

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, 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.

[0002b] In another aspect, 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.

[0002c] In another aspect, provided herein is 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.

[0002d] In another aspect, provided herein is 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.

[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,