CLAIMS

What is claimed is:

1. A composition comprising an oligonucleotide that targets MTRES1 (mitochondrial transcription rescue factor 1), wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and

the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and

the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 614,

wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

2. 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.

3. 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.

4. 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.

5. The composition of claim 4, 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.

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

7. The composition of claim 6, wherein the lipophilic moiety comprises cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, 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.

8. The composition of claim 6, wherein the lipophilic moiety comprises a C_4-C_{30} hydrocarbon chain.

9. The composition of claim 6, wherein the lipophilic moiety comprises a lipid, wherein the lipid comprises myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or a- tocopherol, or a combination thereof.

10. The composition of claim 1, 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.

11. The composition of claim 1, wherein the sense strand comprises an oligonucleotide sequence of SEQ ID NO: 2594 and the antisense strand comprises an oligonucleotide sequence of SEQ ID NO: 2656.

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

13. The composition of claim 11, wherein the phosphate mimic comprises a 5'-vinyl phosphonate (VP).

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

15. Use of a composition comprising an oligonucleotide that modulates the expression of MTRES1 (mitochondrial transcription rescue factor 1) 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 about 12-30 nucleosides in length, and

the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and

the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 614,

wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

16. The use of claim 15, wherein the neurological disorder comprises dementia, Alzheimer’s disease, delirium, cognitive decline, vascular dementia, or Parkinson’s disease.

17. A composition comprising an oligonucleotide that modulates the expression of MTRES1 (mitochondrial transcription rescue factor 1) for use in therapy, wherein the oligonucleotide comprises

(a) an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and

the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and

the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or

(b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 614,

wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

TREATMENT OF MTRES1 RELATED DISEASES AND DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/211,379, filed June 16, 2021, which application is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Neurological disorders are a common problem, particularly in the older population. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0002a] In one aspect, provided herein is a composition comprising an oligonucleotide that targets MTRES1 (mitochondrial transcription rescue factor 1), wherein the oligonucleotide comprises (a) an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or (b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ ID NO: 614, wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

[0002b] In another aspect, provided herein is use of a composition comprising an oligonucleotide that modulates the expression of MTRES1 (mitochrondrial transcription rescue factor 1) 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 the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or (b) an antisense oligonucleotide (ASO) comprising 12-30 contiguous nucleosides in length and a nucleoside sequence complementary to 12-30 contiguous nucleosides of SEQ

ID NO: 614, wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

[0002c] In another aspect, provided herein is a composition comprising an oligonucleotide that modulates the expression of MTRES1 (mitochondrial transcription rescue factor 1) for use in therapy, wherein the oligonucleotide comprises (a) an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and the sense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 614; and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 1754; or (b) an antisense oligonucleotide (ASO) comprising 12-30 nucleosides in length and a nucleoside complementary to 12-30 contiguous nucleosides of SEQ ID NO: 614, wherein the siRNA or the ASO comprises at least one modified nucleoside or modified internucleoside linkage.

[0003] Described herein are compositions comprising an oligonucleotide that targets MTRES1. Described herein are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount reduces a MTRES1 mRNA or protein level. Described herein are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount decreases central nervous system (CNS) MTRES1. In some embodiments, the CNS MTRES1 decreased by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount increases cognitive function or slows cognitive decline. In some embodiments, the cognitive function is increased by about 10% or more, as compared to prior to administration. In some embodiments, the cognitive decline is slowed by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount decreases a marker of neurodegeneration. In some embodiments, the marker of neurodegeneration comprises a central nervous system (CNS) or cerebrospinal fluid (CSF) marker of neurodegeneration. In some embodiments, the marker of neurodegeneration comprises a measurement of central nervous system (CNS) amyloid plaques, CNS tau accumulation, cerebrospinal fluid (CSF) beta-amyloid 42, CSF tau, CSF phospho-tau, CSF or plasma neurofilament light chain (NfL), Lewy bodies, or CSF alpha-synuclein. In some embodiments, the marker of neurodegeneration is decreased by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount increases cognitive function. In some embodiments, the cognitive function is increased by about 10% or more, as compared to prior to administration. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets MTRES1 and when administered to a subject in an effective amount decreases central nervous system (CNS) amyloid plaques, CNS tau accumulation, cerebrospinal fluid (CSF) beta-amyloid 42, CSF tau, CSF phospho-tau, Lewy bodies, or CSF alpha-synuclein. In some

embodiments, the CNS amyloid plaques, CNS tau accumulation, CSF beta-amyloid 42, CSF tau, CSF phospho-tau, Lewy bodies, or CSF alpha-synuclein, is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate,