Basic Research Grants Funded for 2015

Identification of SMN:HuD bound RNAs critical for motor neuron development. Christine Beattie, PhD, at the Ohio State University for $140,000.
Objective: We have found that motor neurons do not develop properly in a SMA animal model in fish, and we hypothesize that this contributes to the motor neuron dysfunction in this disease.
Research Strategy: We are looking at proteins and RNAs that SMN interacts with to ask whether they are important for motor neuron development.
Significance: In SMA, motor neurons fail to function properly, but we do not yet understand why at the molecular level. If we understood this, we could better design therapeutics to specifically target and the exact defect.

Defining the contribution of RNP assembly pathways to the SMA phenotype. Arthur Burghes, PhD, at the Ohio State University for $140,000.
Objective: SMN protein is known to function in the cellular process call RNA protein assembly. This project hopes to definitively show whether or not RNA protein assembly is the critical pathway that is disrupted in SMA when SMN protein levels are low.
Research Strategy: We will study the function of the SMN protein in cell culture and in mice using SMN mutations that occur in SMA patients.
Significance: The basic biological function of SMN that is disrupted in SMA is not known. Using SMN mutations that occur in SMA patients we can dissect the function of SMN and identify genes in the same biological pathway that may serve as novel therapeutic targets.

The role of SMN as a translational regulator. Jocelyn Cote, PhD, at the University of Ottawa for $30,000.
Objective: We have been the first to describe a new function for SMN in the regulation of protein production (called translation) and will perform further experiments to gain a better understanding of how SMN is involved in this new function.
Research Strategy: A series of biochemical, molecular and cellular approaches will be used to explore the therapeutic potential of increasing the levels and/or activity of regulators of SMN function in order to compensate for loss of SMN.
Significance: The identification of the molecular targets that are misregulated due to loss of this novel SMN function in SMA should lead to a more complete understanding of disease mechanism.

Assessing mediators of muscle weakness in SMA mice. Christine DiDonato, PhD, at Lurie Children's Hospital of Chicago for $70,000.
Objective: We will study a special SMA mouse that we have generated that has increased SMN levels in its motor nerves and low SMN levels everywhere else. We have shown that this mouse develops muscle weakness as a young adult, which we believe is due to a problem in the skeletal muscle.
Research Strategy: We will study the skeletal muscles of these mice and various control mice to determine if there are structural defects within the muscle cell. Specifically, we will determine if SMN is indeed localized to the sarcomere and whether there is a problem with muscle cell fusion.
Significance: Our research using these newly developed mice has uncovered the fact that specifically increasing SMN only within the central nervous system does not completely correct everything, as wehave unmasked a skeletal muscle problem. This may have important implications for current and future therapies.

cure SMA

Muscle satellite cell biology and muscle regeneration in Smn- depleted mice. Rashmi Kothary, PhD, at the Ottawa Hospital Research Institute for $140,000.
Objective: Our goal is to better understand how depletion of SMN impacts the generation and function of muscle satellite cells, which help muscle respond to damage, and the capacity of skeletal muscle to regenerate.
Research Strategy: We will study what aspects of muscle satellite cell biology and muscle regenerative capacity are affected upon SMN depletion using genetic mouse models, single myofiber culture, cell biology, and cell transplantation.
Significance: The proposed studies will provide insight into the importance of muscle cell biology at multiple stages of SMA disease progression, using SMN depleted-mice**.**

Novel approaches against spinal muscular atrophy by targeting splicing regulators. Antoine Cléry, PhD, at ETH Zurich for $90,000.
Objective: We aim to identify a new generation of molecules that control the protein splicing regulators of the SMN2 pre-mRNA. Understanding this could lead to promising drugs against SMA and other splicing-related diseases.
Research Strategy: We will screen chemical compound libraries against protein splicing regulators bound to their SMN2 RNA. In addition, we will use our protein structural data to specifically assess the role of a protein-splicing regulator called SRSF1 protein.
Significance: Finding new therapeutic strategies to approach SMA and other splicing-related diseases is a very promising method to correct splicing defects.

Assessing the reversibility of proximal axon abnormalities in SMA mice. Charlotte Sumner, MD, at Johns Hopkins University for $140,000.
Objective: Our objective is to further characterize how the loss of SMN protein causes axonal defects in motor neurons, and to determine whether and when during development they can be reversed by SMN2 splice-switching oligonucleotides.
Research Strategy: We are currently utilizing mouse models to further define this axonal pathology over time and its relationship to motor neuron death. We are also testing whether prenatally delivered SMA therapeutics can prevent these pathologies.
Significance: It is unknown how SMN protein deficiency causes dysfunction and ultimately death of motor neurons. We anticipate that these studies will provide important insights regarding the earliest functional and cellular abnormalities of SMN-deficient motor neurons, which might then guide the timing of therapeutic intervention.

Novel Strategies to Increase SMN2 RNA. Megerditch Kiledjian, PhD, at Rutgers, The State University of New Jersey, for $140,000.
Objective: In order to increase levels of SMN2 mRNA and SMN protein, we have identified a variant form of a protein that when expressed in cells leads to increased SMN2 mRNA and protein. Our goal is to further understand the molecular basis for how this occurs.
Research Strategy: We will be using SMA cell lines from type I patients to determine the molecular mechanism underlying this new way of increasing SMN protein levels in patient cells. We will also devise novel therapeutic strategy in cells with the goal to ultimately treat SMA.
Significance: Therapeutic approaches to increase SMN2 expression should be beneficial in SMA patients. Our objective is to decipher the molecular mechanism underlying this new mode of SMN2 upregulation and implement strategies to utilize in therapeutic intervention for SMA patients.