

CLAIMS:

1. ~~An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of an ATXN3 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar, a sugar surrogate, and a modified internucleoside linkage.~~
2. ~~An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 15-2787.~~
3. ~~An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases, wherein the portion is complementary to:

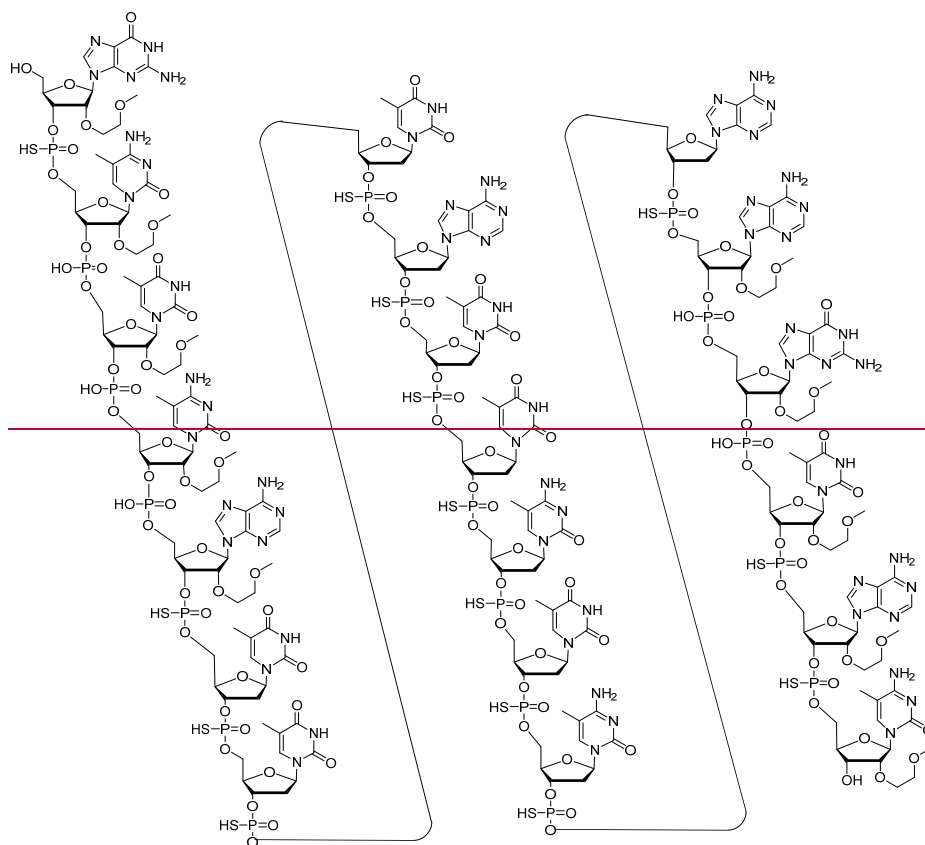
an equal length portion of nucleobases 138-175 of SEQ ID NO: 1;
an equal length portion of nucleobases 392-436 of SEQ ID NO: 1;
an equal length portion of nucleobases 1120-1146 of SEQ ID NO: 1;
an equal length portion of nucleobases 1823-1882 of SEQ ID NO: 1;
an equal length portion of nucleobases 3042-3098 of SEQ ID NO: 1;
an equal length portion of nucleobases 3749-3801 of SEQ ID NO: 1;
an equal length portion of nucleobases 5997-6021 of SEQ ID NO: 1;
an equal length portion of nucleobases 19437-19476 of SEQ ID NO: 2;
an equal length portion of nucleobases 34440-34486 of SEQ ID NO: 2;
an equal length portion of nucleobases 39883-39904 of SEQ ID NO: 2; or
an equal length portion of nucleobases 6597-6618 of SEQ ID NO: 2.~~
4. ~~The oligomeric compound of any one of claims 1-3, wherein the ATXN3 nucleic acid has the nucleobase sequence of any of SEQ ID NOs: 1, 2, 3, 4, or 5.~~
5. ~~The oligomeric compound of any one of claims 1-4, consisting of a single stranded modified oligonucleotide.~~
6. ~~The oligomeric compound of any one of claims 1-5, wherein at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.~~
7. ~~The oligomeric compound of claim 6, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.~~

8. ~~The oligomeric compound of any one of claims 1-5, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.~~
9. ~~The oligomeric compound of claim 8, wherein each modified internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage.~~
10. ~~The oligomeric compound of any one of claims 1-7, wherein at least one internucleoside linkage of the modified oligonucleotide is a phosphodiester internucleoside linkage.~~
11. ~~The oligomeric compound of any one of claims 1-7 and 10, wherein each internucleoside linkage of the modified oligonucleotide is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.~~
12. ~~The oligomeric compound of any one of claims 1-11, wherein at least one nucleobase of the modified oligonucleotide comprises a modified nucleobase.~~
13. ~~The oligomeric compound of claim 12, wherein the modified nucleobase is a 5-methyl cytosine.~~
14. ~~The oligomeric compound of any one of claims 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.~~
15. ~~The oligomeric compound of claim 14, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.~~
16. ~~The oligomeric compound of claim 15, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from -O-CH₂-; and -O-CH(CH₃)-.~~
17. ~~The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic sugar moiety.~~
18. ~~The oligomeric compound of claim 17, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified non-bicyclic sugar moiety comprising a 2'-MOE or 2'-OMe.~~
19. ~~The oligomeric compound of claim 18, wherein each modified nucleoside of the modified oligonucleotide comprises a modified non-bicyclic sugar moiety comprising a 2'-MOE or 2'-OMe.~~
20. ~~The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.~~
21. ~~The oligomeric compound of claim 20, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.~~

22. ~~—The oligomeric compound of any of claims 1-18 and 20-21, wherein the modified oligonucleotide is a gapmer.~~
23. ~~—The oligomeric compound of any of claims 1-18 and 20-21, wherein the modified oligonucleotide has a sugar motif comprising:~~
~~a 5' region consisting of 1-6 linked 5' nucleosides;~~
~~a central region consisting of 6-10 linked central region nucleosides; and~~
~~a 3' region consisting of 1-6 linked 5' nucleosides; wherein each of the 5' region nucleosides and each of the 3' region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2' deoxyribosyl sugar moiety.~~
24. ~~—The oligomeric compound of claims 1-7 or 10-23, wherein the modified oligonucleotide has the following internucleoside motif: soooossssssssooss; wherein,~~
~~s = a phosphorothioate internucleoside linkage, and~~
~~o = a phosphodiester internucleoside linkage.~~
25. ~~—The oligomeric compound of any one of claims 1-23, wherein the modified oligonucleotide consists of 12-22, 12-20, 14-20, 16-20, 18-20, or 18-22 linked nucleosides.~~
26. ~~—The oligomeric compound of any one of claims 1-23 and 25, wherein the modified oligonucleotide consists of 16, 17, 18, 19, or 20 linked nucleosides.~~
27. ~~—The oligomeric compound of any of claims 1-26 consisting of the modified oligonucleotide.~~
28. ~~—The oligomeric compound of any of claims 1-26 comprising a conjugate group comprising a conjugate moiety and a conjugate linker.~~
29. ~~—The oligomeric compound of claim 28, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.~~
30. ~~—The oligomeric compound of claim 28 or 29, wherein the conjugate linker consists of a single bond.~~
31. ~~—The oligomeric compound of claim 28, wherein the conjugate linker is cleavable.~~
32. ~~—The oligomeric compound of claim 28, wherein the conjugate linker comprises 1-3 linker nucleosides.~~
33. ~~—The oligomeric compound of any of claims 28-32, wherein the conjugate group is attached to the modified oligonucleotide at the 5' end of the modified oligonucleotide.~~
34. ~~—The oligomeric compound of any of claims 28-32, wherein the conjugate group is attached to the modified oligonucleotide at the 3' end of the modified oligonucleotide.~~
35. ~~—The oligomeric compound of any of claims 1-26 or 28-34 comprising a terminal group.~~

36. — The oligomeric compound of any of claims 1-35 wherein the oligomeric compound is a singled-stranded oligomeric compound.
37. — The oligomeric compound of any of claims 1-31 or 33-34, wherein the oligomeric compound does not comprise linker nucleosides.
38. — An oligomeric duplex comprising an oligomeric compound of any of claims 1-35 and 37.
39. — An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-37 or an oligomeric duplex of claim 38.
40. — A modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 15-2787.
41. — A pharmaceutical composition comprising an oligomeric compound of any of claims 1-37, an oligomeric duplex of claim 38, an antisense compound of claim 39, or a modified oligonucleotide of claim 40 and at least one of a pharmaceutically acceptable carrier or diluent.
42. — The pharmaceutical composition of claim 41, wherein the modified oligonucleotide is a sodium salt.
43. — A method comprising administering to an animal the pharmaceutical composition of any of claims 41-42.
44. — The method of claim 43, wherein the animal is a human.
45. — A method of treating a disease associated with ATXN3 comprising administering to an individual having or at risk for developing a disease associated with ATXN3 a therapeutically effective amount of a pharmaceutical composition of claims 41 and 42, and thereby treating the disease associated with ATXN3.
46. — The method of claim 45, wherein the disease associated with ATXN3 is a neurodegenerative disease.
47. — The method of claim 46, wherein the neurodegenerative disease is SCA3.
48. — The method of claim 47, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.
49. — The method of claim 48, wherein the symptom or hallmark is ataxia, neuropathy, and aggregate formation.

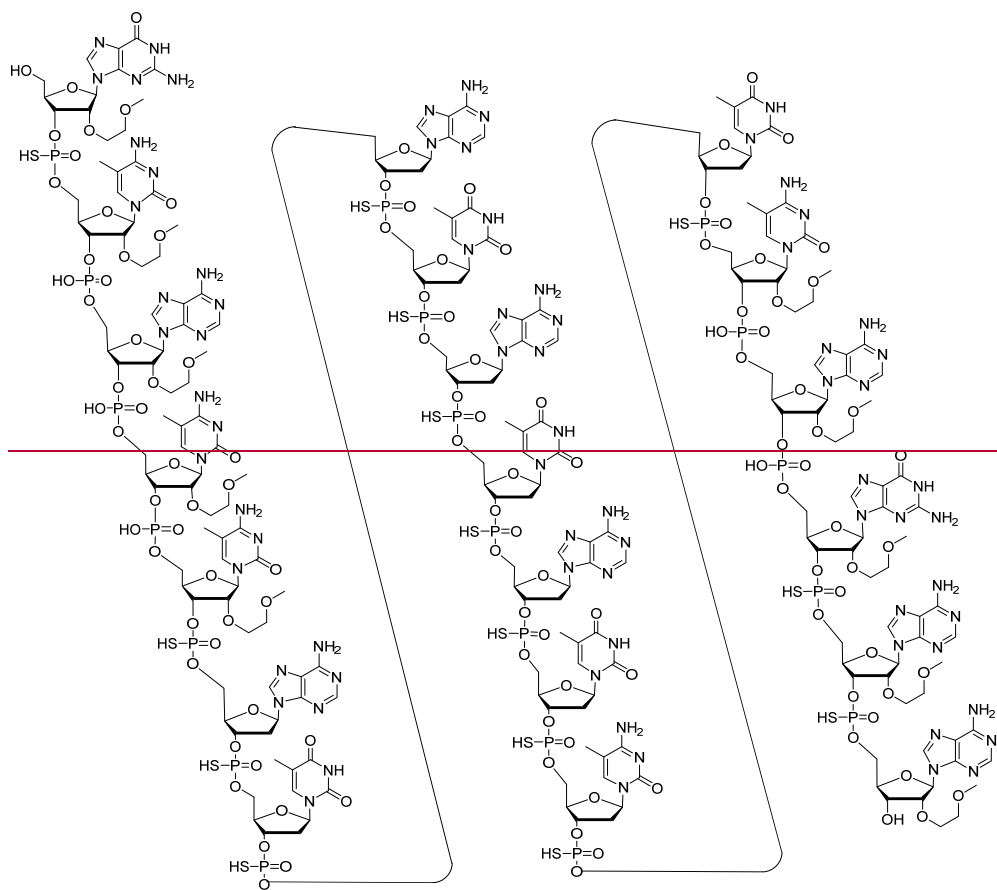
~~50. A modified oligonucleotide according to the following chemical structure:~~



~~(SEQ ID NO: 423),~~

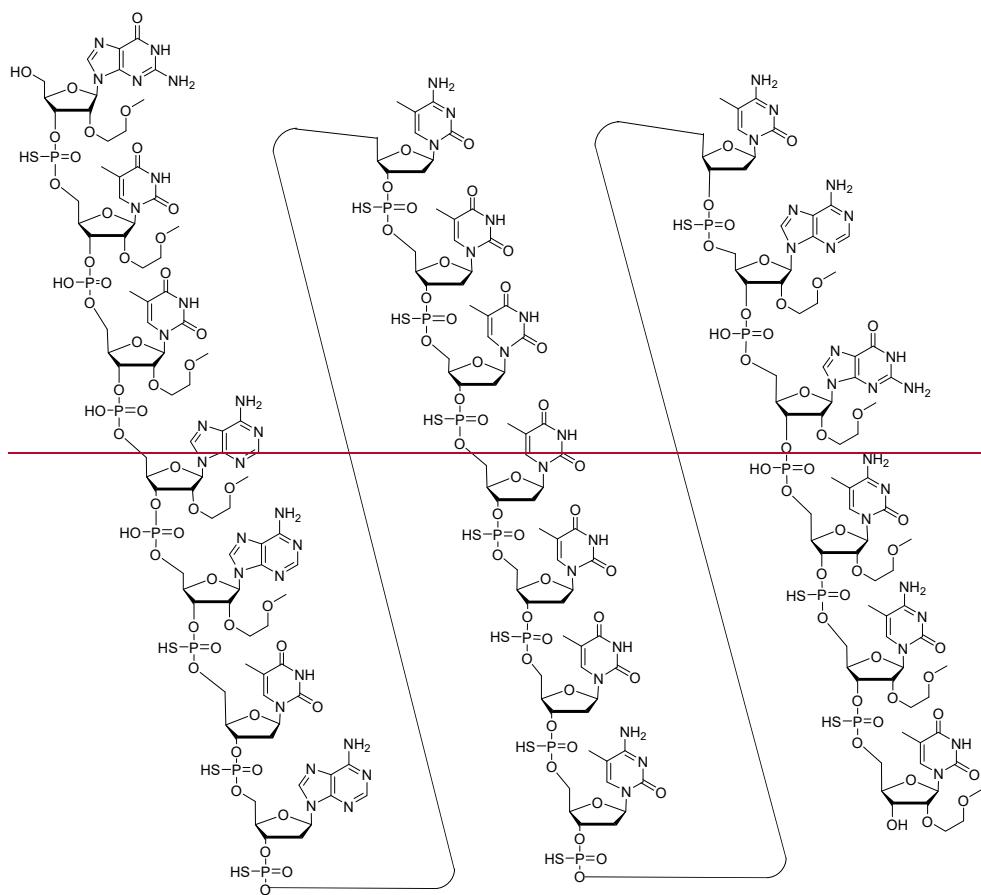
~~or a salt thereof.~~

51. — A modified oligonucleotide according to the following chemical structure:



or a salt thereof.

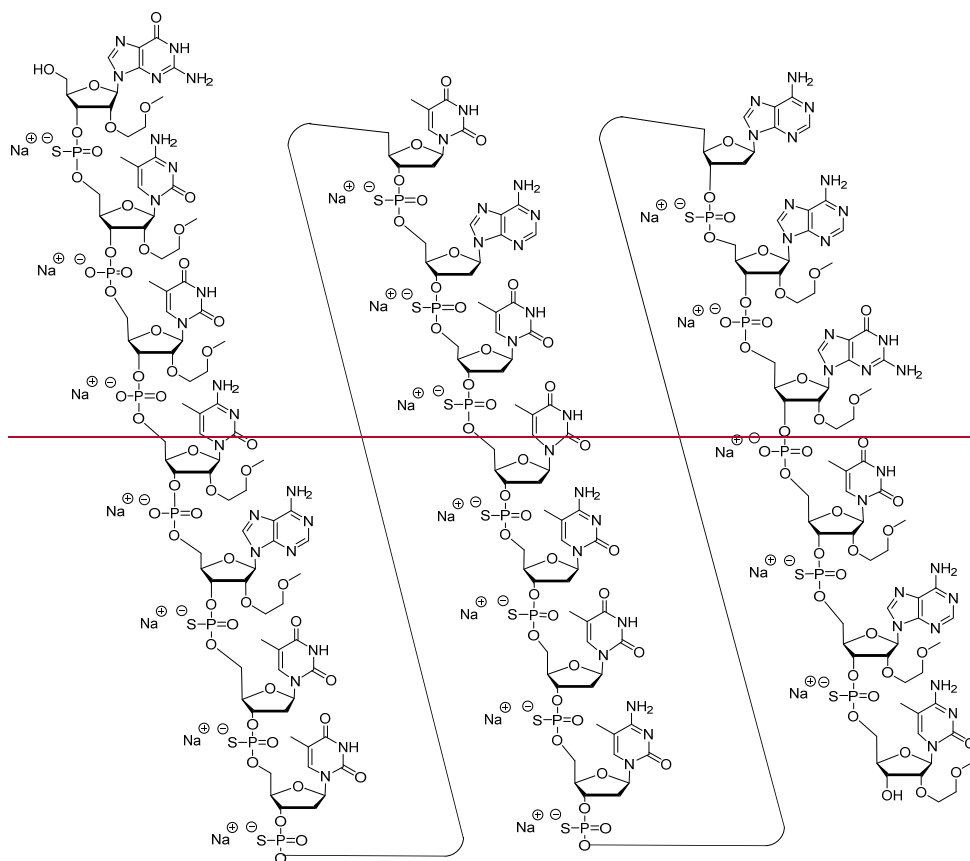
52. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1673);

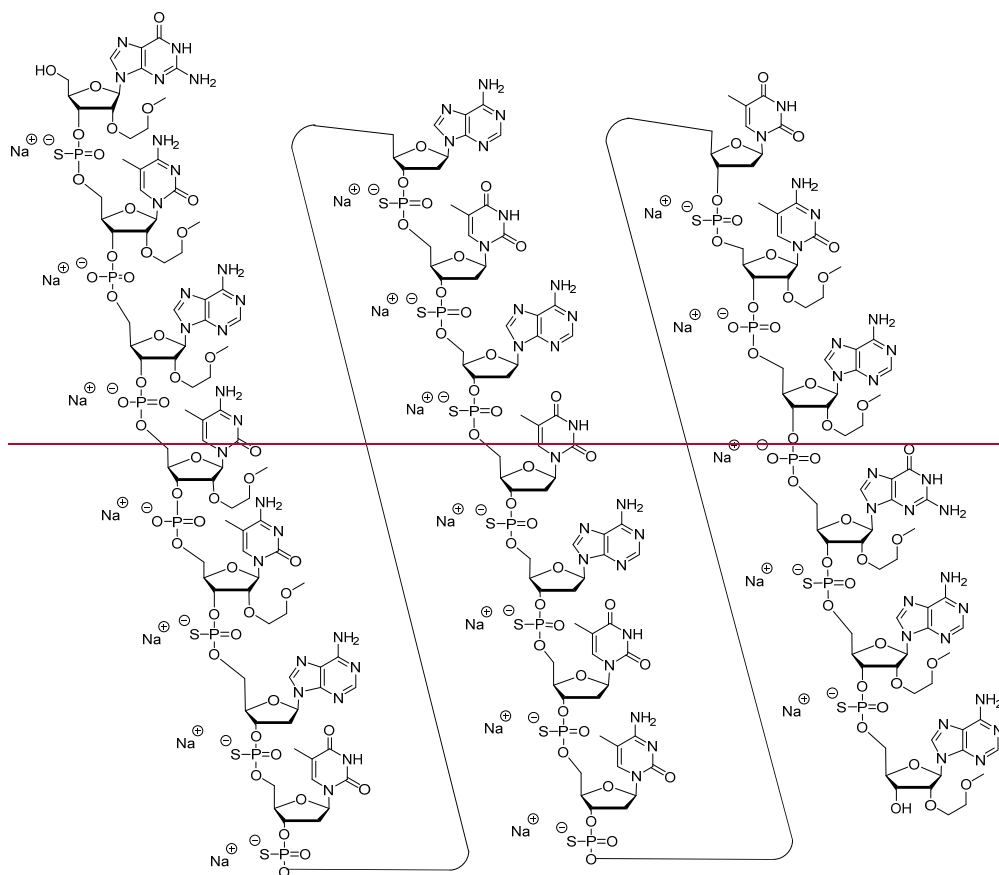
or a salt thereof.

53. ~~A modified oligonucleotide according to the following chemical structure:~~



~~(SEQ ID NO: 423).~~

54. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 1226).

The diagram illustrates a complex polyphosphate chain structure, likely representing a nucleic acid derivative. The structure is composed of multiple nucleoside units linked by phosphate groups. A prominent red horizontal line is drawn across the middle of the structure, indicating a site of cleavage or a specific chemical modification. The structure is divided into three main sections by two vertical lines. The left section shows a chain of nucleosides with phosphate groups, including a terminal nucleoside with a hydroxyl group. The middle section shows a chain of nucleosides with phosphate groups, including a terminal nucleoside with an amino group. The right section shows a chain of nucleosides with phosphate groups, including a terminal nucleoside with an amino group. The structure is highly branched and complex, with many phosphate groups and nucleoside units. The red line is positioned between the middle and right sections, suggesting a cleavage site between these two parts of the molecule.

~~56. The modified oligonucleotide of any of claims 50, 52, or 54, which is a sodium salt of the formula:~~

58.—The pharmaceutical composition of claim 57, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

~~60. A compound comprising a modified oligonucleotide according to the following chemical notation (5' to 3'):~~

~~A – an adenine nucleobase,~~

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G—a guanine nucleobase,
 T—a thymine nucleobase,
 e—a 2' MOE sugar moiety,
 d—a 2' β-D-deoxyribosyl sugar moiety,
 s—a phosphorothioate internucleoside linkage, and
 o—a phosphodiester internucleoside linkage.

61.——A compound comprising a modified oligonucleotide according to the following chemical notation (5' to 3'):
 Ges-^mCeo-Aeo-^mCeo-^mCes-Ads-Tds-Ads-Tds-Ads-Tds-Ads-Tds-^mCds-Tds-^mCeo-Aeo-Ges-Aes-Ae (SEQ ID NO: 1226),
 wherein,

A—an adenine nucleobase,
^mC—a 5-methyl cytosine,
 G—a guanine nucleobase,
 T—a thymine nucleobase,
 e—a 2' MOE sugar moiety,
 d—a 2' β-D-deoxyribosyl sugar moiety,
 s—a phosphorothioate internucleoside linkage, and
 o—a phosphodiester internucleoside linkage.

62.——A compound comprising a modified oligonucleotide according to the following chemical notation (5' to 3'):
 Ges-Teo-Teo-Aeo-Aes-Tds-Ads-^mCds-Tds-Tds-Tds-Tds-Tds-^mCds-^mCds-Aeo-Geo-^mCes-^mCes-Te (SEQ ID NO: 1673),
 wherein,

A—an adenine nucleobase,
^mC—a 5-methyl cytosine,
 G—a guanine nucleobase,
 T—a thymine nucleobase,
 e—a 2' MOE sugar moiety,
 d—a 2' β-D-deoxyribosyl sugar moiety,
 s—a phosphorothioate internucleoside linkage, and

o—a phosphodiester internucleoside linkage.

63.——The compound of any of claims 60-62, comprising the modified oligonucleotide covalently linked to a conjugate group.

64.——The compound of any of claim 1-63, wherein at least one internucleoside linkage of the modified oligonucleotide is chirally controlled.

65.——The compound of any of claims 1-64, wherein at least one internucleoside linkage of the modified oligonucleotide is stereorandom.

66.——A pharmaceutical composition comprising the compound of any of claims 60-65 and a pharmaceutically acceptable diluent or carrier.

67.——The pharmaceutical composition of claim 66, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

68.——~~The pharmaceutical composition of claim 66, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.~~

69.——~~A chirally enriched population of modified oligonucleotides of any of claims 50-55, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular <configuration.~~

70.——~~The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Sp) configuration.~~

71.——~~The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (Rp) configuration.~~

72.——~~The chirally enriched population of claim 69, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage~~

73.——~~The chirally enriched population of claim 73, wherein the population is enriched for modified oligonucleotides having the (Sp) configuration at each phosphorothioate internucleoside linkage.~~

74.——~~The chirally enriched population of claim 73, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at each phosphorothioate internucleoside linkage.~~

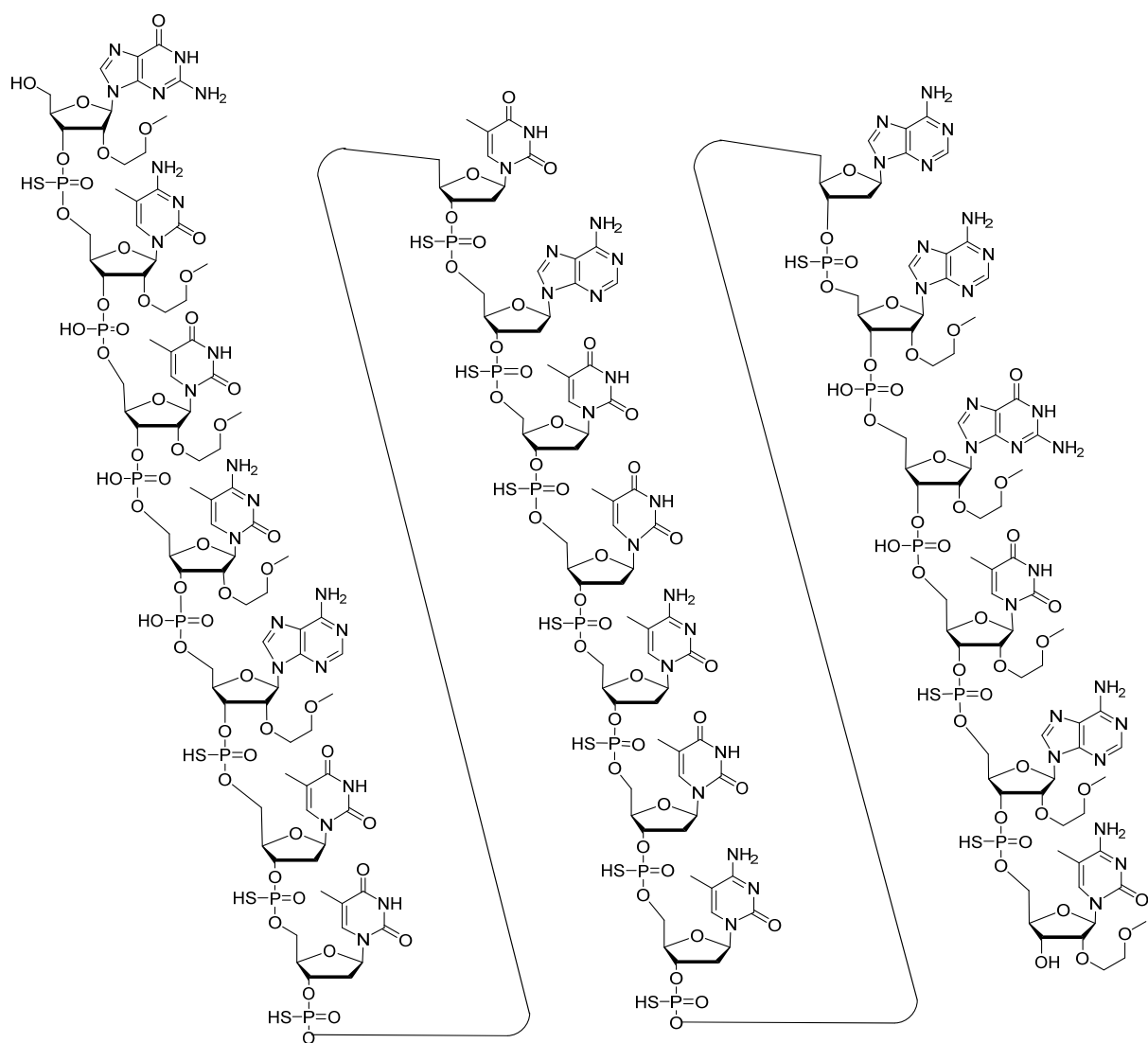
75.——~~The chirally enriched population of claim 73, wherein the population is enriched for modified oligonucleotides having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages.~~

76.——~~The chirally enriched population of claim 69 or claim 73 wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.~~

77.——~~A chirally enriched population of modified oligonucleotides of any of claims 50-55, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.~~

CLAIMS:

1. A modified oligonucleotide according to the following chemical structure:

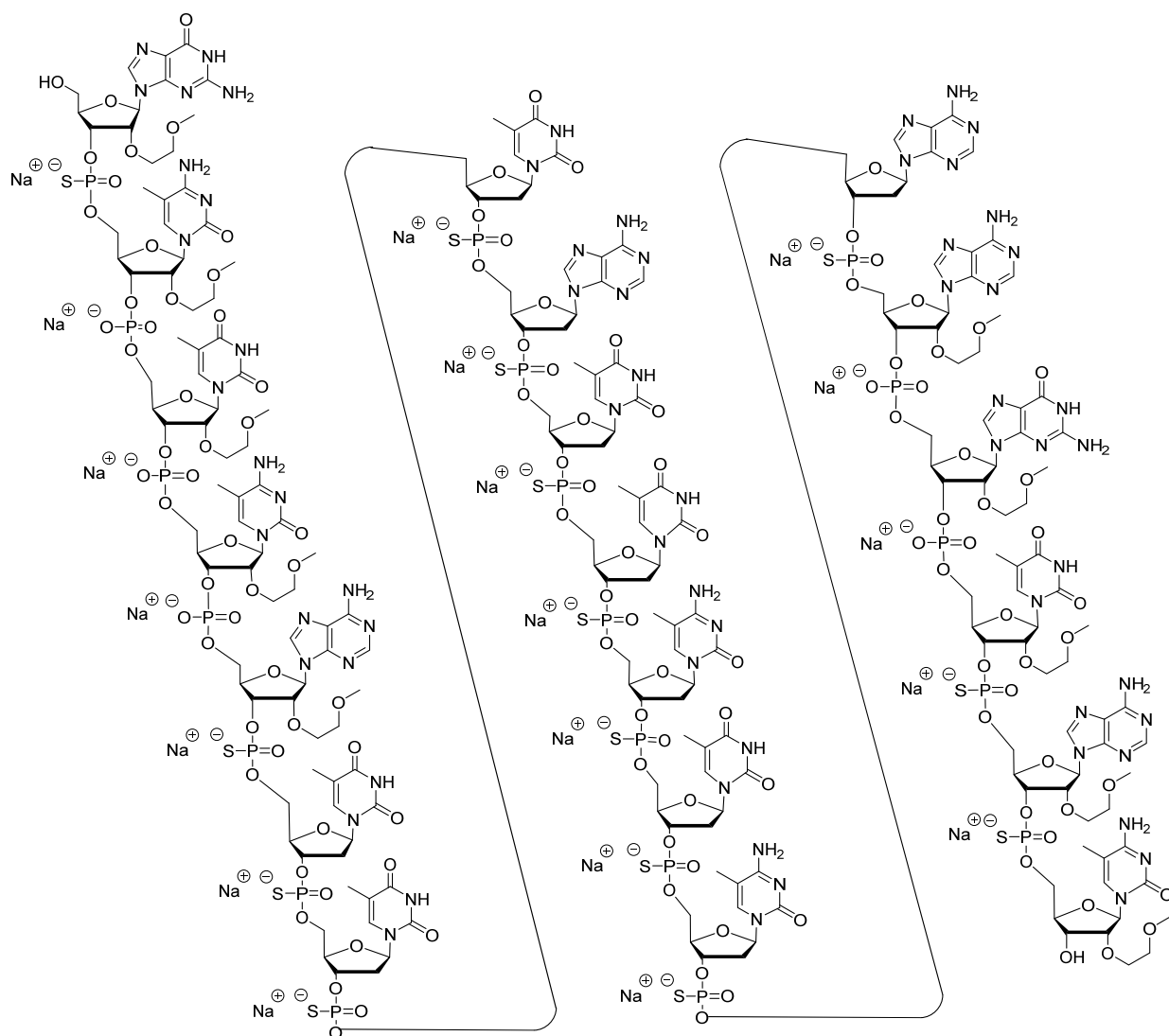


(SEQ ID NO: 423)

or a salt thereof.

2. The modified oligonucleotide of claim 1, which is the sodium salt or the potassium salt.

3. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 423).

4. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

Ges ^mCeo Teo ^mCeo Aes Tds Tds Tds Ads Tds Tds ^mCds Tds ^mCds Ads Aeo Geo Tes Aes ^mCe
(SEQ ID NO: 423); wherein,

A = an adenine nucleobase,

^mC = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase.

e = a 2'-MOE sugar moiety,
d = a 2'-β-D deoxyribosyl sugar moiety,
s = a phosphorothioate internucleoside linkage, and
o = a phosphodiester internucleoside linkage.

5. A population of modified oligonucleotides of claim 1, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

6. A pharmaceutical composition comprising the modified oligonucleotide of claim 1 and a pharmaceutically acceptable diluent.

7. The pharmaceutical composition of claim 6, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

8. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

9. The pharmaceutical composition of claim 7, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

10. A population of modified oligonucleotides of claim 3, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

11. A pharmaceutical composition comprising the modified oligonucleotide of claim 3 and a pharmaceutically acceptable diluent.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

13. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

14. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

15. A population of oligomeric compounds of claim 4, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

16. A pharmaceutical composition comprising the oligomeric compound of claim 4 and a pharmaceutically acceptable diluent.

17. The pharmaceutical composition of claim 16, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition consists essentially of the oligomeric compound and artificial cerebrospinal fluid.

19. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition consists essentially of the oligomeric compound and PBS.

20. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 5 and a pharmaceutically acceptable diluent.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and artificial cerebrospinal fluid.

23. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and PBS.

24. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 10 and a pharmaceutically acceptable diluent.

25. The pharmaceutical composition of claim 24, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

26. The pharmaceutical composition of claim 25, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and artificial cerebrospinal fluid.

27. The pharmaceutical composition of claim 25, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and PBS.

28. A pharmaceutical composition comprising the population of oligomeric compounds of claim 15 and a pharmaceutically acceptable diluent.

29. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

30. The pharmaceutical composition of claim 29, wherein the pharmaceutical composition consists essentially of the population of oligomeric compounds and artificial cerebrospinal fluid.

31. The pharmaceutical composition of claim 29, wherein the pharmaceutical composition consists essentially of the population of oligomeric compounds and PBS.

32. A population of modified oligonucleotides of claim 2, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

33. A pharmaceutical composition comprising the modified oligonucleotide of claim 2 and a pharmaceutically acceptable diluent.

34. The pharmaceutical composition of claim 33, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

35. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

36. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and PBS.

37. A pharmaceutical composition comprising the population of modified oligonucleotides of claim 32 and a pharmaceutically acceptable diluent.

38. The pharmaceutical composition of claim 37, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS) or artificial cerebrospinal fluid.

39. The pharmaceutical composition of claim 38, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and artificial cerebrospinal fluid.

40. The pharmaceutical composition of claim 38, wherein the pharmaceutical composition consists essentially of the population of modified oligonucleotides and PBS.

41. The pharmaceutical composition of claim 6 for use in therapy.

42. Use of a therapeutically effective amount of the pharmaceutical composition of claim 6 in the manufacture of a medicament for the treatment of a disease associated with ATXN3, wherein the disease is a neurodegenerative disease.

43. The use of claim 42, wherein the neurodegenerative disease is SCA3.

44. The use of claim 42, wherein the medicament ameliorates at least one symptom or hallmark of the neurodegenerative disease.

45. The use of claim 44, wherein the symptom or hallmark is any of ataxia, neuropathy, and aggregate formation.

46. The use of claim 42, wherein the medicament is to be administered to a human.