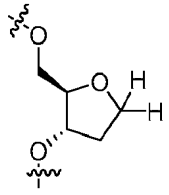
X is selected from $-CH_2-$ and -O-.

47. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



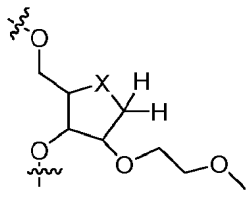
Formula (Iia).

48. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



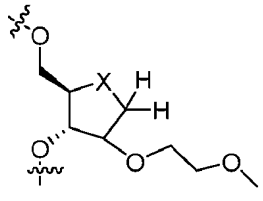
Formula (Iia').

49. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:


Formula (IIi)

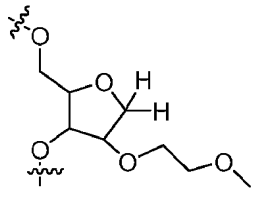
X is selected from -CH_2- and -O-.

50. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:

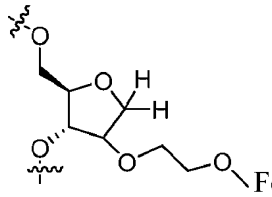

Formula (IIi')

X is selected from -CH_2- and -O-.

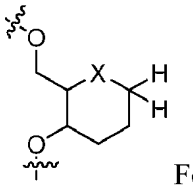
51. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

52. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:


Formula (IIib').

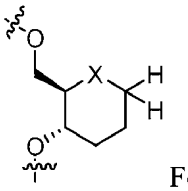
53. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH_2- and -O-.

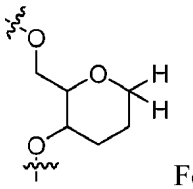
54. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

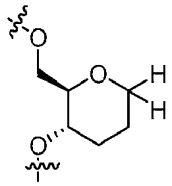
X is selected from -CH_2- and -O-.

55. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

56. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

57. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide further comprises a locked nucleic acid (LNA).

58. (Original) The compound or oligonucleotide of claim 57, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

59. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

60. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

61. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

62. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

63. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

64. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

65. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.

66. (Original) The compound or oligonucleotide of any one of the above claims, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

67. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

68. (Original) The compound or oligonucleotide of claim 67, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

69. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

70. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

71. (Original) The compound or oligonucleotide of claim 70, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

72. (Original) The compound or oligonucleotide of claim 71, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

73. (Original) The compound or oligonucleotide of claim 71, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

74. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

75. (Original) The compound or oligonucleotide of claim 74, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

76. (Original) The compound or oligonucleotide of claim 70, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

77. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

78. (Original) The compound or oligonucleotide of claim 77, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

79. (Original) The compound or oligonucleotide of claim 77 or 78, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

80. (Original) The compound or oligonucleotide of claim 79, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

81. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

82. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

83. (Original) The compound or oligonucleotide of claim 81 or 82, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

84. (Currently Amended) A compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

85. (Currently Amended) An oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, or SEQ ID NOs: 5168-5202.

86. (Currently Amended) The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

87. (Currently Amended) The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~.

88. (Original) The compound or oligonucleotide of any of claims 67-87, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

89. (Original) The compound or oligonucleotide of any one of the above claims, wherein one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage.

90. (Original) The compound or oligonucleotide of claim 89, wherein the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

91. (Original) The compound or oligonucleotide of claim 89 or 90, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

92. (Original) The compound or oligonucleotide of claim 90, wherein the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration.

93. (Original) The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

94. (Original) The compound or oligonucleotide of claim 93, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

95. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein.

96. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein.

97. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein.

98. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.

99. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein.

100. (Original) The compound or oligonucleotide of any one of claims 95-99, wherein increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide.

101. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein.

102. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

103. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient a compound or an oligonucleotide of any one of claims 1-102.

104. (Original) The method of claim 103, wherein the neurological disease selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

105. (Original) The method of claim 104, wherein the neurological disease is ALS.

106. (Original) The method of claim 104, wherein the neurological disease is FTD.

107. (Original) The method of claim 104, wherein the neurological disease is ALS with FTD.

108. (Original) The method of claim 104, wherein the neurological disease is AD.

109. (Original) The method of claim 104, wherein the neurological disease is PD.

110. (Original) The method of claim 103, wherein the neuropathy is chemotherapy induced neuropathy.

111. (Original) A method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide of any one of claims 1-102.

112. (Original) A method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-102.

113. (Original) The method of claim 111 or 112, wherein the neuron is a motor neuron.

114. (Original) The method of claim 111 or 112, wherein the neuron is a spinal cord neuron.

115. (Original) The method of any one of claims 111-114, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

116. (Original) The method of claim 115, wherein the neuropathy is chemotherapy induced neuropathy.

117. (Original) The method of any one of claims 111-116, wherein the exposing is performed *in vivo* or *ex vivo*.

118. (Original) The method of any one of claims 111-116, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.

119. (Original) The method of any one of claims 111-118, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.

120. (Original) The method of claim 119, wherein the oligonucleotide is administered orally.

121. (Original) The method of any one of claims 111-119, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

122. (Original) The method of any one of claims 111-121, wherein the patient is a human.

123. (Original) A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

124. (Original) The pharmaceutical composition of claim 123, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

125. (Original) A method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124.

126. (Original) The method of claim 125, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such 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.

127. (Original) The method of claim 126, wherein the neurological disease is ALS.

128. (Original) The method of claim 126, wherein the neurological disease is FTD.

129. (Original) The method of claim 126, wherein the neurological disease is ALS with FTD.

130. (Original) The method of claim 126, wherein the neurological disease is AD.

131. (Original) The method of claim 126, wherein the neurological disease is PD.

132. (Original) The method of claim 125, wherein the neuropathy is chemotherapy induced neuropathy.

133. (Original) The method of any one of claims 125-132, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.

134. (Original) The method of any one of claims 125-132, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.

135. (Original) The method of any one of claims 125-134, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

136. (Original) The method of any one of claims 125-135, wherein the patient is human.

137. (Currently Amended) A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene

phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

138. (Currently Amended) A method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

139. (Currently Amended) A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

140. (Currently Amended) A method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

141. (Currently Amended) A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133~~5066~~-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5~~5292~~, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

142. (Original) The method of any one of claims 137-141, wherein nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

143. (Original) The method of claim 142, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

144. (Original) The method of any one of claims 137-141, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

145. (Original) The method of any one of claims 137-141, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

146. (Original) The method of claim 145, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

147. (Original) The method of claim 146, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

148. (Original) The method of claim 146, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

149. (Original) The method of any one of claims 137-141, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

150. (Original) The method of claim 149, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

151. (Original) The method of any one of claims 137-141, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

152. (Original) The method of any one of claims 137-141, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

153. (Original) The method of claim 152, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

154. (Original) The method of claim 152 or 153, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

155. (Original) The method of claim 154, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

156. (Original) The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

157. (Original) The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

158. (Original) The method of claim 156 or 157, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

159. (Original) The method of any of claims 142-158, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

160. (Original) The method of any one of claims 137-141, wherein at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

161. (Original) The method of any one of claims 137-141, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

162. (Original) An oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

163. (Original) The method of any one of claims 103-122 or 125-161, the pharmaceutical composition of claim 123 or 124, or the oligonucleotide of any one of claims 1-102 or 162, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

164. (Original) The method of any one of claims 103-122, 125-161, or 163, the pharmaceutical composition of claim 123, 124, or 163, or the oligonucleotide of any one of claims 1-102 or 162-163, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

165. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, in combination with a second therapeutic agent.

166. (Original) The method of claim 165, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), 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.

167. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

168. (Original) The method of any one of claims 103-122, 125-161, or 163-167, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

169. (Original) The method of claim 168, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

170. (Original) The method of claim 168, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

171. (Original) The method of claim 168 or 170, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

172. (Original) The method of claim 171, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

173. (Original) The method of claim 171 or 172, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

174. (Original) The method of any one of claims 171-173, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

175. (Original) The method of any one of claims 171 -174, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

176. (Original) The method of claim 168, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

177. (Original) The method of claim 176, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

178. (Original) The method of claim 177, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

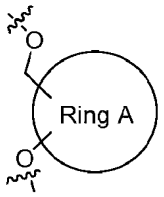
179. (Original) The method of claim 168, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

180. (Original) The method of claim 179, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

181. (Original) The method of claim 180, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

182. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

183. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

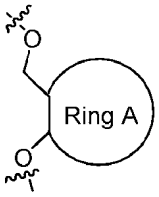


Formula (X)

Ring A is is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  symbol represents the point of connection to an internucleoside linkage.

184. (Original) The method of claim 183, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



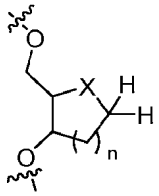
Formula (Xa).

185. (Original) The method of claim 183 or 184, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

186. (Original) The method of claim 185, wherein ring A is tetrahydrofuranyl.

187. (Original) The method of claim 185, wherein ring A is tetrahydropyranyl.

188. (Original) The method of any one of claims 168-181 wherein each of the first, second or third spacers is independently represented by Formula (I), wherein:

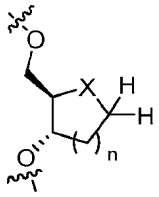


Formula (I)

X is selected from -CH_2- and -O-; and

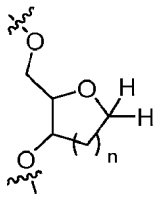
n is 0, 1, 2 or 3.

189. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (I'), wherein:



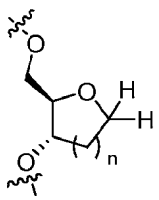
Formula (I').

190. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



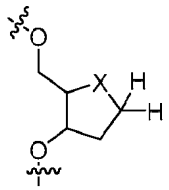
Formula (Ia).

191. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

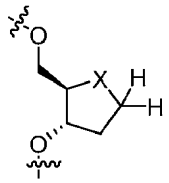
192. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from $-CH_2-$ and -O-.

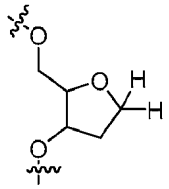
193. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

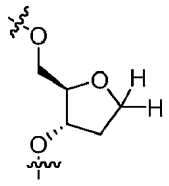
X is selected from $-CH_2-$ and -O-.

194. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



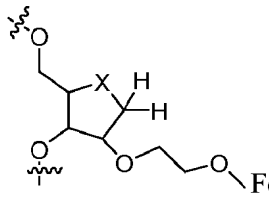
Formula (Iia).

195. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



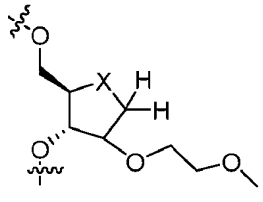
Formula (Iia').

196. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:


Formula (IIi)

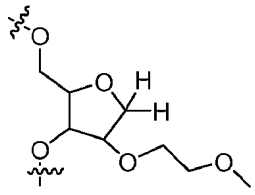
X is selected from -CH_2- and -O-.

197. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:

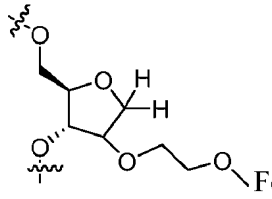

Formula (IIi')

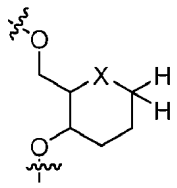
X is selected from -CH_2- and -O-.

198. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

199. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:

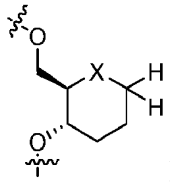

Formula (IIib').The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH_2- and -O-.

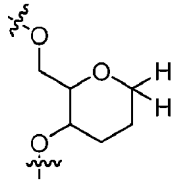
200. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

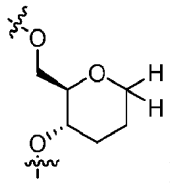
X is selected from -CH_2- and -O-.

201. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

202. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

203. (Original) The method of any one of claims 168-202, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

204. (Original) The method of any one of claims 168-203, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

205. (Original) The method of any one of claims 168-204, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

206. (Original) The method of any one of claims 168-205, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

207. (Original) The method of any one of claims 168-206, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

208. (Original) The method of any one of claims 168-207, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

209. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon.

210. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% reduction of an UNC13A transcript with a cryptic exon.

211. (Original) The compound or oligonucleotide of any one of claims 200-201, wherein reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide.

212. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.

AMENDMENTS TO THE CLAIMS

1. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

2. (Original) The compound of claim 1, wherein the modified oligonucleotide comprises a spacer.

3. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. (Original) An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

5. (Original) The oligonucleotide of claim 4, further comprising a spacer.

6. (Original) An oligonucleotide comprising a sequence that is at least 85 98% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. (Original) The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

AMENDMENTS TO THE CLAIMS

1. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

2. (Original) The compound of claim 1, wherein the modified oligonucleotide comprises a spacer.

3. (Original) A compound comprising a modified oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

4. (Original) An oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage.

5. (Original) The oligonucleotide of claim 4, further comprising a spacer.

6. (Original) An oligonucleotide comprising a sequence that is at least 85 98% complementary to an equal length portion of any one of SEQ ID NO: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is a non-natural linkage, and further wherein the oligonucleotide comprises a spacer.

7. (Original) The compound of claims 1-3 or oligonucleotide of claims 5-6, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides.

8. (Original) The compound of claims 1-3 or 7, or oligonucleotides of claims 5-7, wherein the oligonucleotide comprises a segment with at most 10, 9, or 8 linked nucleosides.

9. (Original) The compound of any one of claims 1-3 or 7-8 or oligonucleotide of any one of claims 44-8, wherein the oligonucleotide comprises a segment with at most 7 linked nucleosides.

10. (Original) The compound of any one of claims 1-3 or 7-9 or oligonucleotide of any one of claims 5-9, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides.

11. (Original) The compound of any one of claims 1-3 or 7-10 or oligonucleotide of any one of claims 5-10, wherein every segment of the oligonucleotide comprises at most 7 linked nucleosides.

12. (Currently Amended) The compound or oligonucleotide of any one of claims 7-11, wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

13. (Currently Amended) The compound or oligonucleotide of any one of claims 7-12, wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

14. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares at least 95% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 51335166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

15. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a sequence that shares 100% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs;

5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

16. (Currently Amended) The compound or oligonucleotide of any one of claims 7-13, wherein the oligonucleotide comprises a segment with at most 11 linked nucleosides or at most 7 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

17. (Currently Amended) The compound or oligonucleotide of claim 16, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 85% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

18. (Currently Amended) The compound or oligonucleotide of claim 16 or 17, wherein the oligonucleotide comprises a segment with at most 6, 5, 4, 3, or 2 linked nucleosides, and wherein the oligonucleotide comprises a sequence that shares at least 90% identity with an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

19. (Original) The compound or oligonucleotide of any one of claims 1-18, wherein the oligonucleotide is at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, or at least 25 oligonucleotide units in length.

20. (Original) The compound or oligonucleotide of claim 19, wherein the oligonucleotide is at least 19 oligonucleotide units in length.

21. (Original) The compound or oligonucleotide of any one of claims 1-3 and 5-20, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

22. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

23. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

24. (Original) The compound or oligonucleotide of claim 21 or 23, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

25. (Original) The compound or oligonucleotide of claim 24, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

26. (Original) The compound or oligonucleotide of claim 24 or 25, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

27. (Original) The compound or oligonucleotide of any one of claims 24-26, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

28. (Original) The compound or oligonucleotide of any one of claims 24-27, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

29. (Original) The compound or oligonucleotide of claim 21, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

30. (Original) The compound or oligonucleotide of claim 29, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

31. (Original) The compound or oligonucleotide of claim 30, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

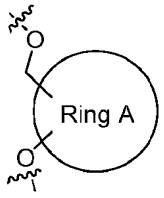
32. (Original) The compound or oligonucleotide of claim 21, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

33. (Original) The compound or oligonucleotide of claim 32, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

34. (Original) The compound or oligonucleotide of claim 33, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

35. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

36. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

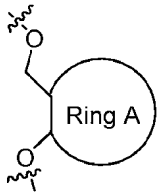


Formula (X)

Ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  symbol represents the point of connection to an internucleoside linkage.

37. (Original) The compound or oligonucleotide of claim 36, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



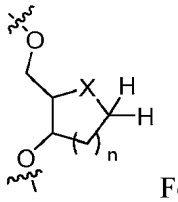
Formula (Xa).

38. (Original) The compound or nucleotide of claim 36 or 37, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, 265yrrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

39. (Original) The compound or nucleotide of claim 38 wherein ring A is tetrahydrofuranyl.

40. (Original) The compound or nucleotide of claim 38 wherein ring A is tetrahydropyranyl.

41. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I, wherein:

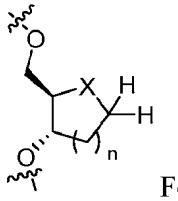


Formula (I)

X is selected from $-CH_2-$ and -O-; and

n is 0, 1, 2 or 3.

42. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula I', wherein:

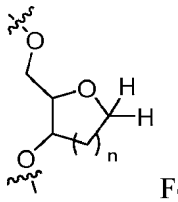


Formula (I')

X is selected from -CH_2- and -O-; and

n is 0, 1, 2 or 3.

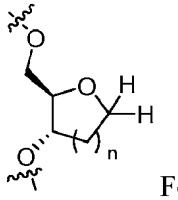
43. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



Formula (Ia); and

n is 0, 1, 2 or 3.

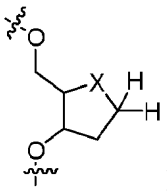
44. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia'); and

n is 0, 1, 2 or 3.

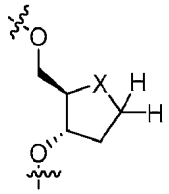
45. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

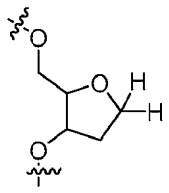
46. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

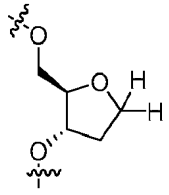
X is selected from $-CH_2-$ and -O-.

47. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



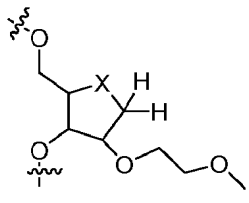
Formula (Iia).

48. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



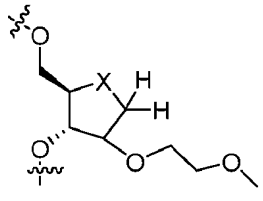
Formula (Iia').

49. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:


Formula (IIi)

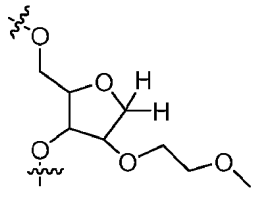
X is selected from -CH_2- and -O-.

50. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:

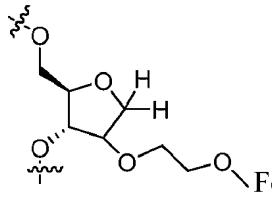

Formula (IIi')

X is selected from -CH_2- and -O-.

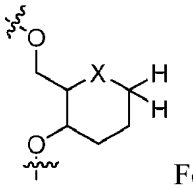
51. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

52. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:


Formula (IIib').

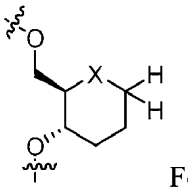
53. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH_2- and -O-.

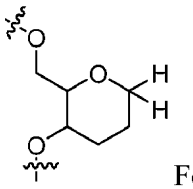
54. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

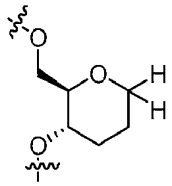
X is selected from -CH_2- and -O-.

55. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

56. (Original) The compound or oligonucleotide of any one of claims 21-34, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

57. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide further comprises a locked nucleic acid (LNA).

58. (Original) The compound or oligonucleotide of claim 57, wherein the locked nucleic acid (LNA) is located at one of positions 4, 7, 9, 12, 15, or 20 of the oligonucleotide.

59. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

60. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

61. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

62. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

63. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

64. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

65. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide is between 12 and 40 oligonucleotide units in length.

66. (Original) The compound or oligonucleotide of any one of the above claims, wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate

linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage.

67. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

68. (Original) The compound or oligonucleotide of claim 67, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

69. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

70. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

71. (Original) The compound or oligonucleotide of claim 70, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

72. (Original) The compound or oligonucleotide of claim 71, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

73. (Original) The compound or oligonucleotide of claim 71, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

74. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

75. (Original) The compound or oligonucleotide of claim 74, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

76. (Original) The compound or oligonucleotide of claim 70, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

77. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

78. (Original) The compound or oligonucleotide of claim 77, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

79. (Original) The compound or oligonucleotide of claim 77 or 78, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

80. (Original) The compound or oligonucleotide of claim 79, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

81. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

82. (Original) The compound or oligonucleotide of any one of claims 1-66, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

83. (Original) The compound or oligonucleotide of claim 81 or 82, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

84. (Currently Amended) A compound comprising an oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

85. (Currently Amended) An oligonucleotide comprising a nucleobase sequence that shares at least 90% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, or SEQ ID NOs: 5168-5202.

86. (Currently Amended) The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 95% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

87. (Currently Amended) The compound of claim 84 or the oligonucleotide of claim 84 or 85, wherein the nucleobase sequence shares at least 100% identity to an equal length portion of any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5.

88. (Original) The compound or oligonucleotide of any of claims 67-87, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

89. (Original) The compound or oligonucleotide of any one of the above claims, wherein one or more internucleoside linkage of the oligonucleotide is a modified internucleoside linkage.

90. (Original) The compound or oligonucleotide of claim 89, wherein the modified internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

91. (Original) The compound or oligonucleotide of claim 89 or 90, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

92. (Original) The compound or oligonucleotide of claim 90, wherein the phosphorothioate linkage is in one of a *R*p configuration or a *S*p configuration.

93. (Original) The compound or oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified sugar moiety.

94. (Original) The compound or oligonucleotide of claim 93, wherein the modified sugar moiety is one of a 2'-OMe modified sugar moiety, bicyclic sugar moiety, 2'-*O*-(2-methoxyethyl) (2'-MOE), 2'-deoxy-2'-fluoro nucleoside, 2'-fluoro-β-D-arabinonucleoside, locked nucleic acid (LNA), constrained ethyl 2'-4'-bridged nucleic acid (cEt), *S*-cEt, tcDNA, hexitol nucleic acids (HNA), and tricyclic analog (*e.g.*, tcDNA).

95. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% increase of full length UNC13A protein.

96. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% increase of full length UNC13A protein.

97. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 200% increase of full length UNC13A protein.

98. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 300% increase of full length UNC13A protein.

99. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 400% increase of full length UNC13A protein.

100. (Original) The compound or oligonucleotide of any one of claims 95-99, wherein increase of the full length UNC13A protein is measured in comparison to a reduced level of full length UNC13A protein achieved using a TDP43 antisense oligonucleotide.

101. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% rescue of full length UNC13A protein.

102. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 50%, 60%, 70%, 80%, or 90% reduction of a mis-spliced UNC13A transcript.

103. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to the patient a compound or an oligonucleotide of any one of claims 1-102.

104. (Original) The method of claim 103, wherein the neurological disease selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, corticobasal degeneration (CBD), nerve injuries (e.g., brachial plexus injuries), neuropathies (e.g., chemotherapy induced neuropathy), TDP43 proteinopathies (e.g., chronic traumatic encephalopathy, Perry Syndrome, Dementia with Lewy body in association with Alzheimer's disease, Parkinson's disease with or without dementia, Limbic-predominant age-related TDP-43 encephalopathy (LATE)), epilepsy, Cerebral Age-Related TDP-43 With Sclerosis (CARTS), facial onset sensory and motor neuronopathy, Guam Parkinson-dementia complex, multisystem proteinopathy, CTE, and synaptic diseases like autism.

105. (Original) The method of claim 104, wherein the neurological disease is ALS.

106. (Original) The method of claim 104, wherein the neurological disease is FTD.

107. (Original) The method of claim 104, wherein the neurological disease is ALS with FTD.

108. (Original) The method of claim 104, wherein the neurological disease is AD.

109. (Original) The method of claim 104, wherein the neurological disease is PD.

110. (Original) The method of claim 103, wherein the neuropathy is chemotherapy induced neuropathy.

111. (Original) A method of restoring axonal outgrowth and/or regeneration of a neuron, the method comprising exposing the neuron to a compound or an oligonucleotide of any one of claims 1-102.

112. (Original) A method of increasing, promoting, stabilizing, or maintaining UNC13A expression and/or function in a neuron, the method comprising exposing the cell to a compound or an oligonucleotide of any one of claims 1-102.

113. (Original) The method of claim 111 or 112, wherein the neuron is a motor neuron.

114. (Original) The method of claim 111 or 112, wherein the neuron is a spinal cord neuron.

115. (Original) The method of any one of claims 111-114, wherein the neuron is a neuron of a patient in need of treatment of a neurological disease and/or a neuropathy.

116. (Original) The method of claim 115, wherein the neuropathy is chemotherapy induced neuropathy.

117. (Original) The method of any one of claims 111-116, wherein the exposing is performed *in vivo* or *ex vivo*.

118. (Original) The method of any one of claims 111-116, wherein the exposing comprises administering the oligonucleotide to a patient in need thereof.

119. (Original) The method of any one of claims 111-118, wherein the oligonucleotide is administered topically, parenterally, intrathecally, intrathalamically, intracisternally, orally, rectally, buccally, sublingually, vaginally, pulmonarily, intratracheally, intranasally, transdermally, intraduodenally, or intracerebroventricularly.

120. (Original) The method of claim 119, wherein the oligonucleotide is administered orally.

121. (Original) The method of any one of claims 111-119, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

122. (Original) The method of any one of claims 111-121, wherein the patient is a human.

123. (Original) A pharmaceutical composition comprising the oligonucleotide of any one of claims 1-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

124. (Original) The pharmaceutical composition of claim 123, wherein the pharmaceutical composition is suitable for topical, intrathecal, intrathalamic, intracisternal, intracerebroventricular, parenteral, oral, pulmonary, intratracheal, intranasal, transdermal, rectal, buccal, sublingual, vaginal, or intraduodenal administration.

125. (Original) A method of treating a neurological disease or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124.

126. (Original) The method of claim 125, wherein the neurological disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), ALS with FTD, Alzheimer's disease (AD), Parkinson's disease (PD), Parkinson's Disease with dementia, dementia with lewy bodies, synucleinopathies, Huntington's disease, Brachial plexus injuries, peripheral nerve injuries, progressive supranuclear palsy (PSP), brain trauma, spinal cord injury, tuberous sclerosis complex, Pick's Disease, tauopathies, primary age-related tauopathy, Down Syndrome, epilepsy/seizure disorder, depression, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), HIV-associated neurocognitive disorders (HAND), multisystem atrophy, amnestic mild cognitive impairment, corticobasal degeneration (CBD) and/or neuropathies such 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.

127. (Original) The method of claim 126, wherein the neurological disease is ALS.

128. (Original) The method of claim 126, wherein the neurological disease is FTD.

129. (Original) The method of claim 126, wherein the neurological disease is ALS with FTD.

130. (Original) The method of claim 126, wherein the neurological disease is AD.

131. (Original) The method of claim 126, wherein the neurological disease is PD.

132. (Original) The method of claim 125, wherein the neuropathy is chemotherapy induced neuropathy.

133. (Original) The method of any one of claims 125-132, wherein the pharmaceutical composition is administered topically, parenterally, orally, pulmonarily, rectally, buccally, sublingually, vaginally, intratracheally, intranasally, intracisternally, intrathecally, intrathalamically, transdermally, intraduodenally, or intracerebroventricularly.

134. (Original) The method of any one of claims 125-132, wherein the pharmaceutical composition is administered intrathecally, intrathalamically, or intracisternally.

135. (Original) The method of any one of claims 125-134, wherein a therapeutically effective amount of the oligonucleotide is administered intrathecally, intrathalamically or intracisternally.

136. (Original) The method of any one of claims 125-135, wherein the patient is human.

137. (Currently Amended) A method for treating a neurological disease in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene

phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

138. (Currently Amended) A method for treating amyotrophic lateral sclerosis (ALS) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

139. (Currently Amended) A method for treating Alzheimer's Disease (AD) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA), optionally, wherein the oligonucleotide further comprises a spacer

140. (Currently Amended) A method for treating frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

141. (Currently Amended) A method for treating amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD) in a subject in need thereof, the method comprising administering to the subject an oligonucleotide comprising a segment with at most 7 linked nucleosides, and wherein oligonucleotide shares at least 85% identity with any one of SEQ ID NOs: 1-1264, SEQ ID NOs: 2529-3792, SEQ ID NOs; 5133-5166, SEQ ID NOs: 5168-5202, SEQ ID NOs: 5209-5221, or SEQ ID NOs: 5235-5573 or any of the sequences in Tables 3A, 3B, 4 and 5, or a pharmaceutically acceptable salt thereof;

wherein at least one (*i.e.*, one or more) nucleoside linkage of the oligonucleotide is independently selected from the group consisting of: a phosphodiester linkage, a phosphorothioate linkage, an alkyl phosphate linkage, a phosphorodithioate linkage, a phosphotriester linkage, an alkylphosphonate linkage, a 3-methoxypropyl phosphonate linkage, a methylphosphonate linkage, an aminoalkylphosphotriester linkage, an alkylene phosphonate linkage, a phosphinate linkage, a phosphoramidate linkage, a phosphoramidothioate linkage, a thiophosphorodiamidate linkage, a phosphorodiamidate linkage, an aminoalkylphosphoramidate linkage, a thiophosphoramidate linkage, a thionoalkylphosphonate linkage, a thionoalkylphosphotriester linkage, a thiophosphate linkage, a selenophosphate linkage, and a boranophosphate linkage, and/or

wherein at least one (*i.e.*, one or more) nucleoside is substituted with a component selected from the group consisting of a 2'-O-(2-methoxyethyl) nucleoside, a 2'-O-methyl nucleoside, a 2'-O-(N-methylacetamide) nucleoside, a 2'-deoxy-2'-fluoro nucleoside, a 2'-fluoro-β-D-arabinonucleoside, a locked nucleic acid (LNA), a tricyclic nucleic acid, constrained methoxyethyl (cMOE), constrained ethyl (cET), and a peptide nucleic acid (PNA)

optionally, wherein the oligonucleotide further comprises a spacer.

142. (Original) The method of any one of claims 137-141, wherein nucleoside linkages that link a base at position 3 or position 4 of the oligonucleotide are phosphodiester linkages.

143. (Original) The method of claim 142, wherein only one nucleoside linkage that links a base at position 3 or position 4 of the oligonucleotide is a phosphodiester linkage.

144. (Original) The method of any one of claims 137-141, wherein nucleoside linkages that link bases at both position 3 and position 4 of the oligonucleotide are phosphodiester linkages.

145. (Original) The method of any one of claims 137-141, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds.

146. (Original) The method of claim 145, wherein only the base immediately preceding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

147. (Original) The method of claim 146, wherein the base immediately preceding the spacer in the oligonucleotide is further linked to a further preceding base through a phosphodiester bond.

148. (Original) The method of claim 146, wherein the oligonucleotide comprises a second spacer, wherein a base immediately preceding the second spacer is linked to a further preceding base through a phosphodiester bond.

149. (Original) The method of any one of claims 137-141, wherein one or more bases immediately succeeding a spacer in the oligonucleotide are linked through phosphodiester bonds.

150. (Original) The method of claim 149, wherein only the base immediately succeeding the spacer in the oligonucleotide is linked to the spacer through a phosphodiester bond.

151. (Original) The method of any one of claims 137-141, wherein two bases immediately preceding the spacer in the oligonucleotide are linked through phosphodiester bonds.

152. (Original) The method of any one of claims 137-141, wherein one or more bases immediately preceding a spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the spacer in the oligonucleotide are linked through phosphodiester bonds.

153. (Original) The method of claim 152, wherein one base immediately preceding the spacer and one base immediately succeeding the spacer are linked through phosphodiester bonds.

154. (Original) The method of claim 152 or 153, wherein the oligonucleotide includes a second spacer, and wherein one or more bases immediately preceding the second spacer in the oligonucleotide are linked through phosphodiester bonds and wherein one or more bases immediately succeeding the second spacer in the oligonucleotide are linked through phosphodiester bonds.

155. (Original) The method of claim 154, wherein one base immediately preceding the second spacer and one base immediately succeeding the second spacer are linked through phosphodiester bonds.

156. (Original) The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least two bases.

157. (Original) The method of any one of claims 137-141, wherein the oligonucleotide comprises a range of bases that are linked through phosphodiester bonds, the range of bases comprising at least five bases.

158. (Original) The method of claim 156 or 157, wherein the oligonucleotide comprises two or more spacers, and wherein the range of bases are positioned between the at least two spacers.

159. (Original) The method of any of claims 142-158, wherein the oligonucleotide is any one of a 19mer, 21mer, 23mer, or 25mer.

160. (Original) The method of any one of claims 137-141, wherein at least one (*i.e.*, one or more) internucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

161. (Original) The method of any one of claims 137-141, wherein all internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

162. (Original) An oligonucleotide and a pharmaceutically acceptable excipient, the oligonucleotide comprising a sequence that is at least 85% complementary to an equal length portion of any one of SEQ ID NOs: 5057-5065 or SEQ ID NOs: 5206-5208, a sequence having 90% identity thereof, or to a 15 to 50 contiguous nucleobase portion thereof, optionally wherein the oligonucleotide comprises a spacer and wherein the oligonucleotide is capable of increasing, restoring, or stabilizing expression of the UNC13A mRNA capable of translation of a functional UNC13A and/or activity and/or function of UNC13A protein in a cell or a human patient of an immune-mediated demyelinating disease, and wherein the level of increase, restoration, or stabilization of expression and/or activity and/or function is sufficient for use of the oligonucleotide as a medicament for the treatment of the immune-mediated demyelinating disease.

163. (Original) The method of any one of claims 103-122 or 125-161, the pharmaceutical composition of claim 123 or 124, or the oligonucleotide of any one of claims 1-102 or 162, wherein the oligonucleotide comprises one or more chiral centers and/or double bonds.

164. (Original) The method of any one of claims 103-122, 125-161, or 163, the pharmaceutical composition of claim 123, 124, or 163, or the oligonucleotide of any one of claims 1-102 or 162-163, wherein the oligonucleotide exist as stereoisomers selected from geometric isomers, enantiomers, and diastereomers.

165. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, in combination with a second therapeutic agent.

166. (Original) The method of claim 165, wherein the second therapeutic agent is selected from Riluzole (Rilutek), PrimeC, Edaravone (Radicava), rivastigmine, donepezil, galantamine, selective serotonin reuptake inhibitor, antipsychotic agents, cholinesterase inhibitors, memantine, benzodiazepine antianxiety drugs, AMX0035 (ELYBRIO), ZILUCOPLAN (RA101495), pridopidine, dual AON intrathecal administration (*e.g.*, BIIB067, BIIB078, and BIIB105), BIIB100, levodopa/carbidopa, dopaminergic agents (*e.g.*, ropinirole, pramipexole, rotigotine), 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.

167. (Original) A method of treating a neurological disease and/or a neuropathy in a patient in need thereof, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 123 or 124, wherein at least one nucleoside linkage of the oligonucleotide is a non-natural linkage, optionally wherein the oligonucleotide comprises a spacer, and wherein the oligonucleotide further comprises a targeting or conjugate moiety selected from cholesterol, lipoic acid, panthothenic acid, polyethylene glycol, and an antibody for crossing the blood brain barrier.

168. (Original) The method of any one of claims 103-122, 125-161, or 163-167, wherein the spacer is a nucleoside-replacement group comprising a non-sugar substitute that is incapable of linking to a nucleotide base.

169. (Original) The method of claim 168, wherein the spacer is located between positions 10 and 15 of the oligonucleotide.

170. (Original) The method of claim 168, wherein the spacer is located between positions 7 and 11 of the oligonucleotide.

171. (Original) The method of claim 168 or 170, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 14 and 22 of the oligonucleotide.

172. (Original) The method of claim 171, wherein the spacer and the second spacer are separated by at least 5 nucleobases, at least 6 nucleobases, or at least 7 nucleobases in the oligonucleotide.

173. (Original) The method of claim 171 or 172, wherein the spacer is located between positions 7 and 9 of the oligonucleotide, and wherein the second spacer is located between positions 15 and 18 of the oligonucleotide.

174. (Original) The method of any one of claims 171-173, wherein the spacer is located at position 8 of the oligonucleotide, and wherein the second spacer is located at position 16 of the oligonucleotide.

175. (Original) The method of any one of claims 171 -174, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 21 and 24 of the oligonucleotide.

176. (Original) The method of claim 168, wherein the spacer is located between positions 2 and 5 of the oligonucleotide.

177. (Original) The method of claim 176, wherein the oligonucleotide further comprises a second spacer, wherein the second spacer is located between positions 8 and 12 of the oligonucleotide.

178. (Original) The method of claim 177, wherein the oligonucleotide further comprises a third spacer, wherein the third spacer is located between positions 18 and 22 of the oligonucleotide.

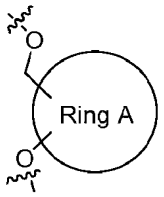
179. (Original) The method of claim 168, wherein the oligonucleotide further comprises a second spacer and a third spacer, wherein the three spacers are located at positions in the oligonucleotide such that each segment of the oligonucleotide has at most 7 linked nucleosides.

180. (Original) The method of claim 179, wherein at least two of the three spacers are adjacent to a guanine nucleobase.

181. (Original) The method of claim 180, wherein each of the at least two of the three spacers immediately precede a guanine nucleobase.

182. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is a nucleoside-replacement group comprising a non-sugar substitute wherein the non-sugar substitute does not contain a ketone, aldehyde, ketal, hemiketal, acetal, hemiacetal, aminal or hemiaminal moiety and is incapable of forming a covalent bond with a nucleotide base.

183. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (X), wherein:

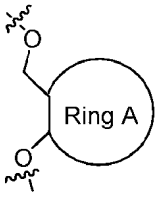


Formula (X)

Ring A is is an optionally substituted 4-8 member monocyclic cycloalkyl group or a 4-8 member monocyclic heterocyclyl group, wherein the heterocyclyl group contains 1 or 2 heteroatoms selected from O, S and N, provided that A is not capable of forming a covalent bond to a nucleobase; and

the  symbol represents the point of connection to an internucleoside linkage.

184. (Original) The method of claim 183, wherein each of the first, second or third spacers is independently represented by Formula (Xa), wherein:



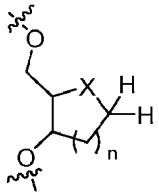
Formula (Xa).

185. (Original) The method of claim 183 or 184, wherein ring A is an optionally substituted 4-8 member monocyclic cycloalkyl group selected from cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; or a 4-8 member monocyclic heterocyclyl group, selected from oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrolidinyl, piperidinyl, piperazinyl, morpholinyl and azepanyl.

186. (Original) The method of claim 185, wherein ring A is tetrahydrofuranyl.

187. (Original) The method of claim 185, wherein ring A is tetrahydropyranyl.

188. (Original) The method of any one of claims 168-181 wherein each of the first, second or third spacers is independently represented by Formula (I), wherein:

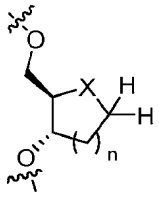


Formula (I)

X is selected from -CH_2- and -O-; and

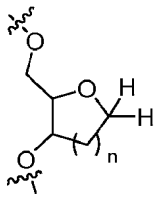
n is 0, 1, 2 or 3.

189. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (I'), wherein:



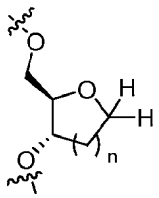
Formula (I').

190. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia), wherein:



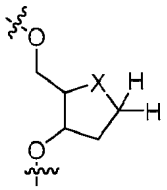
Formula (Ia).

191. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Ia'), wherein:



Formula (Ia').

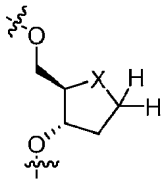
192. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II, wherein:



Formula (II); and

X is selected from -CH_2- and -O-.

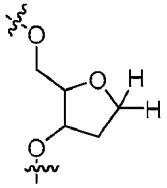
193. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula II', wherein:



Formula (II'); and

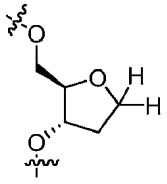
X is selected from -CH_2- and -O-.

194. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia), wherein:



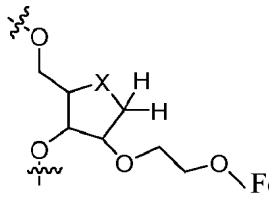
Formula (Iia).

195. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (Iia'), wherein:



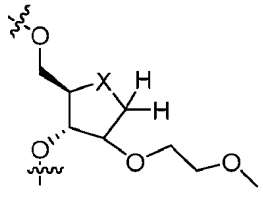
Formula (Iia').

196. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIi), wherein:


Formula (IIi)

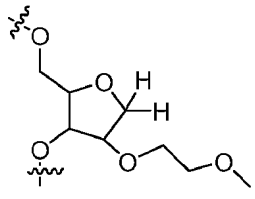
X is selected from -CH_2- and -O-.

197. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIi'), wherein:

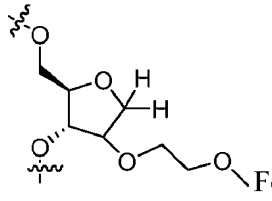

Formula (IIi')

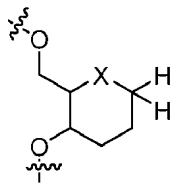
X is selected from -CH_2- and -O-.

198. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib), wherein:


Formula (IIib).

199. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIib'), wherein:

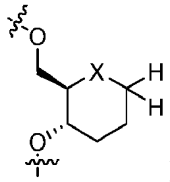

Formula (IIib').The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III, wherein:



Formula (III); and

X is selected from -CH_2- and -O-.

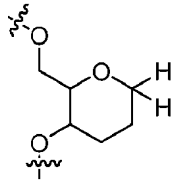
200. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula III', wherein:



Formula (III'); and

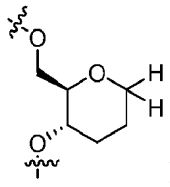
X is selected from -CH_2- and -O-.

201. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa), wherein:



Formula (IIIa).

202. (Original) The method of any one of claims 168-181, wherein each of the first, second or third spacers is independently represented by Formula (IIIa'), wherein:



Formula (IIIa').

203. (Original) The method of any one of claims 168-202, wherein the oligonucleotide comprising the spacer has a GC content of at least 10%.

204. (Original) The method of any one of claims 168-203, wherein the oligonucleotide comprising the spacer has a GC content of at least 20%.

205. (Original) The method of any one of claims 168-204, wherein the oligonucleotide comprising the spacer has a GC content of at least 25%.

206. (Original) The method of any one of claims 168-205, wherein the oligonucleotide comprising the spacer has a GC content of at least 30%.

207. (Original) The method of any one of claims 168-206, wherein the oligonucleotide comprising the spacer has a GC content of at least 40%.

208. (Original) The method of any one of claims 168-207, wherein the oligonucleotide comprising the spacer has a GC content of at least 50%.

209. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 30%, 40%, 50%, 60%, 70%, 80%, or 90% reduction of an UNC13A transcript with a cryptic exon.

210. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 100% reduction of an UNC13A transcript with a cryptic exon.

211. (Original) The compound or oligonucleotide of any one of claims 200-201, wherein reduction of an UNC13A transcript with a cryptic exon is measured in comparison to a level of UNC13A transcript with a cryptic exon detected using a TDP43 antisense oligonucleotide.

212. (Original) The compound or oligonucleotide of any one of the above claims, wherein the oligonucleotide exhibits at least a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction of an UNC13A transcript with a cryptic exon.