PATENT APPLICATION

ANTISENSE OLIGOMERS FOR TREATMENT OF CONDITIONS AND DISEASES

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/550,462, filed on August 25, 2017, U.S. Provisional Application No. 62/575,901, filed on October 23, 2017, U.S. Provisional Application No. 62/667,356, filed on May 4, 2018, U.S. Provisional Application No. 62/671,745, filed on May 15, 2018, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Nervous system disorders are often associated with channelopathy, characterized by the disturbed function of ion channels that mediate neuronal excitability, neuronal interactions, and brain functions at large. Mutations in the SCN1A gene, which is part of the SCN1A-SCN2A-SCN3A gene cluster that encodes alpha-pore forming subunits of the neuronal voltage gated sodium channel, are associated with development of disease number of diseases and conditions, such as Dravet Syndrome (DS) (Miller, et al., 1993-2015, GeneReviews, Eds. Pagon RA, et al. Seattle (WA): University of Washington, Seattle, Bookshelf ID: NBK1318, and Mulley, et al., 2005, Hum. Mutat. 25: 535-542).

SUMMARY OF THE INVENTION

[0002a] Disclosed herein, in certain embodiments, is a use of a pharmaceutical composition in manufacturing a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is associated with a deficient amount or activity of the Nav1.1 protein encoded by the SCN1A gene in the subject, wherein the pharmaceutical composition comprises: an antisense oligomer, and a pharmaceutically acceptable excipient; wherein the antisense oligomer binds to a targeted portion of a pre-mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, whereby the antisense oligomer promotes exclusion of the NMD exon from the pre-mRNA that contains the NMD exon and encodes Nav1.1, thereby increasing the level of processed mRNA encoding the Nav1.1 protein, and increasing the expression of the Nav1.1 protein in a cell having the pre-mRNA, when the cell is treated with the antisense oligomer, as compared to a corresponding control cell not treated with the antisense oligomer, wherein the NMD exon is located at a region from GRCh37/hg19: chr2:166,863,740 to GRCh37/hg19: chr2:166,863,803.

[0002b] Disclosed herein, in certain embodiments, is a use of a pharmaceutical composition in manufacturing a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is associated with a deficient amount or activity of the Nav1.1 protein encoded by the SCN1A gene in the subject, wherein the pharmaceutical composition comprises a viral vector encoding an antisense oligomer, wherein the antisense oligomer binds to a targeted portion of a pre-mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, whereby the antisense oligomer promotes exclusion of the NMD exon from the pre-mRNA that contains the NMD exon and encodes Nav1.1, thereby increasing a level of processed mRNA encoding the Nav1.1 protein, and increasing the expression of the Nav1.1 protein in a cell having the pre-mRNA, when the viral vector is introduced into the cell, as compared to a corresponding control cell that is not treated with the viral vector, wherein the NMD exon is located at a region from GRCh37/hg19: chr2:166,863,740 to GRCh37/hg19: chr2:166,863,803.

[0002c] Disclosed herein, in certain embodiments, is an antisense oligomer that has a sequence selected from the group consisting of SEQ ID NOs: 32-35, 39, 40, 42-45, 49-51, 54-59, 66, 221-224, 228, 229, 231-234, 238-240, 243-248, 255, 304-308, 312-316, 318-324, 326-335, 337-346, 350-354, 356-362, 364-373 and 375-379.

[0003] Disclosed herein, in certain embodiments, is a method of modulating expression of SCN1A protein in a cell having an mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon mRNA) and encodes SCN1A protein, the method comprising contacting a therapeutic agent to the cell, whereby the therapeutic agent modulates splicing of the NMD exon from the NMD exon mRNA encoding SCN1A protein, thereby modulating the level of processed mRNA encoding SCN1A protein, and modulating expression of SCN1A protein in the cell. In some embodiments, the therapeutic agent (a) binds to a targeted portion of the NMD exon mRNA encoding SCN1A; (b) modulates binding of a factor involved in splicing of the NMD exon mRNA; or (c) a combination of (a) and (b). In some embodiments, the therapeutic agent interferes with binding of the factor involved in splicing of the NMD exon from a region of the targeted portion. In some embodiments, the targeted portion is proximal to the NMD exon. In some embodiments, the targeted portion is at most about 1500 nucleotides, about 1000 nucleotides, about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides,