Targeting a SMN lncRNA for the treatment of SMA

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Country

USA

Title of project or programme

Targeting a SMN lncRNA for the treatment of SMA

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NIH (NINDS)

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15/02/2016

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5

The project/programme is most relevant to:

Spinal muscular atrophy

Keywords

Spinal Muscular Atrophy, Motor Neurons, Polycomb, Antisense Oligonucleotides, Transcript

Research Abstract

? DESCRIPTION (provided by applicant): The motor neuron disease spinal muscular atrophy (SMA) is the leading inherited cause of death in infancy and childhood. It is caused by recessive mutations of the survival motor neuron 1 gene (SMN1), but all patients retain one or more

copies of the homologous SMN2 gene that produce inadequate levels of SMN protein due to an alternative splice event. Novel therapeutics including splice-switching oligonucleotides (SSOs) can modulate this splice event thus increasing SMN expression. SSOs are currently being tested in phase III clinical trials in SMA patients, but they have a ceiling effect imposed by existing levels of SMN2 pre-mRNA. The efficacy of SMA splice-modulating treatments could be substantially accentuated by combining such treatments with specific SMN2 promoter activation. In preliminary data, we have identified a novel SMN2- associated long non-coding RNA (SMN-NAT), which is enriched in the CNS and represses SMN2 gene expression via recruitment of the epigenetic modifier Polycomb repressive complex 2 (PRC2). We have further shown that SMN-NAT-targeting antisense oligonucleotides (ASOs) can suppress SMN-NAT resulting in enhanced expression of SMN in cultured cells. In order to further explore whether SMN-NAT regulates SMN2 in human SMA patient cells and in neurons, in Specific Aim 1 we will examine the effects of SMN-NAT ASOs in several fibroblast cell lines derived from SMA patients and controls, in primary neurons derived from severe SMA mice, and in motor neurons derived from SMA induced pluripotent stem cells (iPSCs). In Specific Aim 2, we will further define the role of the PRC2 complex in the epigenetic control of SMN2 gene expression in SMA patient cells and neurons. Finally, in Specific Aim 3, we will examine the therapeutic potential of targeting SMN-NAT by treating severe SMA mice with SMN-NAT ASOs alone or in combination with SSOs and examining effects on SMN expression, behavioral outcomes, and motor unit histology. Together, these studies will characterize novel mechanisms of SMN2 gene control in neurons and determine whether targeting a SMN2-associated lncRNA could represent a new therapeutic strategy for SMA, which has the promise of working additively with splice modulating treatments.

Lay Summary

PUBLIC HEALTH RELEVANCE: Spinal muscular atrophy (SMA) causes severe muscle weakness and often early mortality, but there is an opportunity to develop treatment for SMA by activating survival motor neuron 2 (SMN2) gene expression. This proposal will test whether targeting a new SMN2-associated long non-coding RNA can increase SMN protein and lessen disease in SMA mice. These studies could provide evidence to support further development of this approach for human patients as well as establish whether it has the potential to work additively with other SMA therapeutics, which are already in advanced clinical trials.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Spinal muscular atrophy (SMA)

Years:
2016

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