TREATMENT OF FGG RELATED DISEASES AND DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional No. 63/286,393, filed December 6, 2021, which application is incorporated herein by reference.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 54462-736601.xml, created December 3, 2022, which is 5155 kilobytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

BACKGROUND

[0003] Psychiatric and neurological diseases are widely abundant, and may affect a wide variety of people. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0003a] In one aspect, provided herein is a composition comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 3621.

[0003b] In another aspect, provided herein is a composition comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and a nucleoside sequence complementary to about 12-30 contiguous nucleosides of SEQ ID NO: 3621.

[0003c] In another aspect, provided herein is use of a composition comprising an oligonucleotide that targets FGG in the manufacture of a medicament for improving a mental disorder measurement in a subject, relative to a baseline mental disorder measurement, wherein the composition is to be administered to the subject in an effective amount.

[0003d] In another aspect, provided herein is use of a composition comprising an oligonucleotide that targets FGG in the manufacture of a medicament for decreasing fibrinogen, wherein the composition is to be administered to a subject in an effective amount.

[0003e] In yet another aspect, provided herein is use of a composition comprising an oligonucleotide that targets FGG or the composition as described herein in the manufacture of a medicament for treating a subject having a psychiatric disorder or a neurological disorder, wherein the composition comprising the

oligonucleotide that targets FGG or the composition as described herein is to be administered to the subject an effective amount.

[0003f] In yet another aspect, provided herein is use of a composition comprising an oligonucleotide that targets FGG or the composition as described herein in the manufacture of a medicament for treating a subject having a clotting or coagulation disorder or a thrombophilia, wherein the composition comprising the oligonucleotide that targets FGG or the composition as described herein is to be administered to the subject an effective amount.

[0003g] In yet another aspect, provided herein is the composition as described herein for use in therapy.

[0004] Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets fibrinogen gamma gene (FGG). Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that targets FGG and when administered to a subject in an effective amount improves a mental disorder measurement of a mental disorder. In some embodiments, the mental disorder comprises a psychiatric disorder. In some embodiments, the psychiatric disorder comprises a depressive disorder (e.g., major depressive disorder, persistent depressive disorder, treatment resistant depression and signs or symptoms of depression), post-traumatic stress disorder, mood disorder, anxiety disorder, eating disorder, substance-use disorder, bipolar disorder, personality disorder, schizophrenia, or schizoaffective disorder. In some embodiments, the mental disorder measurement is chosen from the group consisting of a Montgomery-Asberg Depression Rating Scale (MADRS) score, a Hamilton Depression Rating Scale-17 score, anxiety signs and symptoms, eating disorder signs and symptoms, substance-use disorder signs and symptoms, post-traumatic stress disorder signs and symptoms, bipolar disorder signs and symptoms, schizophrenia signs and symptoms, and psychosis signs and symptoms. In some embodiments, the mental disorder comprises a neurological disorder. In some embodiments, the neurological disorder comprises Alzheimer's disease, dementia, delirium, cognitive decline, vascular dementia, headache (e.g., migraine), chronic pain (e.g., fibromyalgia), chronic fatigue syndrome (e.g. myalgic encephalomyelitis), or motor neuron disease (e.g., amyotrophic lateral sclerosis). In some embodiments, the mental disorder measurement is chosen from the group consisting of cognitive function, CNS amyloid plaques, CNS tau accumulation, CSF beta-amyloid 42, CSF tau, CSF phospho-tau, Lewy bodies, CSF alpha-synuclein, headache symptoms or signs, migraine symptoms or signs, chronic pain symptoms or signs, fibromyalgia symptoms or signs, chronic fatigue syndrome (e.g. myalgic encephalomyelitis) symptoms or signs, and

motor neuron disease (e.g., amyotrophic lateral sclerosis) symptoms or signs. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. In some embodiments, 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. In some embodiments, the oligonucleotide comprises a modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HNA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises a 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. In some embodiments, the modified nucleoside comprises one or more 2'fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. In some embodiments, 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. In some embodiments, the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α-tocopherol, or a combination thereof. In some embodiments, the oligonucleotide comprises a sugar moiety attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the sugar comprises N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc), or mannose. The sugar moiety may comprise ETL17. In some embodiments, the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand is 12-30 nucleosides in length. In some embodiments, the antisense strand is 12-30 nucleosides in length. Disclosed herein, in some embodiments, are compositions comprising an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 12-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of SEQ ID NO: 3621. In some embodiments, 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

linkages, 5 or more modified internucleoside linkages, 6 or more modified internucleoside linkages, 7 or more modified internucleoside linkages, 8 or more modified internucleoside linkages, 9 or more modified internucleoside linkages, 10 or more modified internucleoside linkages, 11 or more modified internucleoside linkages, 12 or more modified internucleoside linkages, 13 or more modified internucleoside linkages, 14 or more modified internucleoside linkages, 15 or more modified internucleoside linkages, 16 or more modified internucleoside linkages, 17 or more modified internucleoside linkages, 18 or more modified internucleoside linkages, 19 or more modified internucleoside linkages, or 20 or more modified internucleoside linkages.

[0068] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of FGG, wherein the oligonucleotide comprises the modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HNA), cyclohexene nucleic acid (CeNA), 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified nucleoside comprises HNA. In some embodiments, the modified nucleoside comprises CeNA. In some embodiments, the modified nucleoside comprises a 2'-methoxyethyl group. In some embodiments, the modified nucleoside comprises a 2'-O-alkyl group. In some embodiments, the modified nucleoside comprises a 2'-O-allyl group. In some embodiments, the modified nucleoside comprises a 2'-fluoro group. In some embodiments, the modified nucleoside comprises a 2'-deoxy group. In some embodiments, the modified nucleoside comprises a 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. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside. In some embodiments, the modified nucleoside comprises a 2'-deoxyfluoro nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-NMA nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-DMAEOE nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-aminopropyl (2'-O-AP) nucleoside. In some embodiments, the modified nucleoside comprises 2'-ara-F. In some embodiments, the modified nucleoside comprises one or more 2'fluoro modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. Benefits of the modified nucleoside may include decreased toxicity or improved pharmacokinetics.

[0069] In some embodiments, 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, or a range of nucleosides defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 19 modified nucleosides. In some embodiments, the oligonucleotide comprises no more than 21 modified nucleosides. In some embodiments, the oligonucleotide comprises 2 or more modified nucleosides, 3 or more modified nucleosides, 4 or more modified nucleosides, 5 or more modified nucleosides, 6 or more modified nucleosides, 7 or more modified nucleosides, 8 or more modified nucleosides, 9 or more modified nucleosides, 10 or more modified nucleosides, 11 or more modified nucleosides, 12 or more modified