

CLAIMS

What is claimed is:

1. A composition comprising an oligonucleotide that targets MTRES1, wherein the composition is to be administered to a subject and results in:
 - (a) a decrease in central nervous system (CNS) MTRES1;
 - (b) an increase in cognitive function or slowed cognitive decline; or
 - (c) a decrease in a marker of neurodegeneration.
2. The composition of claim 1, wherein:
 - (a) CNS MTRES1 is decreased by about 10% or more, as compared to prior to administration;
 - (b) cognitive function is increased by about 10% or more, as compared to prior to administration;
 - (c) cognitive decline is slowed by about 10% or more, as compared to prior to administration; or
 - (d) the marker of neurodegeneration is decreased by about 10% or more, as compared to prior to administration.
3. The composition of claim 1, wherein the marker of neurodegeneration comprises a central nervous system (CNS) or cerebrospinal fluid (CSF) or plasma marker of neurodegeneration.
4. The composition of claim 1, wherein the marker of neurodegeneration comprises a measurement of amyloid plaques, tau accumulation, beta-amyloid 42, tau, phospho-tau, neurofilament light chain (NfL), Lewy bodies, or alpha-synuclein.
5. The composition of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages.
6. The composition of claim 5, wherein the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof.
7. The composition of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides.

8. The composition of claim 7, wherein the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HNA), cyclohexene nucleic acid (CeNA), 2'-O-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof.

9. The composition of claim 1, wherein the oligonucleotide comprises a lipophilic moiety attached at a 3' or 5' terminus of the oligonucleotide.

10. The composition of claim 9, wherein the lipophilic moiety comprises cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, ibuprofen, naproxen, dimethoxytrityl, phenoxazine or lipid.

11. The composition of claim 9, wherein the lipophilic moiety comprises a C₄-C₃₀ hydrocarbon chain.

12. The composition of claim 9, wherein the lipophilic moiety comprises a lipid, wherein the lipid comprises myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α-tocopherol, or a combination thereof.

13. The composition of claim 1, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand, and each strand is independently 12-30 nucleosides in length.

14. A composition comprising an oligonucleotide that inhibits the expression of MTRES1, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443.

15. The composition of claim 14, wherein any one of the following is true with regard to the sense strand:

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise 2'-O-methyl modified pyrimidines;

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines;

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines; or

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise 2'-O-methyl modified purines; or any one of the following is true with regard to the antisense strand:

all purines comprise 2'-fluoro modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise a mixture of 2'-fluoro and 2'-O-methyl modified pyrimidines;

all purines comprise 2'-O-methyl modified purines, and all pyrimidines comprise 2'-fluoro modified pyrimidines;

all pyrimidines comprise 2'-fluoro modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines;

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise a mixture of 2'-fluoro and 2'-O-methyl modified purines; or

all pyrimidines comprise 2'-O-methyl modified pyrimidines, and all purines comprise 2'-fluoro modified purines.

16. The composition of claim 14, wherein the sense strand comprises an oligonucleotide sequence of SEQ ID NO: 614 or 2594 and the antisense strand comprises an oligonucleotide sequence of SEQ ID NO: 1754 or 2656.

17. The composition of claim 1, wherein the oligonucleotide comprises a phosphate mimic at the 5' end of the antisense strand.

18. The composition of claim 16, wherein the phosphate mimic comprises a 5'-vinyl phosphonate (VP).

19. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

20. Use of a composition comprising an oligonucleotide that modulates the expression of MTRES1 in the manufacture of a medicament for treating a subject having a neurological disorder, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443.

21. The use of claim 19, wherein the neurological disorder comprises dementia, Alzheimer's disease, delirium, cognitive decline, vascular dementia, or Parkinson's disease.

22. A composition comprising an oligonucleotide that modulates the expression of MTRES1 for use in therapy, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 contiguous nucleosides of SEQ ID NO: 2443.