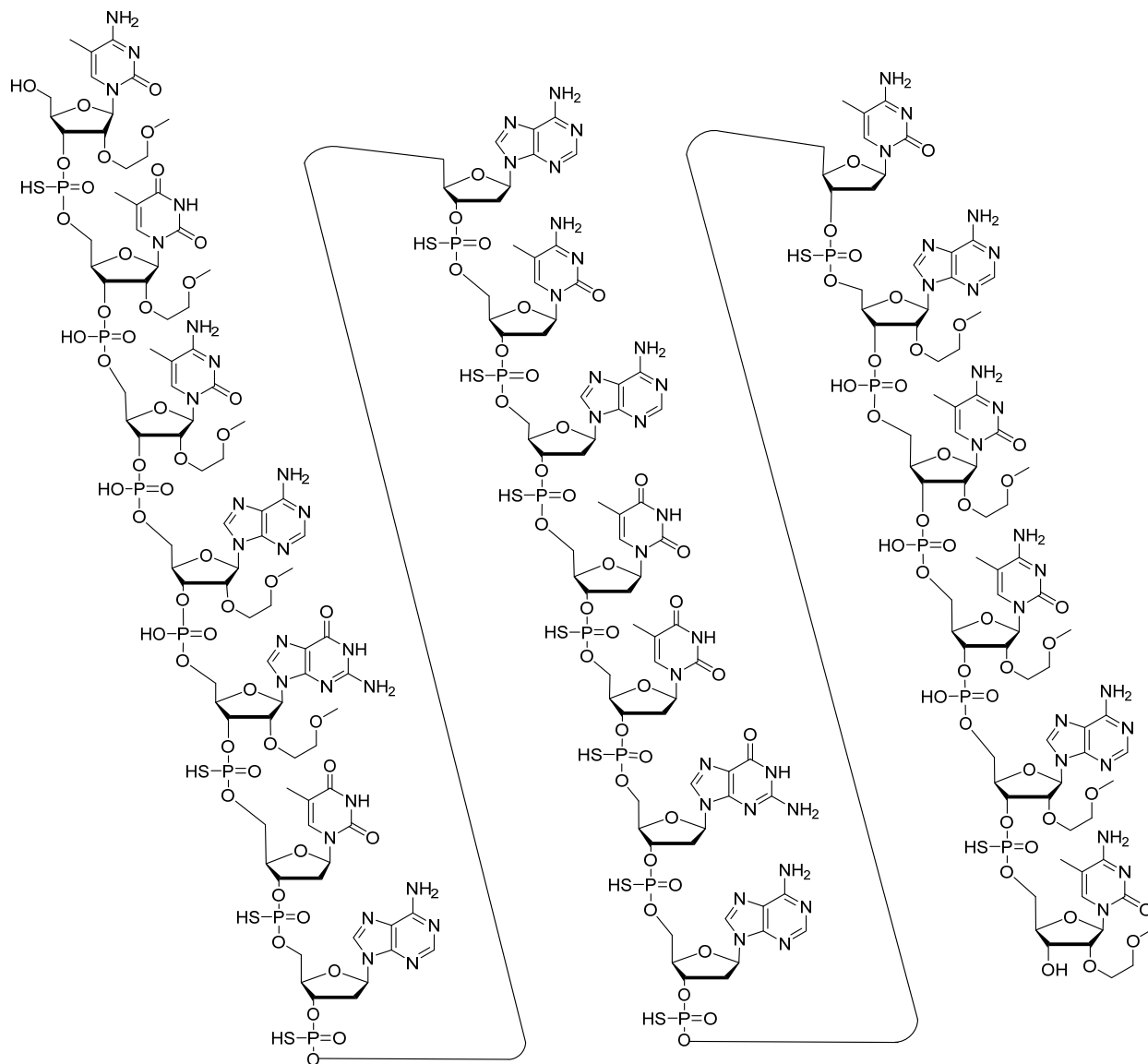


CLAIMS:

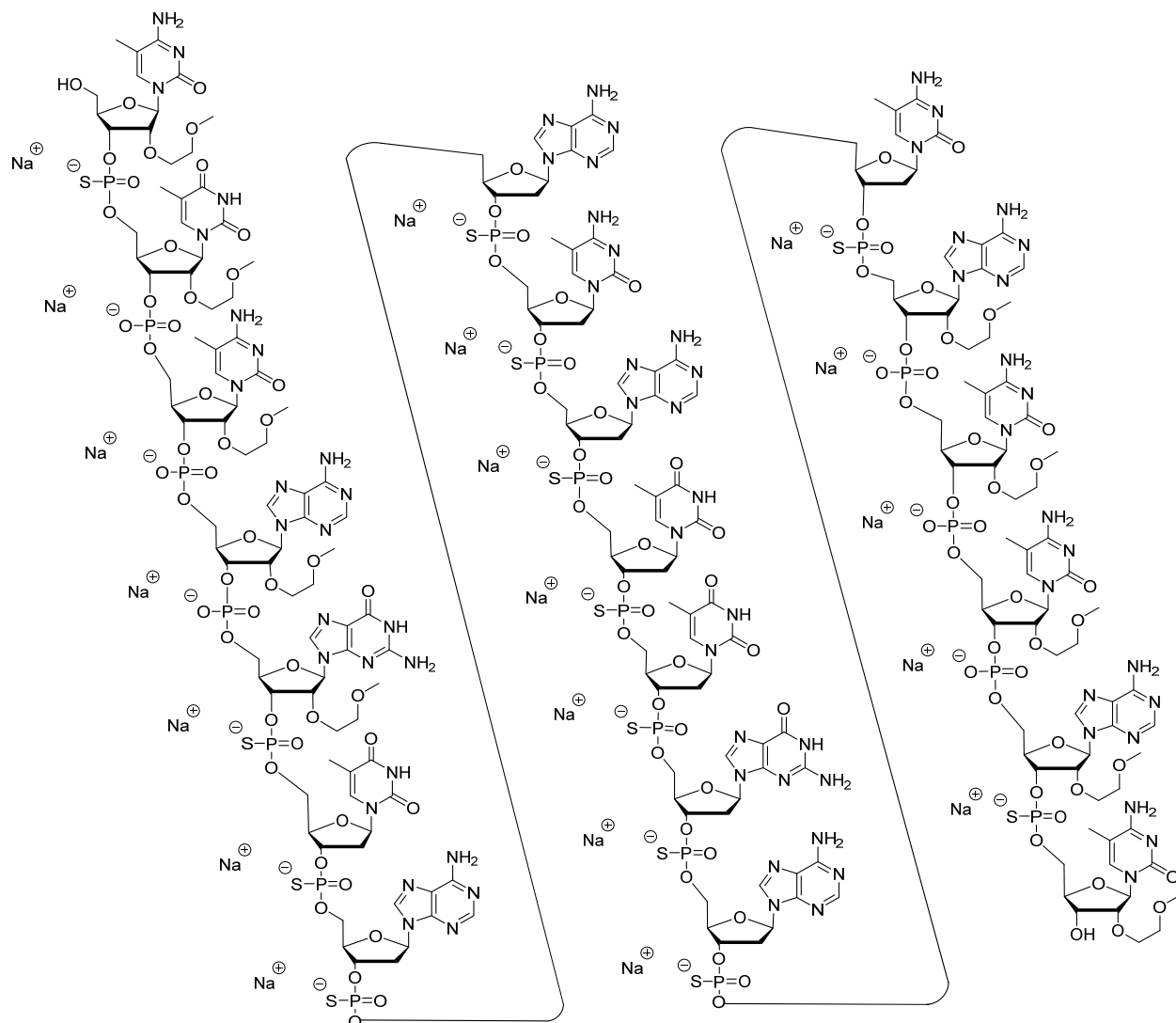
1. Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

2. The use according to claim 1, wherein the modified oligonucleotide is the sodium salt or the potassium salt.
3. Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount

of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical structure:



(SEQ ID NO: 4).

4. Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and
o = a phosphodiester internucleoside linkage.

5. The use according to any one of claims 1-4, wherein at least one symptom of HD is ameliorated.
6. The use according to claim 5, wherein the at least one symptom comprises brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.
7. The use according to any one of claims 1-6, wherein the therapeutically effective amount is 60 mg.
8. The use according to any one of claims 1-7, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg.
9. The use according to any one of claims 1-8, wherein the modified oligonucleotide is to be administered once every 16 weeks.
10. The use according to any one of claims 1-9, wherein the human subject has a mutation in at least one *IT15* gene.
11. The use according to any one of claims 1-10, wherein the human subject has been identified to have a mutation in at least one *IT15* gene of the human subject.
12. The use according to claim 10 or claim 11, wherein the at least one *IT15* gene has any of at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42,

at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, or at least 60 contiguous CAG repeats.

13. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has 27 to 35 contiguous CAG repeats.
14. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has 35 to 60 contiguous CAG repeats.
15. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has greater than 60 contiguous CAG repeats.
16. The use according to any one of claims 1-15, wherein the modified oligonucleotide is to be administered to the CNS of the human subject.
17. The use according to any one of claims 1-16, wherein the modified oligonucleotide is to be administered by intrathecal administration.
18. The use according to any one of claims 1-17, wherein the modified oligonucleotide is to be administered by bolus intrathecal administration.
19. The use according to any one of claims 1-18, wherein HTT RNA is reduced.
20. The use according to any one of claims 1-19, wherein HTT protein is reduced.
21. The use according to any one of claims 1-20, wherein mHTT RNA is reduced.
22. The use according to any one of claims 1-21, wherein mHTT protein is reduced.
23. The use according to any one of claims 1-22, wherein a biological sample from the human subject has been detected to have an amount of mHTT RNA.
24. The modified oligonucleotide for use according to any one of claims 1-23, wherein a biological sample from the human subject has been detected to have an amount of mHTT protein.

25. The use according to any one of claims 1-24, wherein the biological sample comprises cerebrospinal fluid.
26. The use according to any of claims 23-25, wherein the detection occurs before the administration.
27. The use according to any of claims 23-25, wherein the detection occurs after the administration.
28. The use according to any of claims 23-25, wherein the detection occurs before and after the administration.
29. The use according to any one of claims 1-28, wherein brain activity, brain size, or a combination thereof of the subject is analyzed by performing an electroencephalogram (EEG) or magnetic resonance imaging (MRI).
30. The use according to claim 29, wherein the EEG or MRI is performed before the administration, after the administration, or a combination thereof.
31. The use according to claim 30, wherein the therapeutically effective amount is determined or adjusted after performing the EEG or MRI.
32. The use according to claim 31, wherein the EEG or MRI is performed after the administration, and the frequency of the administration is adjusted after the EEG or MRI is performed.
33. The use according to any one of claims 29-32, wherein the EEG or MRI is performed within 1, 2, 4, 6, 8, 12 or 24 hours of the administration.
34. The use according to any one of claims 29-33, wherein the EEG is performed before the administration, and the analysis is performed after the administration, and wherein when an increase of less than 4 Hz in EEG signal power from a first EEG to a second EEG is detected, the frequency of the administration of the therapeutically effective amount of the modified oligonucleotide is subsequently increased.
35. The use according to claim 34, wherein a loading dose is to be administered once about every 4 weeks and a maintenance dose is to be administered once about every 8 or 16 weeks before recording the first EEG, and the administration of the maintenance dose less than about every 8 weeks or less than about every 16 weeks.

36. The use according to any one of claims 29-35, wherein a first EEG is recorded before the administration, and a second EEG is recorded after the administration, and wherein when an increase of less than a 4 Hz increase in EEG signal power is detected from the first EEG to the second EEG, a dose of the modified oligonucleotide that is greater than the therapeutically effective amount is to be subsequently administered.
37. The use according to claim 36, wherein the dose is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 90%, or at least about 100% greater than the therapeutically effective amount.