New Compounds and Methods for the Treatment of Spinal Muscular Atrophy and Other Diseases

Published date: Feb. 1, 2012

Technology description

Summary

Spinal muscular atrophy (SMA) is caused by mutations in the SMN1 gene that result in reduced expression of the survival motor neuron (SMN) protein and a loss of spinal motor neurons. An SMN2 gene paralog that differs from SMN by a single base pair has inadequate expression of SMN to support motor neuron survival. Alternative splicing caused by the single base substitution in the SMN2 gene results in a slightly truncated and highly unstable SMN protein. Drugs that allow translational read through of the stop codons introduced by the alternative splice event have been shown to stabilize the mutant protein, resulting in increased levels of SMN.

A chemical library screen identified indoprofen, a nonsteroidal anti-inflammatory drug, as an inducer of SMN expression in cultured cells. However, indoprofen cannot enter the brain in satisfactory amounts, has a relatively low level of activity and can cause substantial side-effects in part due to its cyclooxygenase inhibitory activity. NIH inventors designed indoprofen derivatives without cyclooxygenase activity that can enter the CNS and increase expression of a SMN protein from the SM N2 gene with increased potency and efficacy. The mechanism of action of these indoprofen analogs appears to be translational readthrough of stop codons introduced by the alternative SMN2 splicing event. In addition to treating SMA, novel drugs that allow read through of stop codons could potentially treat many other diseases caused by such mutations such as cystic fibrosis and muscular dystrophy.
Market:
SMA is a rare genetic disease that affects approximately 1 in 6,000 live births, and is the leading genetic cause of death in infants and toddlers. The projected market size for SMA is between $250 million and $750 million.

Application area

Efficacious treatment for SMA, utilizing indoprofen analogs that increase SMN protein expression
Treatment of any genetic disease caused by premature termination of protein translation

Institution

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