Spinal muscular atrophy: inducing SMN expression

https://neurodegenerationresearch.eu/survey/spinal-muscular-atrophy-inducing-smn-expression/

Principal Investigators

DIDONATO, CHRISTINE J

Institution

LURIE CHILDREN'S HOSPITAL OF CHICAGO

Contact information of lead PI
Country

USA

Title of project or programme

Spinal muscular atrophy: inducing SMN expression

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,703,555.96

Start date of award

30/09/2007

Total duration of award in years

2

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, Motor Neurons, SMN2 gene, electrical property, Adult Spinal Muscular Atrophy

Research Abstract

DESCRIPTION (provided by applicant): Spinal Muscular Atrophy (SMA), a common autosomal recessive motor neuron disorder that is the leading genetic cause of infant mortality. SMA is

caused by the loss of the survival motor neuron gene (SMN1). SMN2, a nearly identical copy gene, is present in all SMA patients but differs by a critical nucleotide that alters exon 7 splicing efficiency. This results in low SMN levels which are not enough to sustain motor neurons and results in a varying clinical presentation. Our previous work focused on defining the dosage requirements of SMN for normal health and restorative therapies for the severe form of the disease. Here, using newly generated mouse models we will focus on the intermediate and mild forms of SMA that have been understudied due to a lack of appropriate mouse models. We will address therapy development questions and disease mechanism in terms of SMN's cellular site of action that contributes to motor neuron dysfunction and disease pathogenesis. In Aim 1, we will determine the timing requirements of SMN inductive therapies in intermediate and mild inducible SMA mice. This will address the potential of SMN-directed therapies to be of benefit after measureable loss has occurred and at advancing points of disease which has yet to be addressed. Here we will use a whole body Smn inductive approach to account for non-neuronal cell types that might impact disease severity. In Aim 2, we will refine the whole body approach to focus on neuronal inductive SMN therapies using our mild SMA mouse. Specifically we will directly determine the therapeutic benefit of splice-switching anti-sense oligonucleotides (ASO) that correct SMN2 splicing. It will address whether this type of drug-candidate, when delivered after disease onset, is capable of maintaining or improving function. Importantly, this study meets an unmet milestone in the clinical development of this drug as well as other SMN inductive therapies which require CNS delivery to patients. In Aim 3 we will compare the intrinsic electrical and synaptic properties of control and age matched SMA motor neurons from intermediate and mild SMA mice throughout their life. We postulate that altered electrical properties contribute to the cellular mechanisms underlying motor neuron dysfunction as a consequence of Smn deficiency. These studies will be performed using neonatal slice and in vitro sacral cord preparations. The in vitro preparation which we have recently developed for use in adult mice, allows intrinsic and synaptic motor neuron hyperexcitability to be assessed through intracellular recordings at time points from neonatal stages throughout adulthood. This will provide unique insights to the physiological state of SMA motor neurons throughout the course of disease. Overall, the research presented in this application will provide important information that is critical towards the development of SMN-dependent as well as independent treatment strategies for intermediate and mild forms of SMA. It also addresses an unmet need in therapy development and provides insight to the underlying cellular mechanism of disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Spinal muscular atrophy (SMA) is caused by reduced levels of the survival motor neuron (SMN) protein. It is currently unknown how late in the disease process SMN inductive therapies can be beneficial in terms of either improving function or halting disease progression. This proposal focuses on 1) determining the latest time that SMN can be re-introduced after disease onset in milder forms of SMA, 2) where it is required, specifically if therapies that only increase SMN within the nervous system can correct all deficits and 3) we will compare the intrinsic electrical properties between control and age matched SMA motor neurons from intermediate and mild SMA mice throughout their life. This will allow us to correlate the physiological state of SMA motor neurons with disease progression. We believe that altered electrical properties are an early event in SMA motor neuron dysfunction. If the electrical properties are altered, identifying the timing, mechanisms and pathways involved could lead to pharmaceutical approaches that are SMN-independent and provide a complimentary approach that targets other pathways besides SMN. All of this research has

important implications for therapy development.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Spinal muscular atrophy (SMA)

Years:
2016

Database Categories:
N/A

Database Tags:
N/A